Drug Research and Development

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Preface

TODAY the drug manufacturer and distributor, the research and laboratory worker, the physician and pharmacist, the advertising counsel and sales representative are all participants in the development of drugs and drug therapy. Collectively, indeed, they deserve considerable credit for the remarkable advances that have taken place in the last decade. But to take their rightful place in modern drug research, development, and promotion each requires a working knowledge, not only of the tasks allotted to him, but also of the program as a whole and what it encompasses and entails.

The purpose of this volume is to promote such an understanding and to present the essential background. It is hoped that it will serve as an important contribution to the development and marketing of drugs and pharmaceuticals under today's conditions and requirements. In the following pages, recognition is accorded the remarkable advances of modern drug therapy, and a step by step explanation is offered of the research and developmental processes that must be followed in formulating the modern drug formula, testing it, readying it for the market, complying with legal requirements, and merchandising, promoting, and advertising the perfected preparation.

The editors have sought to avoid a theoretic presentation of the subjects involved. They have gone to industry, to the universities, to the professions, for their contributors, with the happy result that the various chapters are founded in actual experience and on practical material. Their object has been at all times to make this book useful to those who turn to its pages for guidance and constructive advice. Space limitations, of course, prevent a definitive treatise on each aspect of this important subject but every effort has been made to describe and

elucidate the more commonly encountered activities, practices, and procedures.

It should be emphasized at this point that this book does not deal exclusively with one type or category of drug products, but on the contrary the material presented is readily applicable to every class of therapeutic preparation and device, whether it be the so-called ethical preparation or the "proprietary," the "prescription" or the "over-the-counter" item. All, in the final analysis, require the same rational, scientific, and intelligent handling and approach.

Necessarily, in a volume of this nature, the opinions of each author are, of course, his own, and are to be attributed neither to his company or other affiliation. Each has been extended the utmost liberty and latitude in expressing his thoughts upon the subject he has written.

This opportunity is taken to acknowledge our gratitude to Miss Alice Molander for her assistance in the preparation of the manuscript.

AUSTIN SMITH
ARTHUR D. HERRICK

Table of Contents

Drug Research and Development

1

The Modern Drug Formula

ARTHUR D. HERRICK AND AUSTIN SMITH

IT must be evident to even the most casual observer that medicine today has entered upon an era of unprecedented progress in the field of therapeutics, due in large part to the development of new pharmaceuticals. Among the brilliant scientific advances of this age—a list that includes atomic fission, electronics, and aeronautics—a foremost position should undoubtedly be reserved for the growth of modern drug therapy. Nor is it too much to claim that the discoveries and inventions in this sphere, merely in the last fifteen years, have contributed more to the happiness, well-being, and health of humanity than has any other advancement.

This progress is all the more remarkable in the light of the general ill-repute in which drugs, as an instrument of therapeutics, had been held for many years. At the close of the 18th century, in fact, this paucity of confidence in the efficacy of drugs caused a trend in medical thinking in this country and elsewhere which eschewed the use of these substances for generations. As recently as the first World War, the most useful armamentarium of the average physician was declared principally to be opium, mercury, cinchona, digitalis, and iodine, exclusive, of course, of analgesics, anesthetics and antitoxins. True, many irrational and otherwise worthless medical proprietary mixtures were on the market; what popularity they possessed rested, for the most part, on empirical evidence and persuasive advertising. The number of efficacious products was, however, discouragingly small.

In the early 1930's the tide shifted. And so swiftly has development followed development since then that a survey in

1947 disclosed that over fifty-four per cent of the drugs then in use had been wholly unknown ten years before! Each month, moreover, marks further advances. Penicillin has, for example, opened boundless avenues of research for other antibiotics; the antihistaminics march determinedly toward further alleviation of allergic distress; the sulfonamides have multiplied into a comprehensive group of curative agents. These newcomers, perhaps, constitute the "royal family" of modern drug therapy, but comparable, if less newsworthy, discoveries and improvements can be found in almost every category of drugs.

Not only do new chemical combinations flow with regularity from laboratories throughout the land, but skillful pharmacologists and clinicians continue to discover fresh therapeutic uses and applications for drugs of previously theoretical interest only and others utilized in different conditions. Perhaps the most outstanding example of this trend is sulfanilamide, discovered in the laboratory at the turn of the century and only resurrected for magnificent therapeutic service twenty-five years later.

In a very concrete sense, we have entered an age of *rational* therapeutics—and this realistic and truly scientific approach has returned enormous dividends in health and well-being. It must not be assumed, however, that the methods now employed are altogether new or novel; indeed they have been known for many years. It is pertinent, therefore, to inquire why drug therapy has made such tremendous advances only within the last decade or so. A rather careful analysis discloses that four major factors have contributed largely to this development.

It is perhaps not fully appreciated to what degree the enactment, and particularly the enforcement, of the Federal Food, Drug, and Cosmetic Act have affected the manufacture and distribution of all types of drug products. Its predecessor, the Food and Drugs Act of 1906, was, relatively speaking, merely a policing statute; it confined its objectives generally to safeguarding the integrity of drugs. Its concern with therapeutic claims was limited broadly to fraudulent practices. Despite the esteem in which the American people as a whole held what

they knew as the Wiley Act, a manufacturer could, with perfect propriety, "make any medicine he wanted to and sell it to the people if he told the truth about it," to paraphrase one court's dictum. On economic grounds, the statute had mediocre success; as a beacon, a guide for significant progress in drug therapy, it was, in truth, lacking.

It is improbable, moreover, that the Congress, despite its long wrangling over the provisions, grasped the full implications of the statute it finally enacted in 1938. Certainly it could not anticipate the impetus the law would give to drug therapy; and it is doubtful that it foresaw that compliance with the new requirements of the Act virtually compels the manufacturer and distributor of a drug—whether it be "ethical" in nature or a proprietary—to apply the principles of rational therapeutics to his product if he is not, through inadvertency or otherwise, to find himself violating the law. The strict and unflinching enforcement policy that has characterized the activities of the Food and Drug Administration in carrying out its mandate under the statute has further implemented and directed the course of this development. And finally the courts, after a history of apathy toward therapeutic claims, have reversed themselves to impose on the promoter of a drug product a stern and solemn obligation and responsibility that can only be satisfied by the most careful surveillance over, and knowledge of, the article he sponsors and urges for the prevention, treatment, diagnosis, or cure of disease conditions.

While this is not the place to discuss with any particularity the legal requirements affecting the interstate distribution and marketing of drugs, it is material to recognize how the provisions of this Act have encouraged and necessitated the collection of data about the use and safety and efficacy of products offered to the American public today. The injunction against false or misleading labeling, for example, has forced the drug manufacturer and distributor to recognize the limitations of his product, therapeutically speaking, as well as its possible accomplishments. In framing his claims, he must bear in mind the distinct difference between causal and symptomatic treat-

ment, between specifics and mere alleviation. Not only is he called upon to peruse the scientific literature to find support for his representations but he is also required to appraise and evaluate the conclusions drawn by different investigators.

Similarly, the necessity of preparing adequate directions for use stimulates his study of methods of administration, absorption, distribution of the drug within the body, and dosage. In devising warnings against the misuse of his preparation he has been led to consider problems of synergism, the influence of pathologic states, cumulative action, tolerances, and idiosyncrasies. In determining the identity of the active ingredients in the compound he has been forced to delve into the relative therapeutic and physiological effects of the individual components. Restrictions on dangerous drugs have compelled a knowledge of general toxicology. In short, the manufacturer of almost every drug today, if he is to satisfy the responsibility the law places upon him, must inform himself fully about the pharmacologic and therapeutic properties of his product.

If this is true of preparations already on the market, it is doubly apposite in the case of new and untried drugs. Although the "new drug" provisions of the Federal Food, Drug, and Cosmetic Act are concerned primarily with the element of safety, the close relationship to this factor of therapeutic efficacy, on the one hand, and proper facilities and controls, on the other, is so compelling and material as to necessitate a comprehensive inquiry into all facets of the subject. After several attempts, the Food and Drug Administration impressed upon the drug industry the need of careful systematic research by competent investigators in new drug applications. Literature developed about the technics and requirements imposed by the statute; its wide dissemination undoubtedly had a salutary effect upon the character of the evidence assembled by drug manufacturers and their consultants.

A second factor that has contributed considerably to the current advance in drug therapy has been the activities of the Council on Pharmacy and Chemistry of the American Medical Association. Organized originally to combat irrational medi-

cation and the distribution of worthless preparations, its educational efforts have succeeded to such an extent as to permit it to turn, in recent years, toward the encouragement of valuable drug research and development. In later chapters its program and objectives are presented in detail. Its seal of acceptance and its official publication, *New and Nonofficial Remedies,* are quite familiar; products bear the seal, indeed, as an insignia of progress.

The Council has been criticized in some quarters for its conservative attitude toward new drugs and new claims made on their behalf by eager manufacturers, activated more by the profit motive—and sometimes by enthusiam founded on erroneous advice and uncritical data—than any scientific support. Actually its so-called conservatism amounts to a high sense of evaluation. So searching is its inquiry, so skeptical its scientific attitude toward immoderate therapeutic claims that it has virtually compelled the drug manufacturer seeking Council acceptance to undertake appropriate steps, first to fix the worth of his product for the conditions offered and, secondly, to produce and market it within truly ethical channels.

That World War II has had an accelerating effect on the course of drug research and development is also evident. Penicillin, for example, could not have attained its present level of progress so rapidly without the spur of this conflict. The war made other contributions. The truism that combat makes fodder for cannon was, in a sense, subordinated to another; that war produces fodder for medical research. This work was conducted on the broadest possible canvas. One reads of sulfonamide clinical tests involving over 100,000 men as subjects. And other new medicinals were tested on the same tremendous scale. The global aspects of the war, furthermore, not only permitted verifications under every conceivable condition but at the same time widened the investigations to embrace almost every ill that commonly afflicts the human race.

Nor should we overlook the fact that the war years brought a high degree of prosperity to the drug industry. Facilities were expanded; research budgets attained previously unknown

dimensions; equipment was improved; each manufacturer was encouraged to lift his sights to higher horizons. The war also had its effect on the medical profession, and thus indirectly upon the drug trade. Men and women in the armed forces were indoctrinated with a knowledge of and familiarity with modern medical treatment that will undoubtedly have a meritorious effect on their future reliance on their physicians. The population remaining at home, flushed with unusual affluence, provided themselves with unaccustomed medical attention. We are not concerned here with medical economics; we are, however, emphasizing a situation that brought new remedies to more people and more rapidly than would, except for the impact of war, otherwise have occurred.

These are some of the factors that unquestionably have a bearing upon the swift development of drug therapy within the last few years. Each in itself, however, cannot explain the progress; cumulatively, perhaps, they have quickened the trend. The implementation of the new movement in this direction can, without doubt, be credited to another source.

THE DRUG INDUSTRY'S CONTRIBUTION TO DRUG THERAPY

Despite the acknowledged validity of the previously discussed causes for the notable advances made in drug therapy, the last and perhaps most important factor that has contributed to this progress was the realization, on the part of more and more drug firms, that research and development are "good business." We would be naïve, of course, to assert that it is only within the last decade that drug manufacturers have awakened to the value of an exclusive speciality. The history of the pharmaceutical trade is replete with the financial success that attends the promotion of an effective protected item. The difficulty had been, however, that it was only occasional that a novel product of this nature was produced; of these, too few came from American laboratories. As a consequence, the energies of the manufacturer were directed more toward promotional channels to establish the prominence of a brand name, for example, rather

than toward originating new products or markedly improving an existing line.

One is not too far wrong in remarking that the fundamental barrier to progress during this period was a blind attitude maintained toward the diseases of mankind. In the making of pharmaceuticals, too many were satisfied to accept the role of manufacturing pharmacist or chemist. Some firms directed their efforts at pharmaceutic elegance, at the maintenance of high standards of purity and quality. The more commercial minded actively promoted the most complicated—and most ineffectual—types of "shot-gun" preparations, placing their reliance of therapeutic efficacy on the sheer number of components they could combine in one "specialty." Too few recognized the need or the value of medical research. With myopic indifference to the ultimate fact that drugs are intended for the treatment of disease, they either accepted current pharmacologic "authority" without question, or, swinging to the opposite pole, advanced the most radical, untried, and irrational formulations. In both instances, their task was assumed to have been completed as soon as the sale was made.

Since the introduction of the sulfonamides marked the first development of the present era of drug therapy progress, it is interesting to observe that the original of these was brought to the market by the so-called German dye trust. Sulfanilamide, at the time its derivative was incorporated in the patented preparation, Prontosil, was not a new chemical substance but, on the contrary, had been discovered in the search for dyes just past the turn of the century. It was the laboratory and clinical work, however, sponsored by an industrial firm that demonstrated its use for therapeutic purpose. Due to the brilliant research of British and American investigators in determining that Prontosil apparently breaks down in the body to sulfanilamide, the Germans found themselves with a relatively worthless patent. Nevertheless, they did blaze a trail that drug manufacturers in other countries were quick to follow. Penicillin, also, was buried as a laboratory finding for over a decade until, under the urgency of wartime necessity and with the aid

of governmental funds, its mass production was made possible by pharmaceutical houses.

Today, with full appreciation of the value of drug research and development, industry has accepted a leading role in the task of bringing new remedies to the medical professions and to the public and in finding new therapeutic uses for older substances. It has energized and hastened additional discoveries. It has, moreover, augmented its contribution to modern drug therapy by rapid dissemination of knowledge and technics among physicians.

The factors discussed above, then, may be considered as contributing much to the present progress in drug therapy. Probably there are others of greater or lesser importance. Whatever the full list of causes, however, it cannot be denied that we stand today on the threshold of remarkable gains in this field. So recent has been the development, though, that consciousness of its happening has not yet permeated the thinking of sufficient men in the drug industry. In many, indeed, particularly the realm of remedies for self-medication, it still remains almost unknown. If there is any doubt on this score, one need merely examine some currently available catalogues.

MODERN DRUG RESEARCH AND DEVELOPMENT

There exists, of course, no rigid prescription for evolving a workable, saleable, and profitable pharmaceutical product. The reader who opens this book with the hope or expectation of finding such a rule of success is scheduled for disappointment. Modern drug research and development is not static. Indeed, any attempt to confine it within boundaries of any sort is apt only to restrict the vitality and vigor of its advance. One cannot, for example, describe the development in terms only of chemotherapy; antibiotics, serums, and hormonal preparations have also recreated new interest in biologicals. Likewise, any effort to limit its application to so-called "ethical" medicinals overlooks the fact that it is equally applicable to products dis-

tributed directly to the public—and probably more essential in such cases.

Modern drug research and development constitutes, in its broadest concept, a rule of procedure rather than one of form. It is characterized by new approaches, by new methods. Briefly, it may be viewed as consisting of the application of acceptable and practical scientific principles by drug firms and their personnel and consultants to the origination, verification, production, and marketing of products intended for the prevention, treatment, and diagnosis of disease.

This bald definition—if we can call it that—is faulty, however, in that it ignores other essential elements of the program. One of these, for example, is the need of correlating the entire program, of treating it as an entity. Thus, the chemist in his laboratory, the bacteriologist peering over cultures, the detail man in the physician's office, all contribute their activities to the project in general. Another factor which the definition omits is the necessity of appraisal and evaluation of the data collected. For instance, the mosaic of experimental findings must be assembled into a uniform whole; this calls for the exercise of careful judgment in assigning the facts to their precise and proper position. A third element that bears materially upon the application of the procedure is its timing.

It will be illustrative of what we have in mind to give several examples of how timing of the program may affect its ultimate success. Although this factor is essential in all phases of research and development, it is surprising how frequently errors in judgment in timing or failure to correlate activities arise with the result that a product is released before it is studied sufficiently to determine its important properties or is otherwise thrust before the medical profession or consumer at a most inappropriate time.

For example, some drugs that in other days might have been considered valuable, if only empirically, for their antibacterial properties are now practically obsolete because of the specificity of penicillin and the sulfonamides. Nevertheless they are vigorously promoted with inferences that they are the preferred

agents for the control of bacterial infections even when these are known to respond best to sulfonamide or antibiotic therapy. Sooner or later deception of this sort will prove harmful to the interests of the manufacturer. It is better by far to acknowledge that the preparation is dated so far as modern medical practice is concerned and to realize the futility of hoping for acceptance of a less effective product. Twenty years ago he might, perhaps, have had some hope of success; today he has none. It may be some consolation to firms finding themselves in this position to know that, had the development of penicillin preceded some of the sulfonamides, the latter might not have attained such a broad reception.

Timing has other applications to the success of a program. Of somewhat similar inadequacy is the summer promotion of an agent intended for the relief of upper respiratory infections, and the winter promotion of preparations offered for use in the hay fever season. Nor will the firm that releases publicity for a new drug which will not be available in quantity production be in a happier situation. It, too, will find that it has pulled the trigger without sighting the gun on a target.

These are merely facets to the general rule that modern drug research and development calls for the thoughtful and conscientious application of scientific procedures to all phases of drug investigations, manufacturing, and merchandising. Unfortunately, it must be admitted that despite the guidance offered by governmental and professional agencies and groups, the many excellent articles and treatises on the subject, the array of scientists available for advice and consultation and direction, the genuine and pressing need for research—there still exists a bewildering amount of confusion and, at times, a disconcerting and discouraging lack of knowledge and understanding of these matters.

The reasons for this situation are evident to impartial observers. Perhaps the principal one may best be summarized in the elementary premise that one must first recognize the existence of a problem before one can be induced to seek an answer to it. Nor is it encouraging to be forced to the con-

clusion that this basic awareness is, in many instances, absent. This is doubly regrettable in that ignorance of these fundamental factors not only makes the manufacturer or distributor of drug products a ready victim of charlatanic "experts," but affords no protection against financial loss and legal prosecution. Thus, ignorance of the many regulatory laws that affect drug production and marketing is not a satisfactory excuse in court. Nor will lack of knowledge compensate for financial loss when the product proves a failure as it is almost certain to do. If this volume has no other accomplishment, it will nevertheless have established its value if it helps illuminate the proper road to drug research and development.

THE PROGRAM AS A WHOLE

The objective of most research and development on the part of drug manufacturers is, of course, the eventual introduction of a new pharmaceutical into commerce. As we have already indicated, this is not a simple procedure even in the case of a relatively uncomplicated formula offered for the treatment of comparatively minor conditions. On the contrary, it is fraught with many difficulties, particularly for the uninitiated. This was not necessarily so in the past. Years ago, indeed, almost anyone could market a preparation with little recourse to scientific principles or governmental regulation. The basic requirements of success in those days hinged rather on ingenuity and perserverance. Today, however, a formidable barrier of obstacles stands in the way of even the most experienced and energetic manufacturer or distributor. Indeed, without a working knowledge of many factors, the firm launching a new product on the market will soon encounter the proverbial hornet's nest of troubles.

What does modern research and development in the drug field entail? What difficulties must be met and overcome? What burdens are imposed by the complexities of today's commerce and legal regulations? What types of problems emphasize the need of intelligent and experienced treatment? These

questions can best be answered by reviewing the requisites attending the development of a pharmaceutical under present-day conditions.

When a new drug—if it is to be of any value to its promoter and to the public—is finally ready for introduction into the market it will have been extensively studied and perfected from many viewpoints. The simple designation of the work that usually must be performed illustrates the complications and complexities of the development process. Thus, the chemist will probably have built it in his laboratory, torn it apart, and rebuilt it. Perhaps this exploration of chemical possibilities has been inspired by the thought of circumventing patent problems; more often the product has been developed in answer to a need expressed by physicians or because of an observation made during the course of routine screening procedures. Here it may be remarked that varying degrees of inventive originality enter into the evolution of such compounds. Frequently, for example, attempts are made to develop an effective therapeutic agent merely by modifying the chemical structure of a drug of known action—not always a dependable method since sometimes a minor variation in this connection has the contrary effect, producing an inactive or toxic substance. However, chemists using this method have often produced series of drugs worthy of further study; thus the sulfonamides, barbiturates, and antimalarials have had their genesis in similar studies.

Before the new drug appears on the market, moreover, the pharmacologist will have screened it in animals to establish the precise nature of its action; the clinician will have scrutinized its effects on humans and in various stages of disease conditions; the medical consulting staff will have evaluated these findings to determine whether the extent of therapeutic response warrants marketing the drug; the pilot plant manager or chemical engineer will have considered how to conquer the problems of mass production; the pharmacist will have toyed with the exigencies of pharmaceutic elegance; control experts will have set up flow-sheets and control systems to assure that

the same substance, with no more than permissible deviation from fixed standards, will invariably be obtained; and the manufacturing department will have studied the need of special machinery for melting, mixing, tableting, or capsuling. Frequently, too, the bacteriologist, pathologist, hematologist, surgeon, immunologist, and other scientists may have contributed their knowledge and experience to its development.

But all this was only the beginning of the process of procuring a marketable drug. Experts must devise suitable labels, direction sheets, and brochures; advertising and other promotional personnel must cast plans for gaining recognition for the product, professional or otherwise; legal authorities must consider problems centering about trade-marks, patents, fair trade laws, regulatory restrictions and limitations; package designers must provide adequate protection for the drug as well as attractiveness of container; journal advertising and convention displays must be outlined; and a myriad of distribution problems must be settled.

Nor does this outline conclude the variety of operations that must have consideration. If the drug is "new" within the purview of "new drug" legislation, it must pass the scrutiny of the Food and Drug Administration. And if professional acceptance is sought, it no doubt will be presented to the Council on Pharmacy and Chemistry of the American Medical Association, if only to gain approval to permit the product to be advertised in the Association's journals and in other periodicals, such as the various State medical association publications.

This brief sketch emphasizes the vast canvas of modern drug research and development and what the process as a whole necessitates. The manufacturer or distributor embarking on such a program must do so with knowledge and foresight. Elsewhere in this chapter, and in greater detail throughtout this volume, the precise nature of the problems thus presented, and their solutions, are discussed.

THE NEED OF PLANNING

In the foregoing section we have drawn a picture that is merely illustrative of the countless factors that must be kept in mind during that period in which a drug product is being readied for marketing. It is not, by any means, complete. Others, as we have mentioned, are discussed elsewhere in this volume. Nor is there any need to reiterate that every member of the industry should be familiar with the practices and procedures that constitute proper research and development, and, perhaps of more importance, the necessity for such a program. Indeed, without it, no firm can make substantial progress, and must, in fact, accept the prospect of regression as competition, based on sound research policies, expands and absorbs its market.

Our brief description of what modern research and development embraces emphasizes another factor—the need of planning such a program. Obviously, measures of such tremendous proportions call for an over-all correlation of all steps that are involved. Without comprehensive treatment, without advance conception and agendum, only waste and confusion will ensue. And the same careful study and procedure must be applied to each phase of the undertaking. Each must be projected with a clear picture of the ultimate objective in mind; nothing should be left to chance or haphazard methods.

It will serve to illustrate this observation if we examine for a moment the basic idea for any particular product. The stimulus, the starting point, of modern drug research is, obviously, an idea of this nature. Originating in the mind of one person or evolved in group discussion, it acts as the nucleus for the various steps that constitute drug development. The conception may result, in rare instances, from an inspirational flash; it may, on the other hand, emerge slowly from careful laborious analysis and study; a few are born accidentally or fortuitously.

Although the manner in which an idea may come into being is, in fact, as diversified as the brain of man and it would there-

fore appear manifest that no precise formula for its origination exists, nevertheless there are many approaches to its formulation which may be used, to advantage, by the thoughtful investigator. The latter will discover, as a matter of fact, that concepts for drug research and development fall into a number of broad classifications. This permits, in one case, a special plan of inquiry that may reasonably be expected to culminate in a workable idea; or, once conceived, it allows the researcher to appreciate the limitations of the concept and to plot his subsequent task accordingly. Thus he will find that the usual ideas for drug products may be grouped in the following categories:

(1) A new drug in the sense of a novel discovery, e.g., penicillin.
(2) A new use or application for known chemicals or drugs, e.g., sulfanilamide.
(3) The isolation of active principles, e.g., morphine.
(4) The synthesis of existing biologicals and botanicals, e.g., niacin.
(5) A combination of known drugs to obtain synergism of either potentiated or deficient summation, e.g., the addition of morphine and scopolamine.
(6) The refinement of a known drug, e.g., estrone from estrogenic substances.
(7) The modification of a synthetic compound by adding a new group, e.g., the antihistaminic agents.
(8) A new stabilizer, vehicle, or similar type of material that improves the quality or properties of a medicinal agent, e.g., the Romansky formula in penicillin administration, and gentisic acid to stabilize solutions of thiamin.
(9) A new dosage form that, for example, permits a drug previously administered parenterally to be taken orally, e.g., methyl testosterone.

It is evident from this general analysis that the possibilities available to the investigator are many and diverse, and, what is more, can in most instances serve as the basis of planned research. It was once thought, as Dr. Torald Sollmann has

remarked, that "really new properties cannot, of course, be predicted by known properties [and therefore] their discovery is generally accidental." This is no longer necessarily true. The atomic fission program has, if proof were needed, demonstrated that relatively new and radical drugs may be developed if the program is intelligently and properly devised.

If planning is capable of being so useful in the more fortuitous aspects of drug research, surely its value in the more prosaic phases of development must be evident.

THE NEED OF SPECIFICITY

No one will find fault in the statement that one of the chief objectives of drug research and development is to devise a preparation that possesses specificity of therapeutic action, that is to say, the drug will have a precise effect upon a particular, identifiable condition. So elementary does this observation appear that it may be wondered why the time is taken to spell it out. The truth of the matter is that, like most basic principles, it is all too often lost sight of. In all periods of quickened progress, such as that which has come upon the drug industry in the last decade or so, there is a "time-lag," an inertia, a tendency to retain the practices and policies of the past. And it is only by examining some of these past faults that we are able to emphasize the present-day approach to similar problems.

Many firms, in years gone by, have been reconciled to serve in the capacity of pharmacists, satisfying the needs or wishes of members of the medical profession in an elaboration of the corner pharmacist filling a prescription. The physician, in his general or specialized practice, often was relied upon to dictate the course of "new" developments in pharmacology and therapeutics. The short-sightedness of this policy was aggravated by the now generally accepted premise that the average medical practitioner has neither the time, inclination, nor the facilities essential for effective research. This is not a criticism of the physician, who has clearly demonstrated his extensive interest

in new products born of research and, indeed, today demands their availability.

Dr. Fleming's experience with penicillin, moreover, shows that the average drug manufacturer formerly extended little attention to the activities of the laboratory and university workers. The latters' findings were dutifully reported in the journals of their professions to be read too often only by their fellow scientists. It must be admitted, however, that these reports generally possessed theoretical interest only; nor was there ordinarily any directive agency or force to give them direction and definiteness.

On the other hand, an equal lack of any realistic approach governed the policies of those drug firms who flooded the field with so-called "medical specialties" or "patent medicines," as the case might be. That these companies were enterprising, to say the least, cannot be denied. But their enterprise was confined, so far as drug research and development was concerned, to prettifying an ancient "shot-gun" preparation of some empirical value and marketing it under the most extravagant claims. Others would adopt a likely prescription of a physician whose success with the formula was often only demonstrated by the frequency with which he prescribed it. In few instances was any careful investigation or verification of the efficacy or lack of toxicity of the preparation undertaken.

This vagueness about the precise properties and actions of the average drug product necessitated a corresponding vagueness in the directions for its use. All of us are familiar with the "NERVE TONICS," "BLOOD PURIFIERS," "KIDNEY PILLS," and "LUNG BALMS" of an earlier generation. We remember, too, the many "competent and safe treatments" in one four-ounce bottle for such a diversity of conditions as prostatitis, cystitis, urethritis, sugar diabetes, dropsy, ileo-colitis, gastritis, malaria, inflammation of the bladder, acute indigestion, ptomaine poisoning, rheumatism, backaches, leg aches, or worn-out and rundown feeling. Lest we permit ourselves to indulge in a deprecatory smile at this array of disease conditions—incidentally, drawn from a case decided as recently as 1941—let it be affirmed

at this point that too few firms are even today wholly free of criticism on this score in one degree or another. An elementary example is the marketing of "antiseptic" preparations—although it is common medical knowledge that no compound, or combination, is suitable or effective to combat all types of infective organisms. Another illustration is the "cough preparation," which even if its effects are limited to symptomatic alleviation fails to take into account the material distinction between dry and productive coughs.

In the past, moreover, many firms were satisfied to distribute preparations whose therapeutic advantages were generally confined to symptomatic treatment. The development and marketing of such substances were relatively without complication. Since the manifestations and discomforts of disease are comparatively few in number and just as simple of alleviation, the average manufacturer felt safe in limiting his task to preparations of this nature. With considerable smugness, it was postulated that there are few "specifics" for disease. While this may have been true when the expression was coined, today it lacks substance as an excuse for the failure of progress in research. True specifics have been developed for innumerable maladies; more will doubtless come from the laboratories as time goes on.

This leads us to perhaps the most important rule of modern drug formulation: the necessity that the preparation possess *specificity* of action. In other words, the pharmaceutic, to be entitled to high regard, must be designed to combat a particular and identifiable condition. This does not necessarily mean that only curative agents are worth developing; it refers to every type of drug product. If this approach is adopted—and properly undertaken and consummated—the end-product will not only, in all probability, be an item of considerable value to the manufacturer's list but to therapeutics in general as well.

The search for specificity in drug formulation has the additional advantage of concentrating attention on the diseases and afflictions of mankind. Adopting this objective, one tends to realize that one's position in the scheme of therapeutics is not merely that of technician or mechanic but rather that of

partner and participant in the tremendous task of alleviating human ills. One sees the population of this country as a living, pulsating organism. One notes that an operation is performed every few seconds, that a baby is born every few minutes. One observes that almost 600,000 deaths take place each year in the United States from diseases of the heart and blood vessels; over 175,000 people die of cancer; almost 100,000 succumb to nephritis, and an equal number from pneumonia and tuberculosis. One's efforts are stirred at the sight of four million Americans now suffering from heart disease and over five million from hardening of the arteries and that chronic diseases, by and large, cause over one million deaths a year. These observations become a stimulation and source for further advances in medical research and in the search for better and more effective medication.

Thus, much research remains to be done in the fields of aging tissues, cardiovascular diseases, cancer, hypertension, glandular dysfunctions, kidney diseases, liver disease, and infectious conditions, to mention just a few. If the progressive drug manufacturer will direct his research and development activities toward merely one segment of this mass of human misery, his contribution will bring forth the type of drug formula that counts for prestige and financial success.

THE NEED OF ORGANIZATION

No policy is capable of being effectuated without the active cooperation of an organization to implement and carry its objectives to an accomplished conclusion. This observation is perhaps more apposite to the drug industry than to almost any other type of enterprise. The complexity of activities, the specialized skills and knowledge required, the necessity of integration and correlation—all contribute to the need of a competent and complementary staff.

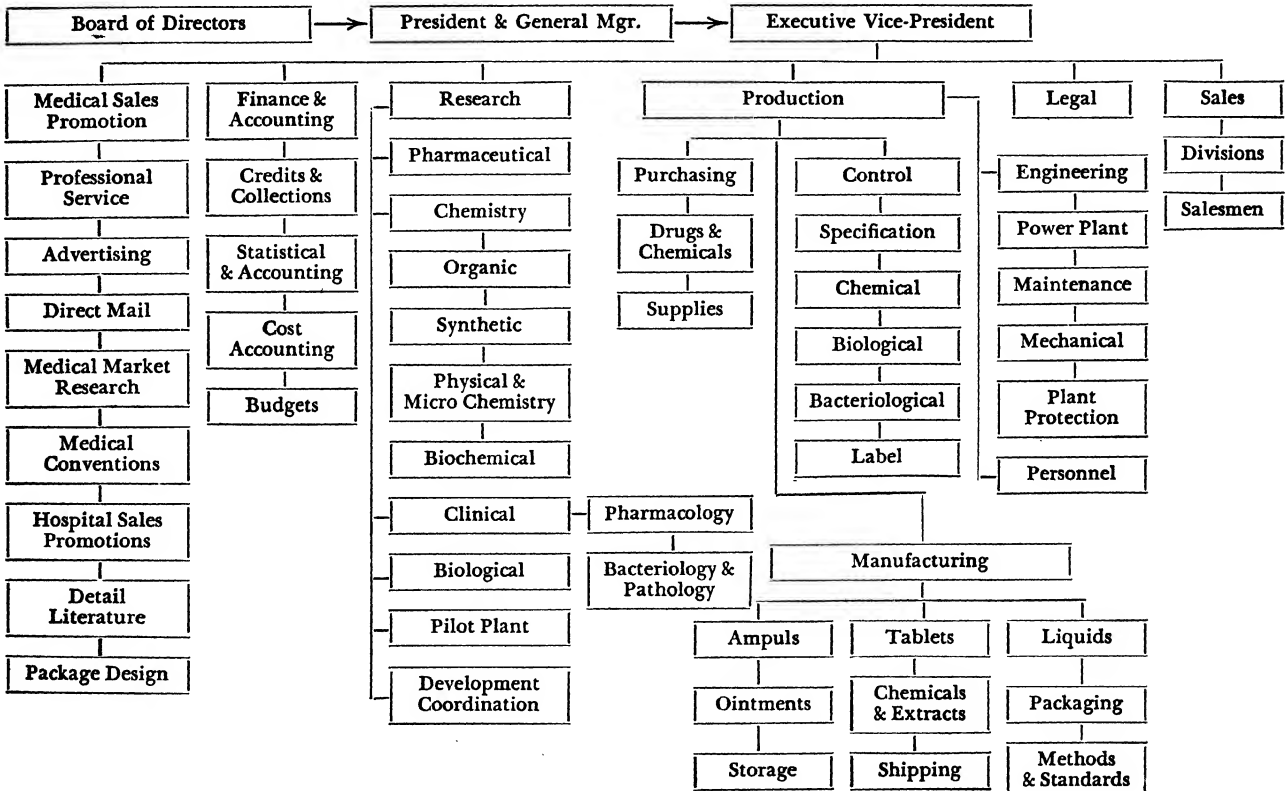
Although organization implies manpower and personnel in its most elementary sense, nevertheless it must also be recognized that, in addition, it calls for the orderly apportionment

and assignment of task in order that each segment be cognizant of its duties and perform them in the most efficacious manner. Despite this segregation, however, it is equally important that the highest degree of cooperation be maintained between departments to the end that the organization functions as an entity.

There is no one commanding rule for a plan or organization in the modern drug plant. In each firm individual factors must control the design eventually adopted. Nevertheless it may prove helpful to propose a theoretical plan and review the general composition of such an organization. A chart delineating a rather comprehensive plan of this sort is presented on page 23. It represents no particular company's but it is a composite of several now in use. At best it should merely serve to emphasize the need for planned organization; it is, it may be repeated, not intended as a model.

At first glance, the most obvious impression gained from studying the chart is the compelling need of cooperation not only between different departments in the same spheres of activity but among the various divisions as well. Thus, the department concerned with medical sales promotion must operate in close conjunction with the sales department; research activities lean on medical market research, on budget department, and on production.

Nor should it be concluded that a plan of organization of this nature and scope is essential to all firms. In the smaller company, or in others whose activities are confined to a relatively few specialties, some of the operations may be merged in one department, or, indeed, in a single individual. But one point calls for emphasis. The development and merchandising of pharmaceuticals today—particularly medical specialties—demands the exercise of each of the functions symbolized by the various divisions and departments charted. To put this another way, no progressive firm can expect to attain an advantageous position in the industry unless, for example, it provides for research, although this program may be confined to one product and the preliminary investigations farmed out to


Board of Directors
President & General Mgr.
Executive Vice-President
Medical Sales Promotion
Professional Service
Advertising
Direct Mail
Medical Market Research
Medical Conventions
Hospital Sales Promotions
Detail Literature
Package Design
Finance & Accounting
Credits & Collections
Statistical & Accounting
Cost Accounting
Budgets
Research
Pharmaceutical
Chemistry
Organic
Synthetic
Physical & Micro Chemistry
Biochemical
Clinical
Biological
Pilot Plant
Development Coordination
Production
Purchasing
Drugs & Chemicals
Supplies
Pharmacology
Bacteriology & Pathology
Control
Specification
Chemical
Biological
Bacteriological
Label
Manufacturing
Ampuls
Ointments
Storage
Tablets
Chemicals & Extracts
Shipping
Liquids
Packaging
Methods & Standards
Legal
Engineering
Power Plant
Maintenance
Mechanical
Plant Protection
Personnel
Sales
Divisions
Salesmen

independent consultants. Similarly, attention must be extended to the problems of production with its various essential control procedures; nevertheless, this need not be directly assumed by a company who elects to have the preparation manufactured for it by a "private label" house. In other instances, control procedures may be sent to outside laboratories.

Indeed, such laboratories can provide a real service for the manufacturer or distributor whose facilities do not permit a similar nucleus in his own organization. They must, however, be carefully selected. While it may seem like a temporary inconvenience, prior investigation of the consultant or laboratory may eventually prevent misunderstanding and embarrassment. The laboratories that are interested in maintaining good relations welcome such investigations. In any event it is well to have a thorough understanding of what is wanted and required when the problem is first presented to a laboratory or other consultant. This arrangement is so important that it is impossible to over-emphasize the necessity for it.

The fact that our discussion has centered about the organization of a firm concentrating on the developing and marketing of medical specialties does not, however, preclude its adoption by the company dealing exclusively in consumer items. Of course, several divisions would, in such a case, be transformed into more suitable ones, although most of them are worth retaining.

THE NEED OF PERSONNEL

In an industry that has evolved at the rapid pace as the drug industry has within the last decade, difficulties in the recruitment and training of satisfactory personnel is almost to be expected. That they have materialized is evident to any careful observer. From the men and women in the manufacturing and finishing departments to even management itself, such weaknesses are apparent, although they may stem from different causes.

Too frequently there has been a failure to instill in the minds of lesser personnel the sense of responsibility and duty essential

to the honest production of pharmaceuticals. Little has been accomplished in impressing the men and women in the plant that theirs is a contribution to national health and security; that their task may be considered a professional one in the same sense as a hospital worker's, a nurse's, and a dental technician's. They have not been inspired to view their jobs as part of the offensive against disease and misery and suffering.

The most carefully designed and installed control system is as effective as the men and women who operate it. By the same token, its purpose may be defeated by the so-called human equation. The serious errors that all too often occur can in large part be attributed to the failure of personnel. Without knowledge and realization of the reasons underlying required procedure, without an active interest and sincere concern in the output of the plant, workers cannot be expected to perform in other than a mechanical and perfunctory manner.

That the drug industry is becoming aware of this problem and of the necessity of solving it is a salutary development. One manufacturer of parenteral solutions, for example, has discovered that girls possessing a high-school education are more competent workers than those without this educational background; the higher degree of training, in which presumably are reflected intelligence and discipline, is evident in an improved output. This step in itself is not sufficient, however. Not only should the training period be expanded and intensified but a better knowledge and understanding of the importance of their tasks should be instilled in workers.

As one advances up the ladder of managerial positions, the situation is scarcely improved, save in the larger, more successful or more recently re-organized plants. In many instances, places demanding extensive responsibility and training are filled by men sadly deficient in these requisites. Inexperienced people head important control and manufacturing laboratory staffs, perhaps solely because they possess one or more degrees. In a few cases, executives of such departments do not have a scientific degree, if any at all. It is not suggested that one must have his doctorate or any post-graduate degree before being

assigned to such a position; but post-graduate training, when combined with practical experience, offers some real advantages provided the training is in an appropriate field. It is indeed short-sighted for management—who, it is pertinent to observe, may be held accountable under the law for the errors of its personnel—to entrust this work to an inexperienced or insufficiently qualified executive.

No one can deny that it is not unreasonable to insist on certain educational and other prerequisites; for example, that department heads, directing manufacturing and control technics, possess at least a degree in pharmacy or in chemistry, together with a fair amount of actual experience in the production of pharmaceuticals. As a matter of fact, as we have indicated, the mere possession of a Ph.G. or B.Sc. degree should not alone qualify a man or woman for this position. Of great importance is the sense of judgment and responsibility that only time and experience can usually develop. Of course, all laboratory and manufacturing personnel need not have these educational requirements and backgrounds; but in their selection, too, care should be taken to obtain competent and intelligent assistants. However, it is impossible—nor is it our intention—to present this subject in its entirety. The problem is mentioned merely to emphasize again the complexities of product research and development and the contribution of personnel to their solution.

Management may have failed fully to appreciate another criticism on this score. As we have observed, until recent years the drug industry was dominated by pharmacists, chemists, and successful salesmen. Not only was this occasioned by the fact that the drug industry largely evolved, so to speak, as manufacturing pharmacists, but many executives have had their early training in one of these fields.

This observance of one specialty has carried over to the new era in drug research and development. It crops up incongruously in unexpected situations. For example, a number of firms now employ chemists, pharmacists, or pharmacy teachers in a consulting capacity not only to advise them as to produc-

tion and compounding problems but also as to pharmacologic, therapeutic, and, indeed, labeling questions. Again, a successful advertising representative may decide therapeutic possibilities while the medical director goes unheeded. This is as absurd as expecting the medical director to design and engineer a new building. In other words, help should be sought in every instance from those best qualified to give it. Of similar fallacy is the willingness to invest thousands of dollars in some piece of equipment that for the moment may permit cheaper or quicker production, at the same time that a niggardly grant is being made to a pharmacologist or clinician for intensely important research which might eventually even obviate the need of the machinery.

These remarks should not be considered as criticism of the ancient sciences of pharmacy and chemistry or of any particular profession. As a matter of fact, the pharmacist, chemist, and others have important and indisputable places in drug manufacture. But modern research and development have equal need of diversified knowledge and training such as is observed in the chemist, pharmacologist, biologist, physician, and other professional, technical, and legal experts.

The problems of personnel are not insoluble. They do require, however, greater attention. There is no doubt that they also call for recognition in the curricula of scientific schools of the country interested in providing special training. Purdue University, for example, has established a course in manufacturing pharmacy. Others will no doubt follow. Recent authority estimated that there were now over 3,000 research workers in the drug industry. As this group increases—and it will as the needs are enormous—it harbors well for the cause of pharmaceutical advance in the future.

THE NEED OF EVALUATION

We have previously had occasion to remark about the importance of impartial evaluation and appraisal of results. This aspect is perhaps the most important single factor in any pro-

gram of research and development. It calls for judgment at each step. It demands astuteness and perspicacity of the highest degree. And frequently it requires a ruthlessness that will, without hesitancy, order the abandonment of an unpromising project despite the investment already put into it.

We would indeed be ingenuous were we to suggest that research in itself will answer all the problems of the drug industry or, in fact, that it will assure success to every company. Research is admittedly speculative in character. In many cases, it is a gamble—a considered and essential risk to the progressive firm but nevertheless a gamble. A number of manufacturers who have invested tremendous sums in large research units will ruefully acknowledge this conclusion. That does not mean that this admission will deter them necessarily from further research explorations but emphasizes the risks involved.

An editorial in *Advertising Age* locates one of the underlying reasons for failure in research projects. Discussing market research, it states in part:

> Research—good, competent, intelligent research—is vital. But the best research in the world won't make a bad product outsell a good one; it won't make a market one bit bigger or better than it actually is; and it won't change any of the immutable laws of economics. Research isn't a mysterious panacea. It is simply a marshalling of existing facts. It ought to be done . . . and done intelligently . . . when a better knowledge of existing facts will be useful and helpful . . . it most certainly should never be done just because every one else is doing it.

If this be true of market research, it is equally applicable to drug research. To conduct a research laboratory because it is fashionable, or because the detail man can point with pride, or because a competitor has had remarkable success with such an undertaking is, of course, wasteful and unproductive. As we have pointed out, research is only justified when it is embarked upon with a clear objective in mind and with careful forethought; it is not a plaything. Too many firms have had their research departments expend considerable time and money on a preparation that does not possibly fit into their over-all program or that calls for far greater capital investment in

marketing than they are ready to allocate. Small companies, particularly, should bear this limitation in mind.

We have emphasized that research must be planned. Obviously, it should have a definite goal. No drug manufacturer would stay solvent very long were he to permit his research director to be a Columbus making sail without compass for uncharted seas and unknown lands while his competitors make use of the latest methods of study with clear objectives as navigational instruments.

It should also be borne in mind that research does not invariably produce a better, more merchantable drug product. There is no assurance that the ultimate development will mark a demonstrable improvement over other pharmaceuticals already available. Naturally there is an inclination to justify the investment expended by promoting the new preparation, despite its dubious advantages. This tendency should be stoutly resisted. The product must be carefully and realistically appraised from every viewpoint; those without merit should be discarded without hesitation. Indeed, if a firm is too tender-hearted to thus treat its own "brain child," the market, in all probability, will be more brutal; and in the long run the financial loss will be the greater.

It is not intimated that this brief discussion discharges all that must be said about the need of evaluation and the methods and criteria of appraisal. The subject, however, is much too extensive to treat at this point. Throughout the text of this volume particular emphasis has been placed on this aspect and the application of the principles there propounded will return valuable dividends in time and in money.

CONSUMER AND PRESCRIPTION FORMULAS

One final word must be said about consumer and prescription formulas before we close this chapter. Cursorily, it may appear to the reader that the apparent emphasis placed throughout this work on the formulation, testing, and marketing of prescription drugs precludes from the operation of modern

methods of drug research and development those items designed to be sold to the public for its unsupervised use and application. Such an impression would indeed be incorrect. As a matter of fact, each procedure described in the pages that follow is, with some obvious exceptions, directly applicable to consumer formulas.

There has been considerable loose thinking about consumer formulas. It is of course undeniable that in the past many over-the-counter items sold to the public warranted the distrust and disdain in which they were held. Often the stinging term of "patent medicine" was justified. Fraudulent and exaggerated claims embellished the labels and the advertising. The formulation and production of these preparations were frequently a haphazard undertaking. Unscrupulous promoters of such nostrums were truly a blight upon the industry. The chasm that separated these articles and the prescription type of pharmaceutical was further widened by a tendency to regard the latter class of products as "ethical drugs." According to some, the implication, of course, was that all consumer items were "unethical"—either in marketing practices or in character.

Today, this disapprobation is, to a considerable extent, unwarranted. Self-medication by the public, within well-defined recognizable limitations, is not a practice that any reasonable man would be inclined wholly to condemn. And to supply such needs with honest products cannot possibly be the subject of criticism. What are considered appropriate drugs for these purposes are described at a later point in this work.

There are, however, two principal indictments that can be drawn against many consumer drug items now on the market. The first, as may be expected, deals with the nature of the claims made upon their behalf. All too often these are colored with highly suggestive implications, not supported by the composition of the preparation. One is inclined to wonder about the necessity of such exaggeration and whether it is really essential for selling purposes. Admittedly in many cases it is. In fact, when government enforcement action forces an amelioration of the representations previously urged, sales of some articles

drop to such an extent as to force their abandonment. Yet if there is a genuine *need* for the product—as their promotors are apt to insist—the public will continue to buy it under its tempered and more truthful advertisement. There appears no good reason, therefore, to employ over-emphasis and exaggeration in the promotion of an honest preparation.

To determine whether there exists such a definite need and whether the drug under development answers that need is one of the principal objectives of modern drug research. The methods described in this volume are relevant to reaching that conclusion. They will prove helpful, moreover, in the preparation and support of claims made on behalf of the product.

The second complaint made against some consumer items now being distributed to the public is that, in many instances, they are poorly formulated. A number are completely irrational combinations, of no discernible therapeutic value. Many have been compounded without the least respect for the most elementary rules of incompatibility; ingredients indicated as "active" are lost in chemical reaction. In other cases, the formulas call for inconsequential quantities of various ingredients, so minute as to have no physiological or therapeutic effect. Of course, this failure has its bright side: if the preparations are ineffectual, they are also free from toxic propensities. The same cannot, however, be said of others which may carry dangerously high amounts of potent substances nor of those preparations that are particularly likely to cause reactions in sensitive individuals.

On the other hand, we also find many formulas unnecessarily complex. A number of ingredients, all possessing a similar therapeutic action, are combined in the preparation, when, in truth, one, in proper dosage, is capable of effecting the results sought. One reason commonly put forward for this intricacy is that it is the only way to discourage competition from others. Without going into the question as to whether anything is actually gained competitively by these attempts at mystification, it may be remarked that any good chemist or pharmacologist may, ordinarily, extend a certain amount of protection in this

regard without resorting to cabalistic means. Here, too, the proper approach to drug formulation is essential.

There are other observations that come to mind in considering consumer and prescription formulas. From the viewpoint of the Federal Food, Drug, and Cosmetic Act, for example, the only factor that distinguishes one from the other is the element of safety. As the regulations are now drawn and interpreted, those preparations whose use is unsafe, except under the supervision of a physician, dentist, or veterinarian, may alone be limited to prescription. All other drugs, with some unimportant exceptions such as solutions intended for parenteral use, may not only be sold directly to the public but, in fact, must be labeled with sufficient information for their intelligent use and application by the layman.

Many large drug firms produce preparations that fall within both categories. Indeed, as new drugs gain in safety of use—the objective of much research, incidentally—a greater proportion of items may lose the properties that now restrict them to prescription and thus become available for "over-the-counter" sale. The impact of this development cannot fail but have an appreciable effect on the calibre and nature of the preparations now being marketed for self-use.

Curiously enough, to the same extent as so-called "ethical" houses are participating in consumer sales as a result of the above development, proprietary firms are entering the prescription drug field, usually through an affiliate or subsidiary company. This increasing trend is symptomatic of several factors. For example, it may indicate a belief that consumer items are on the decline. Again, the development may be occasioned by the conclusion that as drugs gain in specificity of action—heightening the importance of diagnosis—the lay public will turn less and less to vague self-medication. On the other hand, it may be dictated by financial considerations. Although the proper development of a medical specialty calls for a considerable investment, this cannot be compared with the truly tremendous funds that must be expended to introduce a popular consumers' item and maintain its market position.

All this, however, is conjecture. In all probability, it was the lesson learned from the vitamin exploitation that awakened some to the limitations of consumer marketing as compared to "ethical" distribution. These companies entered the field with high expectations, confident of developing an immense lay market for vitamin preparations; they were scheduled for sharp disappointment. Yet as sales of these products steadily declined, their use as therapeutic agents by physicians just as steadily increased until today it is by far the most important outlet. At considerable cost it was finally discovered that a large part of the public will not consistently buy a medicine that fails to display immediate demonstrable effects; vitamins fell within this class.

These two divergent developments make it clear that both consumer and prescription formulas are of importance in the drug industry. As a matter of fact, it is interesting to observe that drug sales in this country are about equally divided in volume between the two types of products. The ratio fluctuates fractionally from year to year; at times proprietaries dominate, at others, prescription-type. But that both have a comprehensive market is clear.

But this will not remain true if those interested in marketing consumer preparations fail to appreciate and to fall into step with the new trends discernible in drug therapy. These manufacturers and distributors should restudy their products—and medical "opinion" concerning some of them—to determine their need and usefulness in the light of modern advances. These include such items as cough mixtures, headache powders, laxatives, "tonics," skin and "cold" remedies, mouthwashes, weight reducers, pain relievers, and douches. Although some of these preparations may be proved helpful in serving the needs of mankind requiring such self-medication, others are of little, if any, value—and a considerable number, if examined scientifically and impartially, are wholly without merit. And of course in developing new products for self-medication the investigational procedures described in this volume should be adopted to assure that they meet modern-day concepts of efficacy and safety.

2

Chemistry of the Formula

AMEL R. MENOTTI

COMPOSITION AND GENERAL TRENDS

THE history of therapeutic agents is inseparably bound to the development of the chemical industry. The historic medicine man depended on chance observations to provide an herbal extract with some assumed healing power for the ills of man. Following this came the development of what must be characterized as "folklore medicine" with its "shotgun" approach to the treatment of disease. Extracts, brews, and decoctions of animal and vegetable origin provided the doubtful remedies employed until the early 20th century. A late 18th century example of this type of therapeutic is found in LaWall, *Four Thousand Years of Pharmacy,* under the title "Godbold's Vegetable Balsam":

> Forty-two different vegetables distilled separately and each made into a separate syrup later to be mixed with the following gums and drugs, viz., gum dragon, gum guaiacum, gum arabic, and gum Canada, these being dissolved in double distilled vinegar with a quantity of storax dissolved in spirits of wine and oil of cinnamon. It is then to be bottled and kept for three years before it is fit to be administered for the cure of consumption, or any asthmatic complaint.

Some of our early chemistry was intricately bound with attempts to produce more potent medicinal products from these natural sources. As the techniques of the chemical laboratory became more refined, however, we observe a gradual transformation in the character of the remedies available for medication. The crude herbal brews yielded to more potent extracts; these, in turn, were resolved into pure crystalline components. Thus, as a result of careful investigation, the "Ma Huang tea"

of antiquity yielded the crystalline ephedrine hydrochloride of today. In other cases, this same careful search failed to show the presence of active components and led to the discard of numerous previously accepted "remedies."

Thus it is seen that the earliest pure chemical substances used as drugs were obtained from natural sources; and for some time, indeed, this continued as the only fount of potent therapeutic agents. At this stage our chemical knowledge was limited to extractive techniques. The fact is that percolation, concentration, and crystallization made up the only armamentarium of the chemist.

The emergence of organic chemistry and the gradual development of synthetic methods slowly changed our total dependence on natural extracts as the prime source of drugs. A true symbiosis can be noted here, because the attempted syntheses of many natural products in turn stimulated the rapid development of organic chemistry. This knowledge was in time applied to the creation of new molecular compounds from which we eventually realized new agents useful in medicine. Thus, there was an intimate link between the establishment of organic chemistry as a well defined science and the development of organic medicinal agents, the prototypes of which were obtained in pure form from natural sources, following which the products were synthesized to decrease our dependence on the natural supply.

When naturally-occurring products possessing physiologic activity are introduced into therapy, modern manufacturing procedure calls for the purification of the active component, and modern techniques of isolation and purification enable rapid strides to this end. An excellent example of this is provided by penicillin where, during the short space of three years, a major industry was evolved around a difficult and sensitive fermentation process which produces an active ingredient in yields of approximately 0.07 per cent in a complex medium. In spite of this, we have witnessed such rapid changes in the quality of marketable penicillin that the pure crystalline active ingredient was made readily available in 1947 at a rate of over

4,000 pounds a month. This is illustrative of drug manufacturing today and indicates that the ultimate objective in the natural product field is the detection of an active therapeutic ingredient from natural sources, followed by the concentration, isolation, identification and possible synthesis of its pure component.

That we have by no means exhausted the storehouse of medicinal agents to be found in nature is testified to by the discovery of penicillin and the present intensified search for other antibiotic agents. Our present stage of knowledge, moreover, will allow us to decrease the interval between the first detection of a natural medicinal agent and its isolation in pure form. The subsequent structural determination and, where possible, synthesis are likewise now accomplished in a few years rather than decades. Thus, although penicillin was originally detected in 1929, the first real effort at its isolation was begun in 1940, culminating in a pure crystalline commercial product by 1946. Although of no practical significance at that time, a synthesis for penicillin was discovered by 1943.

Natural products are today being sought as avidly and intensively as ever and it is a foregone conclusion that compounds with powerful physiologic action will continue to be discovered in natural materials. The biochemist, and with the advent of antibiotics, the bacteriologist and the mycologist are primarily concerned in such a search. Once the pure component has been isolated, the organic chemist is called upon to determine the structure and develop methods for the synthesis of it or similar compounds. Should this be successful, the natural product source may be eliminated as a source of supply, a factor well illustrated in the vitamin field and, to a lesser degree, by the hormone products.

Although purified medicinals of natural origin are, and will continue to be, of great importance, the development of synthetic organic chemotherapeutic agents, having no known counterparts in nature, has produced a great change in the field of medicine since Ehrlich's introduction of salvarsan in 1909. In-

deed, synthetics now account for almost fifty per cent of the total sales volume of ethical pharmaceutical preparations.

Among the outstanding positive trends can be listed the search for new antibiotics and the synthesis of increasing thousands of new organic compounds. The ultimate objective in all cases is, however, the same, that is, the manufacture, either by synthesis or extraction, of a pure chemical substance, properly identified, standardized with respect to safety and activity, and in a stable form for compounding.

OBJECTIVES

A new drug product must have:

(a) Professional Acceptance
(b) Patient Acceptance

While in some instances the requirements are synonymous, there are fine distinctions which must be emphasized depending on the ultimate usage of the medicament. Ethical pharmaceuticals may be used directly by the physician, in which case the doctor or nurse becomes the ultimate consumer, or they may be dispensed on prescription, whereby patient acceptance becomes an important and often determining factor in the efficacy of the medicament. In the first category fall such products as ampul preparations for parenteral medication, serums, vaccines, diagnostic drugs, anesthetics, and bulk intravenous solutions. In the second category, we can mention tablets (which may be prescribed for administration over extended periods), ointments, elixirs, powders, and granular oral preparations which the patient himself may utilize for medication under professional guidance but not under immediate medical supervision. The same rules of purity, specificity of action, stability, and safety govern each preparation in turn. There are, however, some major distinctions which may be considered with respect to consumer acceptance in the two classifications.

PROFESSIONAL ACCEPTANCE

Professional acceptance depends mainly on therapeutic efficacy. Extrinsic qualities, such as the ease of opening ampuls, the settling time of oil suspensions, or the eye-appeal of a package and the legibility of printed labels and instructions, all play a part in professional acceptance and must be considered carefully but are of subordinate interest. More important are the following:

(a) The physician must be assured that a preparation contains the active ingredient in a sufficiently pure form to eliminate side effects caused by accompanying impurities either introduced during the synthesis of organic constituents or not removed during the isolation of biological components.

(b) The active ingredient must be present in sufficient quantity to exert the claimed therapeutic effect and the preparation must possess sufficient stability to insure reasonable "shelf-life" and withstand the exposure necessary for administration. When multiple-dose containers are provided, the contents must be protected against the possibility of contamination accompanying withdrawals, both through the use of adequate closures and by the addition of preservatives.

(c) In most cases, it is desirable to provide the physician with documentary evidence in the form of scientific journal reports from recognized investigators concerning the efficacy, safety, therapeutic indications, and allowable therapeutic claims of the active component of a preparation.

(d) The physician must have assurance not only that adequate control is possible but also that it has been established and is being maintained by the manufacturer.

(e) The ratio between the curative and toxic dose must be sufficiently great to allow for variation in sensitivity of individuals and for normal variations in amounts administered.

(f) The ease of administration of the drug will greatly influence the extent of its usage. Drugs which require highly specialized apparatus, time-consuming techniques, and extended

periods of administration are obviously subject to replacement by competitive products not possessing these disadvantages.

(g) The cost of a medicament must of necessity be considered by the physician—while a drug may be highly successful, its use will be limited if it is beyond the reach of patients with an average income.

PATIENT ACCEPTANCE

The factors listed above concern primarily the efficacy and safety of a drug. When we consider patient acceptance, full recognition must be given the organoleptic properties of the medicament. Thus, the taste, smell, feel, or other factors dealing with sensory perception become important in the acceptance and hence usefulness of the formulation. To illustrate, an oral preparation must be regarded as a poor drug if the taste creates nausea or other unpleasant sensation on repeated dosage. An ointment will see limited use, moreover, if it is difficult to remove, stains clothing, or possesses an unpleasant odor. And, how patients welcome a tablet dosage form in preference to an injectable product producing a similar therapeutic effect!

The package form also plays an important part with the patient, and the ease of measuring the dosage, the attractiveness of the package, and other aesthetic properties of the dosage form should all be given careful consideration.

The safety of a medicament to be used for a prescription must be such that slight over-dosages will not result in harm and the formula should be so compounded that the chances of overdosage are reduced to a minimum.

The frequency of application or the dosage schedule must similarly be considered because of the fact that patients, who must be relied on for the administration of such therapeutic agents, are often untrained individuals. The tendency is to cease medication as soon as beneficial results are apparent instead of pursuing the full course of treatment. This leads to relapses and lessens confidence in both the physician and the drug. Thus, one objective should be to supply the required treatment with a minimum number of applications.

The cost of medication becomes an important factor in patient acceptance; indeed, everything possible should be done to furnish the most effective medication at the lowest cost to the patient.

TYPES OF DRUG FORMULATION

For purposes of general orientation, it is desirable to survey therapeutic drugs of present day interest and to classify them into specific categories. This will provide orientation for the discussion that follows and will serve to indicate where the present emphasis is being placed with respect to the development of new therapeutic agents. Two methods of classification are immediately apparent; the first based on therapeutic uses, and the second based on the source from which a drug is derived. Beginning with the year 1942, *New and Nonofficial Remedies,* the official publication of the Council on Pharmacy and Chemistry of the American Medical Association, has provided a detailed classification of modern drugs based on therapeutic uses. This has proved extremely useful in cataloging commercial preparations and provides a rapid survey of the field to date. A portion of this classification is included below with brief definitions where appropriate.

Classification of Drugs According to Therapeutic Usage

Allergenic Preparations: Preparations used for diagnosis, prophylaxis, alleviation, or "desensitization" in conditions due to hypersensitivity.

Analgesics and Antipyretics: Agents for the relief of pain and depression of temperature.

Anesthetics: Agents which cause loss of feeling or sensation, especially loss of tactile sensibility.

Anti-Infectives: Agents active against bacteria, fungi, viruses and other infectious conditions.

Antispasmodic Preparations: Agents for relieving spastic conditions and for achieving complete muscular relaxation.

Autonomic Drugs: Agents affecting the involuntary nervous system.

Cardiovascular Agents: Agents which affect the heart or blood vessels.

Central Nervous System Stimulants: Agents which stimulate the voluntary nervous system.

Choleretics: Agents which stimulate secretion of bile.

Diagnostic Aids: Agents for determining eye damage, liver function, etc., and x-ray contrast media.

Diuretics: Agents which promote the secretion of urine.

Ecbolics: Agents which promote uterine contractions.

Gastrointestinal Drugs: Antacids, laxatives, anti-ulcer preparations, etc.

Hematics: Agents which affect the blood or its constituents.

Hormones and Synthetic Substitutes: Agents produced in various organs of the body which exert effects on other organs or body functions.

Metabolic Agents: Agents which affect growth and nutritional balance.

Sedatives and Hypnotics: Agents which allay activity and excitement and induce sleep.

Serums and Vaccines: Agents of a complex biologic nature which are used in diagnosis, in prevention, and in the treatment of disease and which depend for their action on various phases and relations of immunity.

Vitamins and Vitamin Preparations.

Classification According to Source

In discussing the development of new drug products, it will be useful to recognize the following classifications as indicative of the source from which an agent is derived.

Biological and Biochemical Preparations: This classification will include serums, vaccines, diagnostic extracts, crude and purified glandular extracts, protein mixtures, pure chemical substances derived from natural fermentation liquids, plants, or animal residues such as the alkaloids, the antibiotics, or the hormones.

Synthetics: This classification will include all of the drugs

which are obtained by synthetic methods, whether they were originally obtained from natural sources or represent new molecular types from the organic laboratory.

Crude Drugs: This classification will include digitalis, cascara, belladonna, podophyllin, aloin, benzoin, and other agents derived from natural sources and used as such.

A survey of specialty items listed by leading pharmaceutical houses indicates the following percentages in the three categories listed above:

Biological and Biochemical Preparations	40 per cent
Synthetics	55 per cent
Crude Drugs	5 per cent

Were a survey of specialty items added within the last ten years made, it would indicate an even greater percentage of increase under Synthetics, with no additions under Crude Drugs.

Biological and biochemical preparations still represent a large part of the total. Nature's great storehouse of therapeutic agents has not been exhausted and recent developments in antibiotics indicate that this is still a rapidly developing field which will provide stimulation for the organic chemical laboratory.

The constant threat to drugs in the biological and biochemical category continues to be the organic chemical laboratory, and, as our synthetic methods become more refined, we can expect a greater proportion of drugs to fall into the class of synthetics. The organic chemical laboratory derives its inspiration from two sources:

1. From the chemical formula of material extracted from natural sources which is used as a guiding principle to synthesize molecular types of a similar nature; and
2. From synthesis of new molecular compounds having no known counterpart in nature which are subsequently screened for physiologic activity of a new type.

The first approach has proved extremely fruitful in the past and will continue to provide the same inspiration in the future. The second approach has seen its major development in the

past few decades. The potential here is unlimited, and major strides in this direction will be achieved in the years to come.

A combination of these two attacks has brought the synthetic field to the point where it now represents roughly fifty per cent of our annual sales of ethical pharmaceutical drugs, as we have noted.

THE LABORATORY AND THE DRUG FORMULA

New drug formulas come from the laboratory and they come only from the laboratory. The number of successful new drugs developed is a direct function of the amount and quality of research effort expended by the laboratory. For example, in the field of sedatives and hypnotics, many hundreds of new barbiturates have been synthesized in commercial and university laboratories. Out of this work have come nearly twenty successful compounds. It is almost a certainty that further synthetic work will result in the introduction of new barbiturates superior to those now available.

The basic discovery by Fourneau and Bovet in 1933, that phenolic ethers of dimethylaminoethanol possessed marked ability to protect against the effects of histamine, initiated intensive research work in many laboratories with the result that by 1947 the 7,000,000 sufferers from asthma, hay fever, and other allergic conditions in the United States alone had at least three powerful new drugs available to alleviate their conditions. Even before this chapter is printed, other anti-histaminic drugs will undoubtedly be announced since this field is quite active at the present time.

Other new drug formulas have come to us, again through the laboratory but not via the synthetic route. The outstanding example is penicillin—first detected by Fleming in 1929, and subjected during the war years to a research program of an intensity rivalling the effort on nuclear fission. The success of this product has touched off new research efforts on a vast scale; again, new drug formulas are certain to result.

This relationship between the laboratory and new developments is not, however, limited to the field of ethical pharma-

ceuticals. As Mr. F. B. Jewett, a research director of the Bell System, explained:

> . . . money expended on properly organized and conducted research and invention is probably the safest and most profitable money industry handles; safest because the very processes employed by such research are an almost absolute guarantee against major technical failures in the end product; most profitable because the return on the investment in research cost is extremely high both in direct money return and in insurance of continued life to the industry.

The importance of the laboratory in relation to new drug formulas demands that the efforts of the research division be guided into channels of greatest interest to the company by frequent and intimate contact between the research director and the executive branches of management. For greater effectiveness in coordination, the research director should serve as a member of the top policy-making group. In addition, it is well to organize a research management committee which will establish broad policies concerning the major allocation of research effort and funds. Once these policies have been established, the responsibility for conducting research along the broad lines laid down by the research management should rest with the research staff. A budget consistent with sound business practice should be provided but here again the allocation of specific funds within the broad policy limitations should be the responsibility of the research personnel. Too much interference from management concerning details of administration and procedures serves only to stifle initiative and leads to endless confusion. On the other hand, the administrative research personnel must be fully cognizant of the policies of the firm concerning markets, financial limitations, and other factors affecting the ultimate fate of a successful research project. In recognizing this responsibility, they must make certain that the successful culmination of a project will find the other divisions of the company and its management prepared to accept the new product and initiate immediate action to develop it for marketing.

Success in terms of new products will be achieved by intimate contacts with fundamental discoveries and by the ability to

visualize possible therapeutic applications for this basic knowledge. Obviously not all efforts will culminate in useful products; hence the success of an over-all program, measured in terms of number of marketable products, must be protected by providing funds and facilities for simultaneous investigations in numerous fields. It has been stated that maturation of research programs provides one marketable product for every five undertaken. It is further estimated that it requires an average of three to five years from the inception of an investigation to the time when a product is available for distribution.

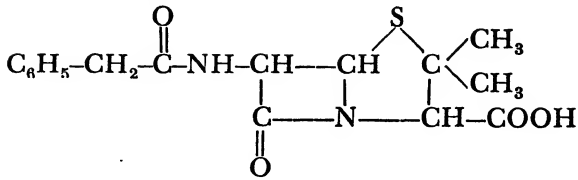
The cost of undertaking research on a major scale is directly proportional to the manpower required. A survey by Darrel H. Voorhies, "The Coordination of Motive, Men and Money in Industrial Research" showed an average investment in buildings, facilities and equipment in excess of $6,000 for each research employee and an operating budget of $5,000 for each research employee, including technical and nontechnical personnel. The total expenditure to be budgeted should bear a direct relationship to the speed with which products are sought and the number of projects undertaken at one time. A survey by Charles Wesley Dunn during 1946 indicated an average expenditure for research in the pharmaceutical industry of approximately three to four per cent of net sales, with some firms spending as much as ten per cent.

THE DEVELOPMENT OF THE CHEMICAL FORMULA

We have thus far given consideration to the broad objectives governing our development of new medicaments. Let us now examine the specific factors involved and the sequence followed in the development of new drug products.

In considering modern therapeutic agents, one can distinguish between two distinct and in most cases separable entities:

1. The *chemical formula* of the therapeutically active ingredient in a preparation. For example, the chemical or constitutional formula of penicillin G is:



2. The *dosage formula* of the finished product, which will be a combination of the chemical formula with excipients, carriers, or other ingredients incorporated to render administration easier or provide for increased stability or lessened irritation. For example, the dosage formula of "Penicillin in Oil and Wax" contains a salt of penicillin, white wax and peanut oil, formulated to provide prolonged blood levels from a single injection.

It is recognized that this division is necessarily arbitrary and that this separation is difficult for some products—particularly in the case of some of the biologicals where the two may be synonymous. However, this arbitrary segregation finds some support in practice. Among the smaller pharmaceutical companies with limited research facilities, operations normally begin with the second step described above. The active ingredients—chemical compounds or biological extracts—are purchased from basic producers and formulated into acceptable dosage forms. Emphasis is placed on uniqueness of formulation and on package design rather than on originality of the active components. The pursuit of products in this category will be discussed below.

An established, successful research group should include among its chief assets adequate facilities and personnel, a tolerant research-minded management group, and a flexible budget. Assuming all this, let us examine the factors which affect the origin and successful development of a new chemical formula. For simplicity, our discussion will concern primarily the development of a new chemical formula beginning in the organic chemical laboratory. The general principles as illustrated will also apply to natural products, the only difference arising in the initial stages during the isolation of the active ingredient.

ORIGIN OF IDEAS

Well-planned research programs are always launched with a specific objective in view, whether this be the investigation of an obscure phenomenon or the development of a product to fit a specific need. Random searches are wasteful of both time and effort and are rarely justified in the industrial pharmaceutical laboratory. It is true that chance observation on the part of personnel engaged in a specific problem, usually a result of keen insight, has sometimes resulted in the initiation of a major program in another direction, but this is the exception rather than the rule.

An active program may originate from any one of the following sources:

Library references. A well-staffed library with all the current scientific periodicals is a stimulating source of inspiration in addition to serving as a fundamental tool during the progress of research. An abstract service should be provided to save valuable time of key personnel and to provide for ready indexing of fields of interest. Not only should periodic surveys of new fields be conducted, but the library personnel should be acquainted with the demands of the various research groups sufficiently to call attention to any new developments published in standard or obscure journals.

University relations. Fundamental research, conducted in university laboratories, eventually finds application in industrial projects. The ability to visualize practical applications for a fundamental discovery leads to major advances and competitive advantages for an industrial concern. Because of this, frequent associations between key personnel and university staffs should be encouraged and fostered. In order to nurture this source of ideas, pharmaceutical companies will do well to recognize the role university research plays in their development and provide active support by means of grants, fellowships, and outright gifts. Fundamentally, we look to the universities as a source of new personnel and original ideas. This is not com-

patible, however, with short-range or applied problems, nor should a company expect university research units to undertake such work for it. As an example, a university group can well be concerned with the development of a new synthetic method for a series of compounds but the routine application of this method to the synthesis of hundreds of derivatives for pharmacologic testing is better relegated to the industrial laboratory.

Medical relations. A competent medical staff is a vital part of the scientific assets of a modern pharmaceutical company. This group will be concerned primarily with clinical testing programs on new drugs, and, to some extent, with promotional efforts in connection with the company's products. Beyond this, it can and should provide a constructive link between the company's research division and the physician, the clinical laboratory, and the medical research centers. In the final analysis, most products of research must find acceptance by the medical profession. Complete acceptance with the maximum benefit accruing to the patient will result only if the closest possible link exists between the laboratory and medical services in general.

Another manner in which this link can be utilized is through the pharmacologic research group. Members of this unit will often possess training in the medical sciences by virtue of the fact that most academic pharmacology departments are in medical schools and by the intimate relation of the two fields. The pharmacologist usually will have had ample opportunity to become acquainted with the application or the specific lack of therapeutic agents. His approach to medical problems will be through research, thus constituting an invaluable source of new ideas for a pharmaceutical research group.

Valuable medical relations from which new ideas can be derived will also include the practicing physician, the hospital pharmacist, attendance at State, regional and national medical society meetings, dental research groups, and the increasing number of local and national public health groups and laboratories.

It is important that active relations be maintained with these

groups and that these not be made exclusively by administrative research personnel. While programs will be initiated by the administrative heads, the ultimate success of many programs hinges on the enthusiasm with which research personnel tackle a problem and, in addition, on their intimate knowledge of the final requirements of a product. Since most chemists and product development personnel rarely possess medical knowledge, it is well to foster their relation with the medical fields. This can be accomplished by attendance at medical meetings, conferences with clinicians, visits to active clinical research centers, and, to some extent, by providing condensed literature reports on medical subjects.

It will be found that these contacts are of particular value in the product development stage of the problem discussed below since this group is concerned with the quality of the ultimate dosage form which will find application by the physician.

Vital statistics. Statistical information accumulated by government agencies, such as the public health services, veterans administration, armed services, by State or regional medical groups, by insurance companies, by international health agencies, and in many cases, by privately endowed institutions and industrial concerns often can provide an over-all picture of the need for new therapeutic agents. These sources also supply at times a clue to the efficacy and the changing requirements of established agents, such as the incidence of allergic response to a specific medicinal or the development of bacterial resistance to an antibiotic or a sulfonamide. Proper use of such data can serve as a source of information for new attacks as well as a guide for established projects.

Conferences. Active discussions between members of the scientific staff and visiting scientists, consultants, members of the executive branches of the company, and others often serve to clarify objectives and to inspire new ideas. Invitations to leaders in academic research fields to visit the laboratories will similarly provide a stimulus for both.

Consultants. No industrial group is ever sufficient unto itself. While one may have competent chemists on the staff and,

among this group, experts in organic chemistry, there will often arise the need for a specialist in one specific series of compounds in the field of organic chemistry. For this reason and also for the purpose of providing outside guidance and advice, many pharmaceutical firms retain, as consultants, specialists from academic or other research centers. This practice aids in keeping industry abreast of academic developments and provides the academic worker with a picture of the industrial laboratory, its needs in personnel, and its approach to research problems. Such a connection obviously extends the research group's field of action, serving to provide in addition a continual source of new ideas.

· *Fundamental Research.* New ideas for applied research will frequently arise from observations made during the course of a fundamental investigation of a chemical or physiological phenomenon. The investigator may not realize the implication of his observations if it does not affect the course of his own research. It is, therefore, the responsibility of research management to see that there is intimate communication between the various research groups, both in formal reports and informal discussions. Close scrutiny of reports which cross departmental lines may likewise provide information which is valuable in an entirely different sphere of activity.

ORGANIZING THE PROGRAM

Once the fundamental idea for a new chemical formula has arisen from any of the sources mentioned above, it must be explored thoroughly, evaluated by means of available information from technical library sources, patent coverage determined, and the competitive picture ascertained in order to determine its ultimate value to the company.

A careful appraisal of the funds required should be made. This survey should also attempt to indicate the ultimate magnitude of expenditure for production if the project is a success. It is obviously useless to attempt a program if an early survey

indicates it to be beyond the financial ability of the company to manufacture.

Consideration should also be given to the number of research chemists necessary for adequate coverage of the problem even though it is often impossible to ascertain its magnitude until the exploratory phase of the work has been completed. Two factors will usually govern here: The first is the relative urgency of the program with respect to time; the second, the relative urgency with respect to other programs already under way or contemplated. It is at this stage that the research administrative heads will be called upon for delicate decisions which must often of necessity be based on judgment alone. No group, however large, will possess sufficient personnel to follow up all promising leads with the desired speed. An open, inquisitive mind is essential at this point, tempered with judgment and experience to enable the discard of unpromising attacks and the concentration on those projects which will ultimately assure the greatest success for the company.

In addition to the chemists involved in the preliminary phases, sufficient thought must be given to the proper facilities for testing the compounds produced. A number of bacteriologists, pharmacologists, and analysts will probably be called upon during the progress of the work. If the synthesis of a specific compound such as penicillin or streptomycin is contemplated, this additional requirement will be limited. If, however, the objective is a new chemical compound possessed of specific pharmacodynamic or bacteriostatic effect, it will be necessary that a pharmacology or bacteriology unit be made an integral part of the program to guide the progress of the work toward the most desirable compound.

Finally, an exact statement of the problem should be drawn up with the proposed plan of attack specified and a rough timetable indicated. Some groups find devices such as responsibility charts, wherein specific allocation of responsibility for each phase of the problem is indicated, useful tools. Others utilize a scheduled progress chart in which the work is laid out in detail with an accompanying time schedule, progress being

charted thereon. It is obvious that such devices, if used, must be adjusted to the specific problems, the personnel, and the size of the laboratory. As pharmaceutical research laboratories grow in size and complexity, it is necessary that more attention be given to proper coördination and planning. Of course, proper care should be exercised so that this coordination does not spell regimentation.

PROGRESS OF RESEARCH

Assignments are made in accordance with the considerations given above. A senior research chemist or project leader is usually assigned the immediate laboratory supervision of the problem. The assistants and technicians report directly to him and he is responsible for the immediate plan of attack, the progress of the synthetic work, and the interpretation and correlation of data. Since in most research organizations the pharmacology, bacteriology, and analytical units are organized under separate departments, the project leader must depend on personnel in other groups to furnish him data on the evaluation of new chemical formulas. There is thus the necessity for active cooperation upon which will depend much of the eventual success of the project.

Assuming that an assignment has been made for the investigation of new chemical compounds which may possess physiologic activity necessary for the treatment or alleviation of a specific ailment, what are the steps which logically follow?

In spite of the present highly developed state of synthetic organic chemistry, very little is known that will allow accurate prediction of the physiologic activity of a new chemical. To date, literally thousands of sulfonamides have been synthesized; yet it is impossible to predict quantitatively the action of new compounds which may be synthesized for such activity. To a large extent, one must still resort to the time honored "inspiration-perspiration formula" to achieve results. Numerous key structural compounds must first be synthesized; these in turn must be subjected to actual tests on laboratory animals to determine whether the required physiologic activity is present. Of

course, in some cases certain guides can be used. Thus, compounds can be modeled after an isolated natural product if one exists, or new compounds can be patterned after structures which may already be known to give the required physiologic response. If these two possibilities do not exist however, one is definitely relegated to random synthesis of countless "model" compounds, followed by pharmacologic testing or screening of all formulas. The results of this may indicate what structures possess some degree of activity. There then follows intensive study of this structural type and the synthesis of numerous derivatives varying one structural element at a time until the most active compound is ascertained. In a few cases, particularly when we are dealing with compounds from natural sources, a number of structures possess some degree of activity. The number synthesized will depend largely on the ingenuity of the research team, on their knowledge of methods of synthesis, and the time at their disposal. It is obvious that the permutations and combinations which can be formed by combining the five elements most frequently encountered in medicinal compounds, C – H – O – S – N, are literally infinite. For this reason we can never hope to exhaust this potential source of therapeutic agents. Instead, the pursuit of products in this field is a challenge holding the greatest promise for the future.

During the course of the synthetic work, active and continued cooperation with an adequate pharmacologic group is vitally necessary. This group serves as the "eyes" for the team, providing immediate results on the physiologic activity of a new compound and thus steering the effort along the most productive path. Inactive compounds can be quickly discarded from further consideration and the main effort concentrated on those structural variants which indicate maximum activity.

An important factor in the choice of the most desirable formula is the toxicity of the compound. In addition to the activity, the pharmacologist must therefore provide accurate data on the therapeutic index or ratio of curative dose to toxic dose for a particular chemical. This information obviously plays an important part in determining the direction of the synthetic

work. Some chemical structures or substituent groups will be found to impart high activity but with a corresponding increase in toxicity. This factor often forces a compromise in the selection of the final formula.

Other factors which must be considered carefully include:

(*a*) Irritation produced on application of the drug
(*b*) Toxic effects produced on continued administration over prolonged periods of time or "chronic toxicity"
(*c*) The number and intensity of the "side effects" noted on administration.

A thorough study of these effects should always be conducted prior to release of the product for clinical study. A preliminary study is often undertaken during the chemical phase of the problem to serve as a guide for the synthesis of new derivatives or the search for new molecular types.

Screening program. Because of the fact that physiologic activity cannot be accurately predicted from the chemical formula, a new chemical compound may have potentialities in therapeutic fields other than that for which it was synthesized. Thus, a compound originally synthesized as an analgesic drug may be found to have anticonvulsant, antihistaminic, sympathomimetic, or other totally unrelated physiologic activity. For this reason, many pharmaceutical firms have established "screening" programs whereby each new chemical may be tested for its ability to elicit a physiologic or bacteriologic response, useful in the treatment of any one of a score of human ailments. This factor should be considered carefully in any synthetic organic research project and appropriate steps taken to realize the full potential of any new chemical formula.

Documentation. Proper and daily documentation of the research is necessary for future reference in reviewing the progress of the work and to serve as legal evidence for patent applications. A bound notebook is essential for this purpose and the transmission of daily reports can be easily accomplished through the use of perforated sheets and carbon copies. The daily rec-

ords should be signed, dated, and witnessed to provide legal evidence of work accomplished.

Communication. Lines of communication between the organic laboratory and other departments, such as pharmacology, bacteriology, analytical, and product development, must be established in a formal but effortless method. Results should, where possible, be transmitted through written memoranda and active discussion between cooperating personnel should be a practice. Departmental barriers should not be allowed to interfere with immediate cooperation between the research men involved in the actual work. In an effective organization a general attack is planned in advance with the aid of administrative heads, and, thereafter, the project leader proceeds with the detailed approach through direct action with supporting departments. The reports which are issued during the progress of the work should serve to keep all interested administrative personnel well-informed of progress. In long-range projects, monthly reports will suffice to provide current information and as a summary record.

Once a new compound has been synthesized with the requisite physiologic activity, intensive pharmacologic study must establish its exact degree of activity and its lack of harmful results on administration in required amounts. Assuming that the compound meets the requirements, it is transferred to the Pharmaceutical or Product Development Department for the development of the final dosage formula.

DEVELOPMENT OF THE DOSAGE FORMULA

After the final chemical formula has been selected in accordance with the considerations presented above, the chemical must be placed in a form that can be administered or prescribed by the physician. The importance of this factor is well illustrated by the fact that numerous small pharmaceutical manufacturing concerns limit their operations entirely to this phase. In actuality, a majority of the products of the larger pharmaceutical houses are also derived from this source. A brief survey

of pharmaceutical company catalogues will indicate that less than five per cent of the chemical compounds employed as active ingredients in dosage forms are developed and manufactured in their own laboratories. The remaining so-called "specialty" items listed are distinctive merely from the standpoint of uniqueness of their combinations with carriers, stabilizers, or agents which may enhance their activity or perhaps the ease with which medicament can be administered to the patient.

In the larger pharmaceutical houses the recognized importance of product development work usually is evidenced by a separate department engaged exclusively in this type of work. Administratively, this department is usually included within the research division because many of the technics, services, and supporting scientific information are similar to those encountered on more fundamental research problems. It is taken for granted that in this unit will be found experts in tablet manufacture, ointment preparation, and pharmaceutical compounding in general. On the more technical side, the personnel should have a working knowledge of the physical chemistry of solutions, emulsions, colloidal suspensions, and the means of achieving these dispersions. They must also be thoroughly acquainted with competitive products and maintain active contact with new drugs and their usage by the clinician. Above all, they must have an intuitive grasp of the factors that provide for professional and patient acceptance. Because of the fact that they will often be called upon to handle new chemical therapeutic agents, a thorough grounding in organic and biological chemistry is useful, if not essential. This is further necessitated by the fact that the chemical industry as a whole is daily making available new compounds calling for the ingenuity of the alert product development man in using these as vehicles, stabilizers, or components which impart other desirable properties to the marketable form of a new drug product. A knowledge of commercially available equipment for drug compounding is likewise necessary. In fact, small scale tablet machines, ointment mills, grinders, mixers, dryers, and, in general, small scale work-

ing models of plant equipment are an essential part of the laboratory.

The prerequisite to ethical therapeutic formulations is the availability of a chemical formula whose development has been traced above. At this stage, it is necessary to decide upon the form in which the drug will eventually be distributed. The most commonly accepted dosage forms include:

(a) Ampuls or parenteral forms
(b) Tablets and capsules
(c) Ointments and suppositories
(d) Elixirs
(e) Liquid preparation for oral or other external use, such as antiseptic solutions, liquid vitamin mixtures, cough syrups, etc.

The general objectives during the course of the development of the dosage form are:

Compatibilities and Incompatibilities. We are in all cases dealing with chemical compounds which may possess definite reactivity towards other components in the mixture. For this reason, a careful study should be made of the compatibilities of the active ingredient to prevent the formation of possible irritants or products which may possess definite toxic properties. This will necessitate not only careful study and knowledge of the chemical formula but also frequent consultations with chemical research personnel responsible for the synthesis and with the pharmacology group involved in the screening and final pharmacologic evaluation.

Stability. An intimate knowledge of the stability of the chemical formula must be obtained and the stability of the dosage form interpreted on this basis. It will often be necessary to formulate numerous dosage forms with varying ingredients to study their stability under different conditions of storage. Frequently it is useful to determine the question under abnormal conditions of storage, such as elevated temperatures and increased humidities. While the data thus obtained are not always directly translatable into shelf-life, they nevertheless do serve as a guide for immediate work. The possible time during

which a drug may remain on a shelf should be carefully considered, appropriate steps being taken to develop dosage forms which will retain the full therapeutic effectiveness after this period. The tools required may include aging cabinets, which can be adjusted to any desired temperature or humidity, and adequate analytical facilities for testing countless formulations during this study.

Organoleptic factors. As pointed out above, the effectiveness of many drugs depends on the ready acceptance of the dosage form by the patient and the ease of administration by the physician. It is, therefore, important to give careful consideration to the aesthetic qualities of a formula, the odor, taste, or other factors affecting the sensory faculties of the patient. Although some attempt has been made at the systematic study of factors affecting taste and odor, there are few training schools which develop men for this work. A careful choice of personnel is necessary because of the fact that individuals differ markedly in their ability to discriminate between the factors making up an organoleptic study. Similarly the cosmetic properties of an ointment, although of no therapeutic value, may assume definite importance to the patient. While taste has little relation to the physiologic effect of a tablet, powder, or liquid oral preparation, it will nevertheless be an important factor to prolonged or repeated dosage. In the final analysis, if medication is refused because of any of the factors listed above, the over-all effectiveness of the dosage form is limited and a new formulation should be sought.

Another phase of this work involves the translation into the manufacturing procedures of the information gained during the investigative phase of this work. If competent personnel, possessing the requisite knowledge, can be provided in the production department, this phase can be handled as a manufacturing problem; otherwise, personnel in the product development unit with some manufacturing experience must supervise manufacturing processes until they become routine and can be turned over to less experienced personnel. The first of these two alternatives is preferred for several reasons.

Thus, if a firm is progressive and is seeking new products or markets, it is dependent on its product development group for new dosage forms. Therefore, the full time of this department can well be utilized in this direction. Also, once it has been decided to manufacture a drug, a multitude of new problems arise and continue to do so as long as the drug is in production. These problems have little to do with the acquisition of new products and include proper adaptation of formula or procedures which must be made to fit larger scale equipment; questions of stability, hold-up time during processing, and other in-process control; and a multitude of minor research problems which must be solved, both during the initial operations and after a process has been operated for some time and the weak points have become apparent. It must be borne in mind that no manufacturing procedure or series of operations is ever perfect, and while referral of a major problem back to research and product development may occasionally be justified, it is obvious that one can preempt the major portion of the time of these departments in this repetitious pursuit, which Dr. C. F. Kettering has aptly phrased as "bug hunting."

During the development of the dosage formula, it will be necessary to study rigorous methods of detection and analysis of the active ingredient, other components of the dosage form, and any suspected impurities. Because the end product is to be used in alleviating pain, suppressing disease, or otherwise treating conditions affecting human lives, there can be no compromise with the required purity, potency, identity or stability of the finished dosage form. Not only must the physician and patient have full confidence that label declarations are truly representative of composition when manufactured but also that the composition of the drug will not have changed after a reasonable shelf-life when it is finally used for treatment.

The product development department must work in close conjunction with research personnel and have access to reports indicating progress of research projects. Even in the initial screening stages of a research project, it is often necessary to call upon this department for suitable dosage forms for pharma-

cologic evaluation. Thus, small batches of tablets, ointments, injectable solutions, or other formulations must be furnished. The selection of the final formula of necessity depends on the results of the pharmacology, clinical, and product development work.

Another of its obvious functions is to provide sufficient material for clinical study. This will also serve to establish the final manufacturing standards and test procedures on an intermediate production scale.

PRODUCTION OF THE DOSAGE FORMULA

Assuming that the product has progressed satisfactorily through the developmental steps and that it has been approved for production, let us examine the factors which must be considered in producing the finished drug.

The personnel of the production department should be composed of a combination of technical, highly skilled and common labor. This personnel should be assembled with a clear understanding of the operations which will be performed by the individual departments. The pharmaceutical industry is a rapidly changing one; products are continually being superseded by others possessing new or improved therapeutic effects. While the production department may not be expected to develop formulations, it is relied on to convert developmental data into plant practice. In a progressive firm, moreover, changes and new products are frequent. For this reason, it is advisable that supervisory production personnel be fully acquainted with the technical aspects of the industry and possess, in addition, a fundamental education in chemistry, pharmacy or engineering.

The choice of personnel as well as facilities depends greatly on the type of formulation the manufacturing unit will be called upon to produce. In a general pharmaceutical operation, activities can be subdivided roughly into the following manufacturing units:

(a) Tableting operation
(b) Ointment department
(c) Elixirs and other bottled liquid preparations unit
(d) Ampul and vial or parenteral solution department
(e) Facilities for bulk powder filling, for encapsulating, or other technics dictated by specialty products

Each of these units requires labeling and packaging operations which can to some extent be used in common in a small plant but must be segregated for maximum efficiency in a large operation. Proper attention to mechanization must be stressed in this phase; it should be given serious consideration for other portions of the manufacturing process where volume warrants mechanical installation.

The operations of the manufacturing units listed above have as a common goal the production of a drug formula—differing only in dosage form. The following factors are common denominators and will compensate close scrutiny:

Manufacturing standards. While it is the function of control to insure that the finished article meets predetermined standards, it is the responsibility of the production department to establish high standards of manufacturing. Unauthorized deviation from accepted procedure cannot be countenanced without the approval of key personnel invested with authority for such changes. Practices of this sort during manufacture may lead to instability, may introduce foreign materials with resultant dangerous reactions or otherwise affect quality. It is always possible for these changes to escape the attention of the most alert control department. Hence the necessity for proper safeguards during formulation.

In-Process control. In many instances, time, effort, and materials can be saved by establishing proper controls during the manufacturing process. Thus, while the quality of the finished product will be checked by the control department, it may be advisable to check composition, purity, or other factors prior to a complicated manufacturing procedure. For instance, a simple check of the composition of the bulk formulation prior to filling

into ampuls may reveal errors in compounding or decompositions which would otherwise only be ascertained in the finished product control.

Training program. Properly informed personnel is insurance against unintentional blunders. Training for both supervisory and operating personnel can be accomplished by properly organized and well executed training programs. The aid of university and other advisory bodies should be enlisted to take advantage of standardized technics and aids.

Working conditions. Environmental factors exert their influence on the effectiveness of operations and indirectly affect quality and quantity of production. Proper light and air should be provided for comfort, and sterile, dry or humid areas planned where operations call for those special conditions.

Equipment. Drug compounding warrants the use of the best in equipment with proper attention to modern instrumentation, materials of construction, and specialized equipment. In recent years new methods of filtration have been made available for parenteral solutions, machinery for washing and sealing ampuls and vials has been improved, and new materials, glass, ceramics or plastics, have become available for transferring liquids.

Once the complexities of a manufacturing operation have been solved and production is well under way, provision should be made for periodic reviews of formulas, technics or controls. Earlier it was indicated that one phase of the product development activities should be handled by technical personnel within the production set-up. This group can be made responsible for these periodic services.

3

Pharmacology of the Formula

HARVEY B. HAAG

IN any consideration of a proposed formulation, pharmacology —the science of drug action—must have close and careful attention. Viewing the term in its fundamental sense, pharmacology may be defined, for practical purposes, as the study of the reaction of living tissue to the introduction of a chemical substance or substances. Essentially a division of biology, it is related both to physiology and to chemistry, but its connection with toxicology, pathology, or therapeutics, should not be overlooked. In fact, in the broadest sense, modern pharmacology bears a relation, direct and indirect, with most of the phases of medical practice, clinical and laboratory, because of its importance in the prevention, diagnosis, and treatment of disease.

In the previous chapter, the chemistry of the formula has had our attention. It has been observed that this subject is intimately concerned with the structure of the pharmaceutical and its various components; in brief, the interaction of these factors as they affect the physical composition of the drug. When we inquire into the pharmacology of the formula, however, our interest focuses on the effects of the substance in its impact upon the human body. Although the close relation of the two subjects is obvious, they clearly differ in their approach and in the objectives of the examination undertaken.

The delineation of the action of any particular drug upon the human organism is, of course, a principal purpose of medical research. Indeed, it is precisely this knowledge which many laboratory and clinical investigations are designed to elicit. The total fund of data thus acquired about the drug and its characteristics and effects may properly be described as its pharmacology.

While it may be surprising to those not intimately acquainted with pharmacology, it is a truism that we are not able, except in the most abstract sense, to anticipate exactly how the preparation will act upon a living structure in advance of these experimentations. Under the circumstances, to attempt to describe the pharmacology of the drug before the completion of such tests is, at best, premature, and, at worst, it results in the loss of the advantages of any rational approach to drug formulation. Such were the errors of the past. A more detailed discussion of laboratory and clinical research will be found in the chapters that follow. Our interest will therefore be confined to a relatively elementary inquiry into the general purposes of the pharmacologic study which must be undertaken to assure the therapeutic efficacy and the lack of undue toxicity of a drug formula. We will have accomplished our objective if we succeed in conveying to the reader a broad picture of what is involved in considering the pharmacology of the formula, and some of the factors that, in any particular instance, may affect the action of a drug on the living organism.

Pharmacology, as we know it today, is a relatively new subject. We need not burden these pages with fine distinctions between the meaning of *materia medica, pharmacognosy, pharmacographia, pharmacodynamics,* and *pharmacology;* these niceties of definition may be reserved for the textbooks. However distinguished, the discovery of substances of use in treating human ills probably dates back to when man first began his search for food. Gradually, our early ancestors came to differentiate between substances that were safe to consume and those that were not. Their experience with the latter group enabled them, as time went on, to discern particular substances which were conceivably useful in case of illness. A body of knowledge accumulated concerning the source, structure, action, dosage, and use of these medicinal materials; these data were eventually assembled and designated as "materia medica."

For many centuries any progress that was made in the treatment of disease by the use of drugs was based largely on the method of trial and error, practiced principally upon humans.

Unfortunately, the results of these crude experiments often, in fact usually, were of little value. In consequence, fantastic and extraordinary theories abounded. For example, the observation that the most active medicines had a bitter or disagreeable taste clothed all such substances with remedial properties. Later the doctrine of "signatures" gained acceptance; this was the belief that herbs resembling in shape or color some organ of the body were useful in treating that organ. The liverwort, lungwort, and blood root were thus allotted their physiological purpose; and even silver was prescribed in lunacy because of its dedication to the moon. Another school saw mystical virtues in chemicals, such as antimony, arsenic, and silver, excluding from the armamentarium of the physician all organic drugs. And as Torald Sollmann has remarked, "Having a well stocked armory, the physician of that day felt that he was not doing his duty unless he gave his patient the benefit of it all, and the 'shot-gun' prescription flourished."

It was only toward the middle of the 19th century that the then newly invigorated physical, chemical, and biological sciences began to exert a strong influence on the medical practices of the day. One result of this awakened interest was the application of experimental, and essentially laboratory, sciences, to the study of drug action, and pharmacology, in its modern sense, came into being. One of the first results of its impact on the existing therapeutics of the day was a "screening out" of those materials that were found to have no demonstrable medicinally useful action, as determined from experimental studies on living tissues of one kind or another. These observations, moreover, made it possible to account for the therapeutic benefits derived from a drug. Thus it led directly to the beginning of modern rational therapeutics as contrasted to the empirical therapeutics generally characterizing the use of drugs until then. It is interesting to note, parenthetically, that screening remains an important function of pharmacology today; only now, substances are screened prior to their introduction into therapeutics, whereas the initial screening tests were performed

on substances and mixtures previously employed for many centuries.

Interesting repercussions attended the development of scientific pharmacologic methods. The enforced abandonment of many compounds formerly regarded as therapeutically useful hastened the disillusion of physicians already skeptical of the value of drugs generally. The situation resulted in a wave of therapeutic nihilism, a sweeping emancipation from all drug therapy, which lasted well into the present century. This negativistic attitude toward drugs was only checked with the introduction of truly dramatic drugs such as the sulfonamides into therapeutics. The change in the trend definitely did not occur until well after the end of World War I. The catharsis thus imposed had, in all probability, a most salutary effect: it forced the discard of a tremendous amount of rubbish and permitted a fresh start. Lest complacency be denoted in this last remark, we might qualify it with the admission that not all the corners of the rooms have been brushed clean yet.

Another contribution made by pharmacology was the use of animal experimentations to determine the relative safety of medicinal compounds, that is, to fix their potential poisonous or other toxic properties. Today this still remains a highly important function of pharmacology. Indeed, it is only by such means that proper and safe dosage can be estimated for a preparation, and the symptoms and treatment of overdosages be ascertained.

THE PROBLEMS OF PHARMACOLOGY

Pharmacology is not an abstract study. Except in the most general sense, one cannot determine the potential action of a drug or a combination of drugs upon the human organism without actual tests. Although to many readers it may border on the ridiculous, we nevertheless do find many otherwise intelligent people in the drug and allied industries gathering their knowledge about the action of a proposed formula solely from the description in a pharmacology text, or even in some cases a medical dictionary—otherwise excellent references within their

purposes. This is not to suggest that no reliance can be placed on reports of actual research, conducted under competent auspices; indeed, to ignore the invaluable contribution of medical and scientific literature would require that every test, no matter how elementary, be reduplicated. The point that does need emphasis, however, is that one cannot predict, with total certainty, the action of a drug or a combination of drugs without actual pharmacologic study of the preparation—whether this study be an original undertaking on the part of the manufacturer or drawn from the original work of others.

As a matter of fact, the action and interaction of a drug cannot be delineated with any degree of categorical definitiveness ordinarily. Little weight can be given to some of the various classifications of drugs as stimulants, depressants, vasoconstrictors, and similar classes, as most drugs cause several effects, rendering futile, in many instances, any preconceived concept of their action. For example, atropine stimulates the vagus center; but it also paralyzes the endings. Consequently, administration of this drug may result in either quickening or slowing of the pulse. Similarly, strychnine may in one dose deaden the vasomotor center; in another excite it.

This last illustration demonstrates that the pharmacology of a drug or preparation is dependent not so much on the *action* of the substance as it is upon the *reaction* of living tissue to its introduction. This, in turn, is governed by such factors as the amount of the drug brought into contact with the organism, the receptivity of the tissue to it, the rate and mechanism of its absorption, and the speed of its excretion. Since it is obvious that, within reasonable bounds, these aspects may be controlled, they loom large in the study of a drug's pharmacologic action.

But before giving consideration to these factors, an important point must be made. Even though the precise pharmacologic effects of a drug be determined, the matter of its *therapeutic* action may frequently remain to be ascertained. The two are not always alike. For example, morphine is recognized by the pharmacologist as having the ability to stimulate the spinal cord; to the physician, however, the therapeutic uses of mor-

phine are wholly different. It follows, therefore, that, although a study of the pharmacologic action of the drug is essential, it must, at the same time, be viewed as only one determination in a series of steps necessary to the final development of the formula.

In the following pages we will review several practical pharmacologic problems that must have consideration if the maximum usefulness and safety of the drug formula are to be attained. Foremost among these is a study of the factors that influence the intensity of systemic drug action. These embrace the dosage administered, the mode of administration, idiosyncrasy in the individual, the age of the patient, the presence of other drugs, certain pathologic states, the sex of the patient, physiologic conditions, and the rate of the drug's elimination. Because of their fundamental pharmacologic significance and practical importance each of these factors will be accorded some detail of discussion.

DOSAGE

Largely influencing the intensity with which a drug acts upon a particular tissue is the amount of the drug to which the tissue is exposed. The dose administered has, of course, a considerable effect upon this circumstance. In the case of most drugs, it has been possible, by extensive fundamental studies involving observations on unicellular structures, isolated organs, various systems of the body, and the animal as a whole, to establish definite ratios between drug concentration and the nature and magnitude of the effect. As may be expected, within limits and with some exceptions, it has been found that the greater the drug concentration—or dose—the more pronounced the effect. It has also been demonstrated that in the case of all drugs there exists a definite "threshold" concentration below which no discernible physiological consequence is produced. Similarly, above a certain dose—individual to each drug and tissue—no further increment in response is obtained, but fatigue or death of the tissue ensues.

In the official compendia and other informative sources, the

amount of the drug for clinical administration in a single application is usually designated as the "average dose." Whether or not this practice is as helpful as it should be is rather doubtful. If it is used to indicate the dose which has been demonstrated, by clinical studies, to be the quantity required for therapeutic benefit by the "average" patient, it is, as we shall see, subject to considerable adjustment to the individual patient. On the other hand, if it is intended to suggest the amount of the drug administered by the average physician, it might be better to supplant it by the term "usual dose," as has been advocated. As a matter of fact, physicians generally appreciative of the role that individual susceptibility plays in regard to drug response, look upon such dosage statements as figures indicating safe amounts about which they can develop a satisfactory dosage schedule. For example, a patient may not require the quantity recommended—although this is rather rare since such statements usually veer toward the conservative side—or he may demand and tolerate several times the stated amount.

Ideally, the dose of a drug for man is that amount that produces the desired therapeutic effect without, however, causing any harmful or disagreeable side-effects. However, the inherent biologic differences existing between individuals makes this almost impossible of attainment. Not only does the therapeutic dose vary from subject to subject, but, to complicate matters further, even from time to time in the same subject.

To the drug manufacturer, this naturally raises a problem frequently insoluble. In most instances the law calls for a statement of the dose. Of course, this statement should provide a quantity of therapeutic value; on the other hand, it should avoid any possibility of toxic reactions or unpleasant side-effects. The problem is aggravated where, as in the case of strychnine, for example, the active and fatal dose are relatively close together. In preparing directions for the physician under these circumstances, it is perhaps advisable to advance as much information as is possible to permit him to handle necessary adjustments in dosage intelligently.

Considerable attention must, moreover, be given to the *daily*

dose of a preparation, whether intended for administration under the supervision of a physician or by the layman. While the rate of excretion is, of course, the material factor in fixing any periodic medication, there is a tendency to prescribe and to take certain medication three or four times a day, a fact that should have recognition by so dividing the single dose that it constitutes but one-third or one-fourth of the daily dose. On the other hand, there are many drugs that are administered but once a day, either for the sake of convenience or because it is unnecessary to administer the drug more frequently. Obviously, it is important not to confuse the needs and dosages for such drugs.

MODES OF ADMINISTRATION

The mode of administration has a considerable influence upon the rate of intensity with which the drug acts upon the organism, and, in some instances, upon whether or not it will have any therapeutic or physiologic effect at all. Generally, the method of administration is governed upon whether a local action is sought or whether its effectiveness is dependent upon its distribution through the body; in the latter instance, to obtain a "systemic effect." Local applications need not concern us; the problems involved are relatively simple save where this method is used to secure systemic action by absorption.

Unfortunately, there is no standard rule fixing the mode of administration in every instance. Frequently this is dictated by the nature of the medicine and the necessity of introducing it into the system in sufficient quantities to assure its effectiveness or to control its action.

The oldest, safest, and, as a general rule, most acceptable route of drug administration for the production of systemic effects is to give the drug by mouth. From a practical point of view, moreover, it constitutes the route of choice for all systemic medication. However, although it is the hope of physicians generally that ultimately all drugs may be so prepared as to be suitable for oral administration, nevertheless, there still remain many valuable medicinals that cannot be so administered. One

reason for this is that some drugs are simply not absorbed into the blood stream from the stomach and intestines; an example is streptomycin. Others, such as insulin, are destroyed by the secretions of the gastro-intestinal tract.

Some attempts have been made to prevent this destructive action from taking place in the stomach and also to prevent the drug from irritating this organ by coating medicaments with a material that does not dissolve readily in the stomach, but will in the intestines; these are called "enteric coatings." This treatment is, however, not always effective. For example, some drugs are destroyed or so altered as to become therapeutically ineffective by certain metabolic products of organisms or by the organisms themselves normally found in the intestinal tract. Penicillin is thus attacked. Others have proved more toxic by the oral route of administration than when given by injection—tryparsamide is an illustration—due to changes wrought by the secretions and contents of the gastro-intestinal tract.

Certain other circumstances limit the use of oral administration of drugs. First of all, the taste may be repulsive; although in many instances this can be remedied by employing a flavoring agent or by using the drug in pill or capsule form. Again, the drug may irritate the stomach, causing nausea and vomiting, and intestines, in which case it will induce diarrhea. If this tendency exists, it can be somewhat minimized, particularly in so far as the stomach is concerned, by giving it well diluted or after meals or in an "enteric coated" preparation. In other instances, moreover, consideration must be given to the fact that absorption of drugs from the gastro-intestinal tract into the blood stream is, as a rule, neither as rapid nor uniform as when they are given by injection. Thus, diseased conditions of the stomach and intestines, the state of the circulation, the presence of food, may contribute to the slowness and uncertainty of absorption following oral administration. Finally, it is not feasible to give drugs orally to unconscious patients or to those suffering from persistent nausea and vomiting, or to those who, for one reason or another, are non-cooperative.

Although the term "parenteral administration" actually means

administration of a drug by any route other than by way of the gastro-intestinal tract, usually, however, it is employed to indicate injection immediately underneath the skin (subcutaneously; hypodermically), into the muscle (intramuscularly), or into a vein (intravenously). In the great majority of instances, these modes of administration produce a more prompt and more certain effect than oral administration; this is particularly true of intravenous injection, followed by intramuscular, and, in lesser degree, by subcutaneous injection. Largely because of this rapidity and certainty of effect the dose of a drug given parenterally is usually less than that administered orally. Thus, with but few exceptions the intravenous dose is the smallest, the oral the largest. Attempts have been made to formulate general rules covering the ratio of the oral dose to the various parenteral doses. However, since this proportion varies from drug to drug, it is apparent that no universal formula can be applied.

There are other advantages of the parenteral methods of drug administration over the oral one. Obviously the matter of taste, the possibility of local action on the gastro-intestinal tract, the effect of digestive juices, and similar factors are obviated when the drug is injected. Furthermore, difficulties are avoided in so administering drugs to the unconscious patient and others where oral medication is inadvisable or impossible.

On the other hand, we must recognize some definite disadvantages incident to the parenteral administration of drugs. The product used for parenteral or, indeed, for any injection type administration, must be especially refined and sterile; this, of course, increases its cost. Again, sterile precautions must be employed at the time of administration. Nor should we overlook that, except in the case of insulin, it usually calls for administration under professional supervision. In some instances, moreover, there is a certain amount of pain associated with this route of administration, making its use unpleasant.

Subcutaneously administered drugs are apt to be more painful than those given by the other parenteral routes due to the abundant sensory nerve supply of the subcutaneous tissues. Absorption from subcutaneous administration, as indicated

above, is also the slowest of the routes because of the relatively poor blood supply in this area. This also makes local infection more likely to occur following subcutaneous injection.

On the other hand, absorption follows intramuscular injection rather quickly due to an abundant blood supply. Moreover, the injection is less painful in the absence of many sensory nerves. When intravenous injection is resorted to, there is ordinarily very little pain from the drug itself and, of course, the problem of absorption does not enter the picture because the drug is injected directly into the circulating blood. Intravenous injection, however, is one of the most dangerous routes of drug administration; it should therefore be reserved for emergencies and for those drugs that are not effective by any other route. One of the dangers seems associated with the speed of injection; generally the greater the speed, the greater the chance for an untoward accident to occur. This is due, in large part, to the fact that a rapid intravenous injection creates such a high concentration of the drug in the column of blood reaching the heart and other vital structures that it produces an immediately poisonous effect. Another reason for the increased hazard incident to intravenous administration rests with its irrevocability and irreversibleness. Thus, if an overdosage is given, nothing can be done to slow down absorption as is possible with most other forms of drug administration. Once in the blood stream, the drug is indeed beyond recovery, usually barring any efficient means to prevent or retard its action.

Another method of administering drugs to produce a systemic effect is by insertion into the rectum, usually in the form of suppositories. This mode of giving drugs obviates many of the disadvantages of oral administration. Unfortunately, however, for the most part absorption from the rectum is slow and very uncertain. In addition, certain drugs produce rather severe local irritation to the mucous membrane of the rectum, particularly if there is already some existing damage. Consequently, except where it is desired to produce a local effect on the mucous membrane of the rectum or to clean out the lower bowel, there are only a few rational places in therapeutics for this route

of drug administration. The same is true of drugs placed in the vagina for the production of systemic effects.

There are several other modes of drug administration that employ the injection technic. Some drugs, such as certain of the local anesthetics, on special occasion are injected directly into the cerebrospinal fluid, by way of the spaces between the vertebra of the lower part of the spinal column, for the purpose of developing higher concentrations of the drug in the nervous tissue bathed by the cerebrospinal fluid than would be desirable or safe by other routes of administration. This method of administration is referred to as intraspinal, intrathecal, subarachnoid or sub-dural. Before a drug is so administered, however, special experimental studies should be made regarding the toxicity of this mode of administration, the possible destructive action on the tissues of the central nervous system, and other special side-actions that may be produced.

Similar in principle to the intrathecal use of anesthetic drugs is the injection of local anesthetics in or around nerve trunks and fibers to produce local anesthesia. When this involves blocking a nerve trunk it is referred to as conduction anesthesia; when it involves blocking only the peripheral nerve fibers it is called infiltration anesthesia because the anesthetic is not injected into every part of the tissues but only into relatively few areas from which it infiltrates into other non-injected zones.

On rare occasions of emergency a drug, usually epinephrine, is injected directly into the chambers of the heart—intracardiac injection—to stimulate a failing or non-functioning heart.

In children, again under rare circumstances, materials are injected into the abdominal cavity (intraperitoneally) from which absorption into the general circulation can take place rapidly. Present in this mode of drug administration is the danger of the injection needle perforating some abdominal organ such as the urinary bladder or intestine. Drugs given intraperitoneally must be shown to be non-irritating and also to be absorbed promptly, otherwise adhesions between the various abdominal organs may result.

Drugs may be administered by application to the skin or

mucous membrane for the production of systemic effects. When so applied by way of the skin the procedure is called inunction. The usual manner of administering drugs to produce a systemic effect through the mucous membrane is to place it under the tongue (sub-lingual administration). The mucous membrane directly under this organ is quite thin and the blood supply very abundant; hence with a suitable drug this mode of administration is capable of producing effects comparable in speed and intensity of action to that of the intravenous route. In connection with the application of drugs locally to the skin and mucous membrane to produce systemic effects, it is well to bear in mind the possibility of absorption of drugs from these areas when drugs are only intended for local medication. As examples of this hazard are the many cases of systemic mercury poisoning reported following the use of mercuric chloride solution for vaginal douches.

The technic referred to as the administration of drugs by iontophoresis permits a high concentration of the drug in the tissues immediately beneath the site of application to be developed. A galvanic electric current is applied with one pole over the area to which the drug is applied and the other at some distance, thus facilitating penetration of the drug through the skin or mucous membrane.

Because of the vast surface area involved, the thinness of the lining membranes and the abundant blood supply, absorption of drugs from the respiratory tract, familiar as administration by inhalation, can be very rapid. At present this route of drug administration for the production of systemic effects is reserved largely for the volatile and gaseous anesthetics such as ether and cyclopropane, although aerosol therapy—the administration of drugs in a finely divided spray—is useful under some circumstances.

Although there are still other modes of administering drugs —for examples, into the bone marrow or the corpus cavernosa of the penis—for the production of systemic effects, those mentioned comprise the most frequently considered ones. In studying the pharmacology of any proposed drug formula the

principles discussed must have attention and necessarily should have an advanced position in the scheme of experimentation.

IDIOSYNCRASY

It has already been indicated that, in so far as the intensity of drug action is concerned, individuals vary in the extent of their response to a given dose of a drug. This is a quantitative differentiation. For instance, one patient may require, and tolerate without showing any signs of poisoning, several times the usual dose. On the other hand, another may need only a fraction of the customary dosage to obtain a therapeutic response and, in fact, may develop typical symptoms of poisoning if this amount is but slightly exceeded. The former patient would be said to be tolerant, the latter susceptible to the drug.

Persons may also vary as to the type or kind of response to a drug; this is a qualitative differentiation. As an example, instead of showing sedation after a dose of morphine a patient may become excited. Likewise, the use of phenolphthalein may in one individual bring on a skin rash, or some other classical phenomenon of allergy, not normally observed. Such cases of qualitative deviation from the norm are classified as instances of drug allergy, particularly when the skin or mucous membrane is involved.

Both quantitative and qualitative variations from normal in drug response may be congenital or acquired. Unusual drug responses of these several kinds are referred to generically as cases of idiosyncrasy to drugs, although the term, unless qualified, is usually restricted to mean increased susceptibility or an abnormal qualitative response.

While idiosyncrasies of the qualitative type are rarely noted in experimental animals, the quantitative type involving relative tolerance or relative susceptibility appears apparently as frequently in observations on animals as in those on man, the actual range of doses involved varying from drug to drug.

AGE OF THE PATIENT

Concentration of a drug in the tissues of the body following administration of a given dose will naturally be related to the weight of the body; thus the smaller the weight, the less amount of drug needed to achieve the desired concentration and consequent physiologic effect. Hence, it is largely because of the difference in weight between adults and children that the latter require smaller doses of drugs than their parents. There are many rules dictated by experience as valuable guides in arriving at the dose of a drug for a child when that for an adult is known. Probably the best known of these is based on differences in weight (Clark's rule). This rule fixes the dose for a child (an individual 12 years old and under) by using the following equation:

$$\frac{\text{Weight of child (lbs.)}}{150 \times \text{adult dose}}$$

The denominator "150" supposedly represents the weight of the average adult in pounds. While this and other formulas are rather widely used, it is well to remember that they are not universally applicable to all drugs. For instance, frequently the young child is, on the one hand, more susceptible than adults to the depressing effect of morphine, and, on the other, more tolerant to the cathartic effect of cascara than one would be inclined to expect on the basis of weight differences. The drug manufacturers would be wise to determine individually the dose for children of each new drug rather than to arrive at it by relying solely on general and arbitrary rules. In this connection, laboratory experimentation on animals will be found to give important leads.

As patients become older (60 years and over) they require less of a drug than during younger adulthood. This is probably, in part, related to a lessening of body weight, but there are other unknown factors that apparently play an important role. It might be noted that the whole question as to the effect of age

on drug response needs to be considered much more extensively than it has been up to the present time. This is especially true and pertinent now that the span of life is growing longer. There is a definite need for the development of what might be called geriatric pharmacology, both from the clinical and experimental point of view, and, of course, its application to therapeutic articles on the market.

PRESENCE OF OTHER DRUGS

The nature and magnitude of action of one drug may be markedly influenced by the simultaneous presence of a second. In one instance, the second ingredient might tend to nullify some, or indeed all, of the effects of the first. This is known as drug antagonism. Obviously the presence of two drugs in a formula, one of which completely neutralizes the effect of the other, characterizes the mixture as wholly irrational and without therapeutic value. On the other hand, if one component produces, along with its beneficial effects, certain undesirable reactions which a second can prevent or minimize, then this type of drug antagonism can and should be put into use.

Two drugs having like physiologic effects are said to be synergistic one to the other. This synergism may be of the additive type, by which is meant that the total effect of the two is no more than would be expected from the sum of their individual effects. However, when the effects following the administration of two drugs is greater than would be anticipated on the basis of individual performances, the type of synergism is referred to as potentiation. Usually, unless otherwise qualified, the term synergism implies potentiation.

Much can be learned concerning drug antagonism and synergism from laboratory experiments on animals, and this question must be exhaustively studied pharmacologically whenever a preparation contains more than a single active ingredient. It may be remarked briefly that many formulas now on the market would be aided by a competent review of this nature.

PATHOLOGIC AND PHYSIOLOGIC STATE

The presence or absence of disease can appreciably alter the nature and extent of drug response. For instance, antipyretic drugs, such as acetophenetidin, in ordinary doses have no effect on normal temperature, but in febrile states they tend to lower it. As another example, digitalis tends to increase the output of the heart when it is given to patients suffering from heart disease, while on the other hand, it may decrease the output when administered to normal individuals. Again, persons suffering from intense pain can tolerate doses of morphine which, in its absence, would produce definite signs of poisoning.

This possible difference in response to drugs in health and disease should always be borne in mind in attempting to transfer the results of experiments on healthy subjects and animals to situations existing in the sick. Experimentally it is possible to create in animals certain counterparts of diseased conditions encountered clinically; this is especially true in regards to infectious diseases. Unfortunately, however, there remain many clinical conditions which cannot be duplicated experimentally. For instance, it has not as yet been possible to create in animals the equivalent of the chronic type of heart failure associated with edema displayed by patients suffering from auricular fibrillation. To create these conditions experimentally is one of the goals of pharmacology in its progress toward further rationalization of therapy and development of new and better drugs.

SEX

There seem to be relatively very few instances where sex affects the intensity or quality of drug response, except of course for the differences in weight between the male and female. As an example of the effect of sex *per se* on drug activity, it has been demonstrated experimentally that female rats are more susceptible to barbiturates than male rats. Among clinicians there is also an impression that women are more apt to become

excited from morphine (morphine idiosyncrasy) than men, although actual factual data bearing on this are very scarce. It should be borne in mind that on occasion one sex may show a reaction to a drug not noted in the other sex due to anatomical differences. To illustrate, an irritant cathartic administered to a male produces only increased motility of the intestines; in the female this action is sometimes associated with an alteration in uterine motility.

Just as the presence of disease can influence drug action, so the physiologic state of the subject can likewise play a similar role. As an example might be cited the activity of certain drugs which are used for their effect on the uterus. Thus, posterior pituitary solution has little or no effect on the non-pregnant human uterus in the usual dose. As pregnancy progresses, however, further and further toward term, posterior pituitary solution becomes increasingly active in augmenting the force and extent of contraction of the uterus, reaching its maximal effectiveness in these respects at the time of labor. Similarly, drugs which are used to induce sleep appear to be most effective if administered at or about the usual bedtime, and medicaments intended to increase gastric secretion are regarded as being most active when given at meal time. Along these same lines are observations showing that certain antispasmodic drugs act most definitely as such in the presence of spasm of smooth muscle such as might occur in the intestines and gallbladder. The significance of the role of the physiologic state of the tissues in their response to a drug has only rather recently been appreciated from a clinical and experimental point of view, and much of importance can be expected as studies bearing on this are pursued with increased vigor. Obviously, it is of material importance and interest to the drug manufacturer in his search for the most optimal results from the use of his preparation.

RATE OF DRUG ELIMINATION

The rate of drug absorption has been discussed in the section dealing with enteral and parenteral modes of drug administra-

tion. It was emphasized that the greater the rate of absorption the greater the intensity of effect. In reference to the effect of drug elimination on the intensity of drug action, it is obvious that the slower the rate of elimination of the drug from the body the more intense and prolonged the drug effect. We use the term elimination here to indicate both the true elimination of the drug as such and its change (detoxification) by the body into a less active compound or compounds, and their elimination.

The kidneys are the organs most frequently involved in drug elimination. As is to be expected, impairment of kidney function can be shown experimentally and clinically to act to decrease elimination of certain drugs and thus increase their systemic effect. Again, while being eliminated some drugs themselves might injure the kidney with the consequence that the drug is not as promptly eliminated from the blood stream as normally, and as a result there is an increase in systemic activity. In addition to the kidneys the large intestines is the other primary route whereby drugs are eliminated from the body.

The great detoxifying organ of the body is the liver; with but relatively few exceptions all drugs are altered in their passage through it. When for some reason the liver does not detoxify a drug as promptly as usual, the drug can accumulate in the body to a point where unusually intense effects are produced.

It is apparent that the frequency of drug administration must be correlated to the speed of absorption on the one hand, and rate of detoxification and elimination on the other. The rate of absorption being equal in the case of two drugs, the one having the slower rate of detoxification and elimination will require less frequent administration and hence possibly smaller dosage than the other. Also in this connection, a drug having a slow rate of detoxification and elimination, such as digitalis, is more apt to lead to "cumulative" phenomena on repeated administration because the rate of detoxification and elimination may gradually fail to keep up with the amount being administered and absorbed.

All these factors are of the utmost materiality in determining

how toxic a drug actually is. It is only one—although without question the most important—of the questions that a careful pharmacologic study can answer.

LIMITATIONS OF EXPERIMENTAL PHARMACOLOGY

We have attempted to emphasize throughout this chapter that any study of the pharmacology of the formula is but one phase of the research that must be undertaken if an acceptable preparation is to result. In this connection it must also be borne in mind that experimental pharmacology has very definite and distinct limitations. Sollmann has also stressed the restrictions attending pharmacologic research. Discussing animal experimentation, he has pointed out in his monumental work that:

> Care must be used in applying the results of experimental pharmacology to man. The neglect of this precaution, the drawing of far-reaching conclusions from limited experiments is seen all too frequently. Pharmacology can not be held responsible for misapplication of its data. Its scope is limited primarily to its own results and not to their application, although it may legitimately suggest the latter. It should not be made to replace therapeutics, but should aim to place well-studied tools in the hands of the latter. If this limitation is realized; if the therapeutist will carefully study the results of pharmacology and will utilize and interpret them in the light of bedside experience, then pharmacology will be of very great value to medicine.

4

Laboratory Research

M. L. TAINTER

THE PURPOSE OF LABORATORY RESEARCH

WHEN an idea has been conceived for a new drug, or a formulation of pre-existing drugs, it becomes the duty of the research laboratory to develop the medicament to the point where it is suitable for clinical test and, if these prove satisfactory, for eventual commercial introduction. The activities going into advancing the project to the stage of commercialization are manifold, many making demands on the research laboratory. Our present discussion deals with the objectives of the research and development laboratories, and their organization for efficient operation. It also necessarily embraces the mechanics by which a research project is initiated and pursued, since systematized operations are required not only for efficiency but also for maximum prospects of success.

In other chapters the chemical tests and pharmacological and other experiments in the biological field, needed in most cases for a new product, are presented in detail. The present chapter, therefore, will be restricted to the more general aspects of laboratory research and will concern itself with the framework within which the individual experiments are most efficiently carried on.

The description of the laboratory, as it will be presented in the subsequent paragraphs, envisages a rather large, completely integrated, organization where substantially all fields of medicinal research are conducted. It will be recognized immediately that only a relatively few companies will have need for the complete organization delineated. Indeed, those dealing with restricted problems may require only a fraction of the establish-

ment described, obviously permitting its reduction in proportion to the size of the operations contemplated.

Again, in some organizations many of the activities will be carried out by a single person or small laboratory group. This is on the whole acceptable if the amount of work involved does not justify having more restricted or, rather, more specialized duties for each individual. Where there is enough of any one type of work to justify it, however, the greater the specialization, the more efficient becomes the operation. On the other hand, a division of activities can, in very large organizations, be carried to too great a degree, since such specialization may create difficulties in correlating the activities of large numbers of individuals. The point at which efficiency is promoted by specialization of functions can only be determined by a careful evaluation of the problems of correlation and integration arising under particular conditions. Realization that the optimum degree of specialization of the staff is a problem calling for careful consideration is an important factor in its solution.

OBJECTIVES OF THE RESEARCH LABORATORY

The research and development laboratory plays a number of functions in the development of a new product. One of the first of these must be the selection of the proper main ingredient for the formula, or, perhaps, to develop this ingredient through the process of chemical synthesis if a drug already available is not to be utilized. It may also select adjuvants to combine with the main drug to modify its effects in the desired direction.

The research laboratory will further have to establish the methods of administration of the drug or preparation since this bears on the formula to be developed. Having settled on the channel of its administration, the size of the dose must then be determined together with its dosage form; it is obvious, of course, that the type of preparation will vary markedly between a liquid solution to be swallowed, an ampul preparation to be injected, or a suppository. After these factors have been decided, the laboratory has to establish the strength of the preparation in

terms of concentration or content per unit. These are matters which oftentimes do not require much special consideration; their answer is usually implied from the proposed use of the product. However, there are many kinds of medicaments in which they can only be settled by detailed study, since a product may have several possible modes of application, or the dosage may differ depending on the type of disease condition for which the product may be designed.

With answers to these general considerations regarding the form of the medicament and desired dosage at hand, the laboratory is faced with the responsibility of establishing its activity by appropriate tests.

Moreover, the laboratory is responsible for determining not only that the product is efficacious for the disease condition in which it may be used but that, in addition, it will be safe under the prescribed conditions. For this purpose, the laboratory will be called upon to determine toxicities from acute, subacute, and chronic administrations. This will require that the formula, and possibly its individual ingredients, be submitted to experimental scrutiny under a wide variety of conditions. For instance, it is necessary to ascertain on almost all products the acute toxicity resulting from the administration of single large super-therapeutic doses. In view of the present standards of bioassay test methods, it may be anticipated that an evaluation of the LD_{50} together with the slope of the dosage response curve will almost invariably be demanded. In many cases, there will also be needed a comparison of the mean lethal dose with the anticipated effective dose, that is, the dose which must be administered to produce the requisite medicinal response. A comparison of the ratio between these two estimations indicates the degree of safety or what is sometimes called the "therapeutic ratio" or "margin of safety."

Similarly, data are needed for almost every type of formula as to its subacute toxicity, that is, the toxicity which might develop from giving therapeutic or super-therapeutic doses over periods of two to three weeks. The size of the doses that will have to be administered in such tests, and the duration of the

treatment are matters which have to be decided for each individual product. This calls for consideration of the type of action of the ingredients of the formula, since this may modify what would constitute a subacute as opposed to an acute experiment.

Finally, if there is any possibility that the compound in question might be used over more than a brief period of time or in repeated doses, the question of its chronic toxicity becomes of great importance. In order to explore such potentialities, there would have to be instituted experiments wherein the formula was administered to experimental animals for months, or possibly even years, depending on all relevant circumstances. As more is learned of the chronic toxicities of drugs, the importance of these long-term experiments increases. Certainly, chronic toxicity determinations that were entirely acceptable ten years ago would in many instances be considered quite inadequate by present standards.

Another type of toxicity which must be looked for is that expressing itself in side actions rather than in an exaggeration of the therapeutic response. An example of what is meant by the term "side action" is evident in the case of digitalis. This is a drug used for its effects on the heart, over-dosage resulting in disturbances in cardiac action, and finally stoppage of the heart. However, a side effect of digitalis is the production of vomiting, or in lesser degree, of nausea. Obviously, unpleasant or dangerous side effects are matters of considerable consequence, inasmuch as they greatly hamper the free use of the drug. The primary toxicity, that is, toxicity produced by an excessive degree of the therapeutic response, ordinarily can be controlled adequately by an adjustment in the dosage to keep it within the therapeutic limits. However, since they are not necessarily dependent upon activating the mechanism of the therapeutic response, side actions may be induced at dosage levels not related to the therapeutic, and therefore constitute serious complicating factors. Ordinarily, side effects are more difficult to uncover and, hence, to study than are the primary actions, because they are not as easily elicited in the laboratory as are the therapeutic effects. In some cases, moreover, they are

caused by personal idiosyncrasies, and therefore disclose themselves in only a portion of the experimental subjects. In general, it may be said that while these factors are looked for and studied wherever possible, the laboratory can seldom predict the complete story on side effects as eventually uncovered by extensive clinical work in patients.

Another objective of the laboratory experiments must be to demonstrate that the proposed formula is adequately stable for commercial distribution and use. This requires the setting up of aging experiments to reproduce as closely as possible the most extreme conditions of temperature, humidity, and similar circumstances to which the drug may be exposed. Probably this is one of the most neglected phases of the development of drugs; indeed, some formulas on the market at the present time are demonstrably unstable, even to a degree which may impair their full clinical value.

After the ingredients, concentration, and similar elements of the formula have been decided upon, the research laboratory may be called on to manufacture a supply of this material sufficient for study in the clinic or field tests. This involves the small scale manufacture of the combination and its ingredients. From this experience may come development of practical methods for production under commercial conditions. Properly carried out, such studies also lead to establishment of the methods of finishing the product, that is, of transforming the bulk chemicals into a finished medicinal compound suitable for distribution to the patient by the pharmacist. The selection of the proper kind and style of container and package and perhaps of the labeling requirements will ordinarily be tentatively established by the practical experience of the laboratory in producing experimental batches.

This research material must be analyzed for purity, stability, and identity in much the same way as will the finished product in regular commercial production. It follows that control procedures must be initiated in the research laboratories to insure these factors and others. As a result of the experience thus gained formal control specifications will probably be evolved

applicable to the commercial material. Indeed, it is desirable that such work in the research laboratories be performed with the realization that the analytical and testing experience so acquired will form some basis for the formulation of adequate control procedures in commercial practice.

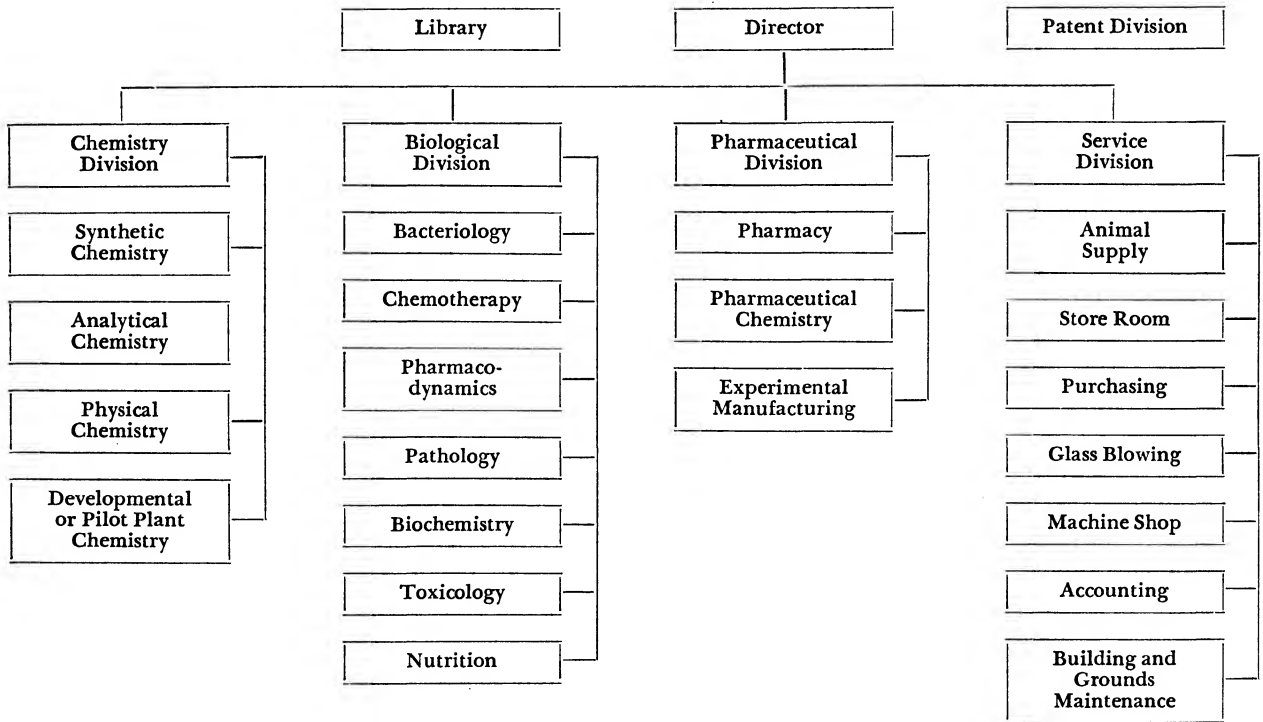
GENERAL PLAN OF ORGANIZATION OF THE LABORATORY

The organization diagram for the research and development laboratory will, of course, vary with the conditions governing in each instance. A type of organization suitable for one laboratory may be quite impractical for another. Nevertheless, having an organization scheme is important if only because it helps to establish orderly and systematic channels for attacking problems, with clear lines of authority and responsibility, and thus minimizes duplication of effort. Such a diagram illustrating how a hypothetical laboratory may be organized is shown in Figure 1.

At the head of the laboratory is the director with whatever assistants he may need. The laboratory may be divided into three major functioning units: *(a)* a chemical division, to conduct all the chemical operations involved in the synthesis or later study of the drug or formula, *(b)* a biological division, to deal with tests relating to the reaction of the living organism to the proposed preparation, and finally *(c)* a pharmaceutical division in which studies concerned with the effective and elegant preparation of the product for its use by the ultimate consumer are carried out.

Chemical division. In this hypothetical organization, the chemical division will need laboratory units devoted to the synthesis of the chemical compounds required, if these are not already available. In addition, analytical laboratories to conduct the appropriate chemical analyses to determine purity, freedom from contamination, and related chemical measurements are essential. These laboratories may be assisted by a physical chemistry unit where measurements are carried out with special equipment, such as spectrophotometers, polarographs, refractom-

Figure 1: *Organization of Hypothetical Research Laboratory or Institute in the Medicinal Field*



eters, molecular stills, and other physical apparatus not generally used in chemical laboratories.

Finally, a chemical development laboratory is useful to modify the small laboratory glassware size of operation to one suitable for manufacture on a larger scale. Almost invariably, commercial size batches require changes of conditions of temperature, stirring, pressure, etc., for maximum yields. In this chemical development group, consequently, special attention will be directed to improving the efficiency of the process so that maximum purity and yield are secured, thereby reducing the cost.

Biological division. The biological division may have its activities apportioned in many different ways. There will commonly be needed a bacteriological unit where studies on antiseptic power, sterility, and related phenomena are undertaken. Related to these bacteriological studies may be a department of chemotherapy where the etiotropic agents of infectious diseases are studied in the living host and the curative power of the drug in question evaluated. The lines of division between the chemotherapy and the bacteriological groups may be difficult to draw; indeed, the functions may be completely combined, depending on local conditions.

The biological division also must carry on pharmacodynamics, which may be defined as studies on the responses of the various integrated functions of the body to the drug. In many laboratories, pharmacodynamic studies are combined with chemotherapy under the general head of pharmacology. Studies on the rate of absorption, blood levels, tissue distribution, detoxification, and excretion of the drug may also be needed. From such studies appropriate directions for route and frequency of medication, size of dosage, etc., may be evolved. A biochemical laboratory, interested primarily in the chemical aspects of drug medication in the living body, will probably carry on the above investigations more efficiently than if they are pursued by those whose biological orientation is merely physiological.

Finally, the biological division is almost certain to require the expert services of a pathologist. In the studies of the toxicity of the compound, some of the most important conclusions have

to be drawn by inspection of the tissues of the medicated animals both at autopsy and by microscopic examination. Competent pathologists who are interested in the study of animal tissues are extremely rare, so that this is one of the most difficult types of information to obtain in the entire field of drug investigation. The human pathologist attached to a hospital or clinic is not likely to have had adequate experience with the study of animal tissues to be completely familiar with normal variations in animals and the types of lesions to be anticipated from exposure to various products. Therefore, an animal pathologist, if such can be obtained, is a person of unusual value to an organization where there is enough work in progress to keep him occupied.

Pharmaceutical division. The pharmaceutical division is staffed with pharmacists, expert in developing a formulation and combining this in as elegant a form as possible. In addition, the pharmaceutical division is likely to be called on to do some small scale manufacturing for the production of research materials. Through this valuable experience is gained, permitting the formulation to be developed to a more practical stage than would be the case if the pharmacy laboratory utilized only minute quantities. In this way, too, the final manufacturing formula and directions for processing may well be evolved by the pharmaceutical division.

Patent division. If there is any considerable amount of new drugs or formulas being developed, there will probably be needed a patent division, staffed by those specially trained in this type of legal work. The patent group must be unusually well-oriented in chemistry, since their major concern is with details of chemical syntheses. Of course, where the scale of operations is small, outside assistance can be called on for the necessary processing. However, the high costs of this work on an individual fee basis frequently makes it economical to employ full-time patent attorneys for even relatively small organizations.

Having a full-time patent staff available is an asset also in another way. Advice is frequently needed as to whether preferred or feasible chemical syntheses are covered by previous

patent claims. Similarly, valuable suggestions are oftentimes secured from study of the patent literature, particularly in a rapidly developing field. There are often extremely helpful implications to be drawn from what is not claimed in an issued patent. It is not too much to say that an imaginative and skillful patent expert, in a full-time capacity, will contribute much in this way beyond the mere processing of patent applications.

Library. Scientific work cannot be performed without continuous reference to published articles, reviews, abstracts, and other varieties of scientific literature. A well-stocked library, therefore, is practically indispensable, and should be situated where it may be conveniently consulted at all times. Of course, if the research organization has access to a nearby library, then the need for owning one is obviated. But when such facilities are not readily available they must be provided within the research organization.

Where the research staff is small, there is a strong urge to borrow the journals needed, rather than to subscribe to them and to purchase back files. However, if the time of those using the library is worth anything, it can be readily demonstrated that the delay occasioned by having to borrow from outside libraries is more expensive in the long run than any saving in library costs. The journals subscribed for by the library can be confined to those frequently used, thereby keeping the costs in line with the needs.

Employing the services of a professionally trained librarian will usually be a good investment. The service that can be rendered by such an individual in helping to locate references, compiling bibliographies, abstracting articles, and similar tasks, will save more than the salary expended. The filing and classification of references, reprints, and other literature can seldom be done properly except by or under the supervision of a professional librarian. Similarly, the purchase of books and periodical literature from the most advantageous sources can be expected of the librarian; this may result in important savings.

Circulation of current journals to various members of the research staff will serve to keep them in touch with develop-

ments in their fields as they arise. The librarian can also search the index journals for titles of particular interest to the matters in hand. In this way more obscure articles are less likely to be missed.

The many other ways in which an alert library staff earns its keep can best be summarized in the statement that investment in a well run library cannot help but be profitable to the research organization.

Service departments. The scientific parts of the research laboratory will have to be supplemented by certain departments organized for service. One such department will probably be that of animal supply. This is particularly desirable where more than one person in the research laboratories uses animals. A centralized animal supply not only leads to increased efficiency in obtaining, feeding, and handling the animals, but also reduces the total expense in comparison to a number of smaller animal colonies. Again, the laboratories will ordinarily depend on the central supply for the animals routinely needed, thus saving the scientific staff from the distraction of supervising the operation of an animal colony.

The laboratory will also require a storeroom for supplies and materials. This may be operated as an extension of the purchasing department, or, at least, will be kept stocked by the purchasing department through one method or another. Certainly a great deal of time of the scientific personnel and some expense can be saved if there is available a purchasing agent, experienced in the types of materials needed for various laboratories, to seek out the most advantageous sources of supply.

Furthermore, a laboratory of any considerable size can readily utilize the services of a glass blower, with a considerable saving in glassware costs. A good glass blower can repair and make glass apparatus, saving his salary many times over, if there is enough work to keep him busy. The avoidance of delay in repairing some kinds of apparatus may in itself represent a considerable source of saving. It is not easy to state at what level of operations a glass blower's services become economically desirable; but in most instances, this can be readily arrived at by

a study of the amount of glass blowing expense incurred by the laboratory and the amount of glassware being bought which might have been repaired or made locally if a glass blower had been available.

Some laboratories may find a machine shop a money saving installation. This will be particularly true in those organizations where there are many people working in the biological field. The biological laboratory equipment which can be purchased through commercial channels is meager in variety, and often-times is poorly adapted for special purposes. The average scientific investigator is not a skilled machinist. If he attempts to develop a special piece of apparatus by personal fabrication, the expenditure of time of this highly paid individual may be more than what it would cost to have the job done by a skilled instrument maker or machinist. Here again the question of the relative cost of a machine shop can be settled only by study of the circumstances prevailing in each individual organization.

Another service function with which a laboratory must concern itself is an accounting department, wherein the time expenditure on various projects is recorded and the costs of various investigations charged off in an appropriate manner. This department should be responsible for seeing that the cost of each research or developmental project is properly segregated so that the director or others responsible can know the expenditures on each at all times. Any system should be designed to avoid burdening scientific personnel with too much detail. Indeed, the time and annoyance caused the research staff in trying to establish with too great exactness the cost of some particular research may be entirely out of proportion to the prospective benefits of such an accurate cost figure. Full appreciation should be shown here to the law of diminishing returns. However, there will be no difficulty in arriving at a reasonable approximation of the cost of each research study if the accounting procedures are devised in some simple well-standardized form. Here, again, the objectives of the organization may modify greatly the amount of attention to be devoted to this phase of the research laboratories' operations.

Finally, among the service functions carried on in the research laboratory, attention must be given to building maintenance. Repairs, janitorial services, and related functions must be directed by some one who preferably is not one of the research personnel; obviously, responsibility of this nature would divert the attention and time of a research worker from his primary functions.

The individual laboratory. The research laboratory as described consists, when fully developed, of a considerable number of individual research units each carrying on more or less specialized functions. At the head of each of these units, there ordinarily will be a "head of the laboratory" who will have doctorate training or its equivalent, although in some instances men with special experience not having academic degrees may serve as very efficient and satisfactory heads of such units. The ability and background of the man is more important than some arbitrary measure of academic training. The laboratory head will ordinarily be assisted by a number of scientifically trained individuals whose number depends upon the type of problem being attacked, the facilities available, and the number of people whom the head can efficiently direct in their researches. These assistants will ordinarily have college training in their special fields of work. Assisting these scientific workers will be one or more laboratory assistants or technicians to help wash glassware, carry on simpler standardized procedures, run messages and errands, and, in general, perform the semi-skilled operations of the laboratory.

It probably is a matter of economy to use as many of these semi-skilled or skilled individuals below the doctorate level as may be efficiently applied to the problem in hand. As a matter of fact, one good scientific worker, with doctorate training, can direct the activities of a considerable number of less highly trained assistants. This will give him extra pairs of hands to carry out the results of his thinking. Within reasonable limits, therefore, the greatest results per dollar expenditure are secured by giving the most highly trained scientist as many assistants as he can efficiently direct. It may be noted that this is one place

where the industrial laboratory differs from university laboratories; in the latter, the problem is usually one of employing or training as many scientists as the limited funds will support, whereas in the former the emphasis is to accomplish the maximum per unit expenditure.

In the light of what has just been said, there will obviously be people of different levels of responsibility and training within the laboratory. Probably, in any but the simplest organization, these differences will have to be recognized by giving appropriate titles reflecting the various levels of responsibility and training. Such titles can be similar to those commonly employed in a university or research institute, although many industrial research organizations have found it desirable to develop a system of titles of their own, since it is not always easy to fit industrial personnel into a framework of rank developed for university academic purposes. The number of different ranks and the titles needed can only be decided in the light of the local situation and the degrees of complexity of the staff.

It probably is desirable, particularly in the early years of a person's scientific career, that he be given an increase in rank at three to five year intervals, in recognition of his growing maturity and experience in his chosen field. However, the basic principle should never be overlooked that a higher rank cannot be considered a substitute for an increase in compensation; nor should one be used to avoid granting a merited increase in the other.

The small laboratory organization. The extensive laboratory organization described in the paragraphs above will only be suitable in its entirety for larger companies. Many smaller organizations will need merely one or a few of the basic units described. For these, the selection of facilities will have to be governed by the projects to be studied. The laboratory can be constituted of as many of the individual working groups as are needed. Since such needs will vary with each setup it is not possible to describe the smaller laboratory in any more concrete terms. In general, it will be a duplication of the larger organization in miniature, with many functions being carried

on by each individual, and with the simplest possible administrative organization needed to promote the total objectives.

Outside collaboration. Some firms will find it undesirable to operate a laboratory or may wish to supplement their own by outside researches. Commercial laboratories are available for carrying on studies in practically all fields. They will formulate programs for investigation, devise formulas, obtain the necessary data and carry projects as far towards completion as may be desired of them. For this service the fee is either a lump sum or a "cost plus" figure, generally fixed to include the costs of the research and a reasonable profit.

Commercial laboratory research may prove more economical and reliable for special purposes than to attempt to undertake it oneself, particularly if a continuous program of investigation is not being carried on. Usually, indeed, it is the most economical way of conducting the short-term project where facilities and staff are not available on a permanent basis.

If the research project or formulation has scientific novelty or real importance, university investigators can often be interested in studying the problem. In these instances, it is customary to make the institution a grant of funds to provide for all expenses associated with the projects. An academic investigator will ordinarily not receive any personal compensation for his studies beyond his regular salary, especially if the studies are to be presented in scientific publications. However, in special circumstances consultation fees may be paid to the investigator when approved by the institution concerned.

TYPES OF RESEARCH AND DEVELOPMENT

The choice of the problems to be studied in the research laboratory is naturally governed by the objectives of the organization. Ordinarily, this is determined by the director after consultation with all those interested or concerned. Some research can be considered as pure exploratory speculative investigation into the unknown. Thus, chemical groups are studied or new materials investigated in an attempt to discover a form

of activity or medicinal power which might be utilized. Indeed, it is only through such "wild-catting" that possibilities are uncovered even though there be no reason to suspect their existence. It is from such experiments that major developments in research occur, opening new fields for exploration and study. In this general group of so-called pure research the risks and uncertainties are the greatest. Nevertheless, the prospective yields, granted a reasonable degree of luck and good fundamental insight, are higher than from the more mundane type of developmental research.

The second type of research consists in the systematic exploration of groups of compounds, where it is known that therapeutic activity already exists. Here, for instance, members of a family are studied to select the optimum degree of activity. The hazards in this type of research are minimal, but the returns correspondingly decreased. A variety of this type of experimental work is the development of formulas to put a medicament, already well understood, into a more favorable form for medicinal use. Much indeed may be accomplished in this way to add to the efficiency and value of products, even though the elements of scientific discovery are not necessarily prominent in the investigations.

In carrying on laboratory studies in the biological field a considerable use may be made of so-called screening tests. These are standardized tests applied to a group of products to test their activity on some physiological function under standardized conditions. Such a screening test may be considered as an exploratory mechanism to determine whether activity of some special kind is possessed by a compound or group. The test oftentimes is designed in such a way that the potency of the compound, in comparison with others of similar nature, can be determined. If a sufficient battery of screening tests can be devised to embrace major fields of pharmacological research, the opportunity is afforded for uncovering activities in unsuspected groups of compounds by submitting all materials under investigation to the screening procedure. Many important compounds have been found as a result of having been screened for activity

in some field quite different from that for which they were primarily prepared.

When activity has been discovered through screening tests or observations, the product or a formula should be studied intensively so that details of its action may be established in all the fields where this may be of importance. For example, an antiseptic known to be able to kill bacteria must, in addition, be investigated to determine whether it has effects on the vital functions of the body before the limitations imposed on its use can be properly evaluated. Since the details of the studies appropriate for elucidation of these facts are set forth in another chapter, this problem can be dropped for the moment.

After the laboratory has studied the application of the drug in question on experimental animals, information probably will be needed as to the prospective dose for human application. Some idea about this ordinarily is obtained from the magnitude of the dose required for animals. However, verification of the human dose must still be had by cautious administration to human subjects in the laboratory. Therefore, as a final phase of the laboratory investigations, some human tests must almost invariably be conducted to establish dosage and degrees of tolerance in a preliminary way before full scale clinical studies on sick individuals are undertaken. The various aspects of such clinical studies will be discussed in detail in another chapter, so that additional discussion on this can be deferred.

USE OF ANIMALS IN RESEARCH

The efforts of scientists to improve health and medicinal agents through animal experiments are continuously hindered by a perverse, but wholly human, resistance on the part of some recipients of the benefits of such labors. The resistance arises largely as opposition by a vocal and well organized minority to the experimental procedures by which new medical knowledge is created. In some cases the motivation is purely emotional, being compounded in part from elements derived from maternal instincts misdirected to lower animals, and in part

from excessive sentimentalism. However, it must be recognized that there are some who actively oppose the major tenets of the scientific method, including even an implied denial that improved health is a beneficent resultant of medical research. United by these motivating forces, small groups have organized to oppose, by all available means, experimental procedures in the fields of medicine and biology involving the use of living animals. Funds have been collected through donations from well-meaning but misinformed individuals. Legacies have provided steady endowment income which a paid secretariat must spend by maintaining a continuous pressure of agitation in the legislative halls of the country. Therefore, it is worth while to summarize in broad outline some of the reasons for animal experimentation in drug development and the justification for this form of procedure.

Life processes must be studied in animal experiments. Differences are very small in the functions of the organs of the common laboratory animals, such as mice, rats, rabbits, cats, dogs and monkeys, from those of man. These animals have the same type of circulation and the same respiratory organs. They take their food into a gastro-intestinal tract that functions very much like man's and uses the same digestive juices. The waste products of their bodies are discharged through excretory organs whose functions mirror accurately those of the human apparatus. When they move, their muscles contract under the control of impulses sent from a central nervous system similar to that of the human in all essential particulars. Since the materials used for energy by these contracting muscles are the same as in the human, the thermodynamics of human conversion of chemical materials into mechanical energy and heat can be studied and understood on the basis of the information obtained from the lower animals. Hence it is that the study of human drug responses in health and disease may be carried out mainly through study of similar processes in laboratory animals.

Before a new drug can be used safely on a sick human being much has to be known of its mechanism of action, of its persistence in the body so that the frequency of dosage can be properly

controlled, and of its side effects to learn whether there might be adverse reactions which would minimize the value of the compound. For every new preparation now used in human or veterinary medicine there are thousands which have been tested and found unsuitable in some essential feature through preliminary experiments on laboratory animals. In some of these studies unsuspected or unpredictable toxic effects have been uncovered. If the application of the drug had been explored only by giving it to human beings, these toxic actions would have resulted, at least, in impairment of human health, and possibly, even in loss of human life. The pharmacologist cannot authorize a drug's administration to either sick or well human beings until all the information which can be obtained from animal experimentation is in hand, and until this demonstrates affirmatively that its use in humans is justified. If animal experimentation were not permitted, there would be no alternative to carrying on wide-spread tests on humans, unless most of our hopes for more effective medication were to be abandoned.

Legal requirements for the use of animals. There are definite legal requirements which compel the use of animals in the development and production of many medicinal agents. The *United States Pharmacopoeia* and the *National Formulary,* the two legal standards for drugs of major importance, specify the criteria for purity, freedom from undue toxicity, and other standards which have to be met before drugs can be distributed. The use of living animals is required for either the production or testing of a very considerable number of drugs by these official volumes. Examples of drugs in this category have been listed below in Table I.

It will be seen that they comprise biological materials, such as serums and vaccines, arsenicals, cardiovascular drugs, particularly in the digitaloid field, and vitamins. Animal tests are required for the standardization and assay of these materials because it has been found impossible to develop satisfactory alternative methods. The animal tests take longer, and generally are apt to be less precise than chemical reactions under

optimum conditions, so that if chemical methods were available, they would be preferred. However, in spite of the best efforts of all concerned, it has not proved feasible to substitute chemical procedures for animal tests on the products listed.

So long as people fall ill with scarlet fever, diphtheria, measles, tetanus, heart failure, rickets, and a lengthy list of other ailments, animals will have to be used to standardize the drugs with which to treat them. Failure to standardize drugs in laboratory animals before human use would simply mean that the assays would have to be done on patients afflicted with these diseases, with a resulting increase in human suffering and misery and an inevitable decrease in the accuracy of standardization.

Food, Drug, and Cosmetic Act requirements of animal experiments. In recent years an additional governmental control mechanism has evolved also requiring that animal experiments be carried out. The Federal Food, Drug, and Cosmetic Act states, in essence, that a new drug cannot be introduced until it has been examined and found to be safe by the Food and Drug Administration. The administrators of this Act are trained investigators who have a special knowledge of drug testing and actions, and who spend much time scrutinizing the evidence submitted. As a matter of standard procedure, they generally require that there be, for each new drug, data on its actions in normal animals, as well as in disease organisms if suitable experimental procedures are available. Therefore, a manufacturer of pharmaceutical agents is not able to introduce a new remedy without first presenting data concerning it derived largely from animal experiments. This naturally has to be supplemented by human tests, where these are possible, but the basic information is initially derived from laboratory work on living animals.

The humanitarian aspects. There are standard humanitarian rules to govern such experimentation, which all laboratories have voluntarily adopted and follow. These rules state, in essence, that all procedures must be carried out under full anesthesia if they are likely to be so painful that they would call for

the giving of an anesthetic if carried out on a patient. In operations in which the recovery of the animal is necessary for the completion of the observations, moreover, full aseptic precautions are taken in just the same way as for the same operation in a hospital. The animals are given the same kind of postoperative care as patients, so that their chances of complete and prompt recovery are maintained to the highest degree. It is ordinary common sense to use all these precautions since, without them, uncontrolled variables may be introduced into the experiment, rendering the conclusions uncertain. A characteristic set of laboratory rules governing the use of animals is given below:

Rules Regarding Animals

I. No animals shall be used which have not been either raised by ourselves or purchased through the purchasing department from regular animal supply dealers.

II. Animals in the Laboratory shall receive every consideration for their bodily comfort; they shall be kindly treated, properly fed, and their surroundings kept in the best possible sanitary condition.

III. No operations on animals shall be made except with the sanction of the Director of the Laboratory, who holds himself responsible for the importance of the problems studied and for the propriety of the procedures used in the solution of these problems.

IV. In any operation likely to cause greater discomfort than that attending anesthetization, the animal shall first be rendered incapable of perceiving pain and shall be maintained in that condition until the operation is ended. Exceptions to this rule can be made only by the Director personally, and only when anesthesia would defeat the object of the experiment. In such cases an anesthetic shall be used so far as possible and may be discontinued only so long as it is absolutely essential for the necessary observations.

V. At the conclusion of the experiment the animal shall be killed painlessly. Exceptions to this rule will be made only when continuance of the animal's life is necessary to determine the result of the experiment. In that case, the same aseptic precautions shall be observed during the operation and so far as possible the same care shall be taken to minimize discomforts during the convalescence as in a hospital for human beings.

Frequency of operative experiments. The erroneous impression is fostered that operative experiments are the common or

invariable way of using animals in the laboratory. However, as a matter of actual fact, operations are generally carried out on only a small percentage of animals utilized. Indeed, for every animal subjected to an operative procedure there may be hundreds observed only in feeding and growth experiments, where the effects of diets, vitamins, and other food constituents are under test. As a specific example, in one research institute, where the problems were broadly representative of medical research as a whole, less than two per cent of the animals were utilized for operative purposes. While the proportions between various types of experiments will be different from one laboratory to another, depending on the problems being studied, it will be a very exceptional laboratory dealing with restricted problems where there will not be many more animals used for non-operative experiments than for other types.

Source of laboratory animals. Commercial raising of most animals for sale to laboratories is carried out on an adequate scale to supply the needs for research under usual conditions. Available generally from such stock raisers are mice, rats, guinea pigs, hamsters, rabbits, pigeons, chickens, ducks, and other species. Animals, such as frogs and turtles, which can be collected wild are also available seasonally.

It has been the general experience that cats and dogs cannot be provided at an economically feasible cost by commercial breeders. Since large numbers of these animals are uselessly destroyed in pounds, a portion of them can sometimes be obtained when local regulations do not interfere. Others may be purchased from regular animal dealers, who obtain their stock by buying up unwanted animals from various sources.

ORGANIZATION OF RESEARCH ACTIVITIES

The more complicated and extensive the researches of an organization, the more necessary becomes some mechanism of classifying the studies under way that they may be efficiently followed and the day-to-day results observed. One method of simplifying this is to have each study set up in the form of an

individual research project. A project is then considered to be the study of a specific problem carried on by a laboratory group, or, if different phases of the project are taken up by specialists in diverse fields, by a series of laboratory groups. The initiation of the research project ordinarily arises from discussions participated in by the executive group of the laboratory. This may result, as we have already stated, from suggestions made by the laboratory staff and evolved in conferences, from scientific reading by members of the organization, or through a multitude of channels from outside sources. A concept of the project and what it involves is then developed through discussion with the laboratory personnel who are to conduct the experiments. It is a good idea to set up the project under a title or a numerical designation at the time it is assigned to a laboratory group or groups for study.

Notebooks. The work in each laboratory on the project must be very carefully recorded in appropriate notes of the day-to-day experiments and results secured. These notes should be kept in some permanent form. Preferably they should be entered in ink in a permanently bound book, so that there is no chance that loose sheets may be displaced or lost. It is also important that all calculations and similar numerical operations be computed only in the notebook in order to allow a check on the accuracy of the calculations if desired later. All experienced in laboratory work have had occasion to wish that they were able to return to the calculations involved in taking some quantity of a drug or chemical to determine whether a mistake in weighing or calculating required amounts was made. An aberrant result may appear in a series of experiments which could easily be explained by a mistake in the amount of drug or chemical. After the experiment is concluded, however, there is no way of checking back on this if the weighings are not recorded as part of the notes of the experiment, and the calculations governing the quantities taken are not preserved. Perhaps incorporating these calculations as part of the permanent notebook record does not add to the neatness and elegance of the laboratory notebook, but it makes it so much more valuable as a record of what

actually was done as to excuse the untidy appearance as a minor consideration.

It should be pointed out that, where patent rights or other similar property values may be involved in the research, these laboratory notebooks are an almost indispensable part of the record of the case. Whether an individual laboratory notebook is kept for each project by each man working on it, or whether one man has a notebook which includes all his laboratory activities must depend on local circumstances. Certainly, if a man is working on several projects simultaneously, as may sometimes be the case, there is something to be gained by having a special notebook for each project so that all the data on the subject are consolidated in one place.

Progress reports. The research data should be summarized periodically in formal progress reports to the laboratory heads and to the executives of the research department responsible for coordinating and integrating the various phases of the attack on the problem. The optimum interval between these reports will vary with the kind of researches, but it is probable that only in exceptional instances can regular periodical progress reports be dispensed with entirely. Certainly, only in the smallest research organizations, where everyone is able to keep in intimate touch with all that goes on from day-to-day, will periodical summaries be unnecessary.

These reports have a great additional value to the investigator in permitting the evaluation of the status of a problem by those working on it at regular intervals. It too often happens that investigators fail to organize their study in such a way that the most efficient and logical approach is followed. Having to write a report on the status of the project while it is still in progress will occasionally uncover unsuspected areas where data are inadequate; and is almost sure to result in more efficient prosecution of the entire study than if this detailed evaluation is left until later when the project is considered to be complete.

Naturally, the results will be assembled at the conclusion of the study by a final report summarizing the whole project and presenting the findings *in toto*. This will largely be based on

the progress reports, if these have been written carefully and are in an appropriate form. These reports are particularly useful where work on a project is going on simultaneously in more than one laboratory, or under the direction of more than one specialized group. In these instances they serve to keep all informed of the advances achieved by their colleagues, thereby assisting in the correlation of the work going on throughout the organization, and sometimes resulting in helpful suggestions from those only secondarily concerned.

PREPARATION OF RESEARCH SUPPLIES

An important part of the research laboratories' function is to prepare the material needed for research by the various laboratories or outside investigators. This may involve the actual synthesis *de novo* of the chemical compound, if the product involved is not available through commercial sources, a task ordinarily carried out by the synthetic organic chemists. The accuracy of their synthesis and purity of their product are determined by regular organic analytical procedures.

When the basic ingredients of a formula are available, then the research material will be compounded in an appropriate pharmaceutical form by the pharmacy research laboratories. As we have noted, the experience thus gained in making the product on a small laboratory scale will form the basis for full-size commercial production. It is much easier, of course, to resolve difficulties of synthesis or formulation when working with small laboratory batches than to have to deal with them when large and expensive commercial size batches of material are involved.

The point at which the size of the research material production becomes too large for the research laboratories to handle is a matter peculiar to each specific case. Extensive research material, such as may be needed for a wide clinical study of a potentially valuable new compound, may require manufacture of practically full-size commercial batches. If the formula has been properly developed on a small scale in the research labora-

tories, the regular commercial production equipment can usually be used for the research order without too much difficulty, thus contributing added experience regarding the problems which may be encountered in full scale operations.

Ordinarily, it is not necessary to insist that a complete and perfect formula be available at this research stage of the studies, inasmuch as this may necessitate an expenditure of effort out of proportion to the needs for preliminary tests. This is particularly true when it is realized that possibly only one out of every ten products sent out for clinical study eventuates into an item subsequently made as a routine commercial product. Judgment should, therefore, be exerted at this point to determine how far the efforts to complete the formula should be carried without running into a fruitless amount of extra effort. Naturally, if it is certain that the item will be made a matter of commercial production, then at this research order stage a completely satisfactory formula should be developed and no efforts should be spared to insure that this objective is obtained.

It is necessary also to bottle, package, label, and carry out the other necessary portions of finishing the product for distribution even on research materials. In some cases this presents problems for solution and at the same time provides answers which will be used eventually for the commercial process. An example of this might be the problem of selecting the proper glass for a bottle or ampul, or stoppers for a solution.

Although it will be discussed in detail in another chapter, the point should be made at this time that research material cannot be distributed to outside collaborators unless formal releases, couched in the language of the Federal Food, Drug, and Cosmetic Act have been obtained that the material is to be used solely for experimental purposes by qualified investigators with facilities for carrying out the necessary experiments. This is a separate problem from securing Food and Drug Administration clearance for commercial distribution.

DEVELOPMENT OF CONTROL METHODS

The research laboratories have the opportunity to develop experience in the procedures needed for control of the purity, sterility, strength, and other factors of prospective new commercial material. It is necessary that every formula which may be sent out for medicinal use be analyzed chemically before it leaves to determine that the material sent out is authentic and of appropriate purity. Evidence is also needed in some cases that it is of correct potency. In addition, many types of materials, particularly solutions intended for injection, must have bacteriological releases to establish that they are sterile and, therefore, not apt to induce infection when injected. The research laboratory should be under obligation to see that such control tests as may seem desirable are carried out on the article even while the product is still in the research stage. Such analyses or determinations may be done in laboratories specially equipped for the purpose, or, if it is more suitable, they may be carried out by the regular control laboratories of the organization.

If these determinations involve development of new methods, as frequently may be the case with a new product, it ordinarily will be better to have the control methods developed by the research staff, who can take the time to develop the specifications and analytical procedures in a more leisurely atmosphere than that which the regular control department is apt to enjoy. Such preliminary control experiments can then be embodied in tentative specifications and submitted at an appropriate time to the official control group in the organization for their acceptance or modification in any desirable direction. Thus, through the combined efforts of the research and regular control staffs, a more thorough consideration of the entire problem of appropriate control requirements is obtainable than if this were left to the last moment to be settled while the organization is under pressure to produce the material commercially for distribution with a minimum of delay.

The individual types of determinations needed for the control of drug products can only be settled by considering the problems involved for each individual item. Chemical tests to establish the identity of the material are indispensable, although they may be only qualitative where quantitative methods are not available. Feasible quantitative chemical determinations, moreover, will help to establish the degree of purity or the concentration of the compound in question. It should be a matter of routine to determine that important toxic materials, such as heavy metals or alkaloids, are not present in a preparation if they represent contamination.

The pharmacological laboratory may study the potency of the products in terms of some measurable response of the living organism. In the case of a drug like epinephrine, for example, this might be the blood pressure raising power. In the case of a vitamin, it could well be the potency in relieving the symptoms of vitamin deprivation in a suitable laboratory animal. Hormones may be studied for their power to affect some one of the bodily functions with which they are directly concerned. These tests should be selected judiciously in conjunction with consideration of the type of information that may be needed on the product in question.

The bacteriological approach to control may require phenol coefficient determinations, or some other test of antiseptic power if the phenol coefficient is not desirable or applicable. Sterility determinations will be required on a great variety of both solid and liquid materials to demonstrate that bacteria are not present, or, in the occasional product where complete sterility is not required, that the bacteria present are in acceptably small numbers, or are of unobjectionable varieties. Not only bacteria, but molds and fungi must be looked for, since these have the power of making a product unsuitable for use just as easily as does bacterial contamination. Here again, the bacteriological specifications are set up only after critical evaluation of each special situation, fortified by the experience gained in manufacture of experimental batches at the laboratory level.

COST ACCOUNTING

Almost all places doing research under commercial auspices and many of those carrying on development of medicinals under philanthropic or university conditions are, or should be, concerned with the true cost of the work conducted. In industrial fields, this is a matter of real importance, inasmuch as the cost of studies must bear some realistic relationship to the prospective value of the results that may be obtained.

It obviously is practically impossible to set up a rigid budget for the solution of a research or development problem. The reason for this is that the process of scientific discovery is unpredictable. No one can tell at what precise time in the future some member of the laboratory staff will have that flash of genius which constitutes discovery of a new drug, and therefore be able to predict the amount of money which must be expended on the research. However, the larger the scale of operations, the greater leeway there is for readjustments of the cost of individual projects, since the closer is the approach to normal expectation of accomplishment per unit expenditure. The most that should be attempted is probably to fix a reasonable estimate for the project in question. This is governed by the size of the market of the prospective product and the tentative estimate of the earning power of the discovery. After such a budget has been established, and the funds expended without completing the project, it becomes a matter of careful evaluation whether additional funds should be provided or whether it should be abandoned as being unpromising.

The mechanism whereby records of costs are maintained will vary with the type of bookkeeping system used in each laboratory. If the suggestion given above is followed of pursuing individual research problems under headings of specific research projects, then charges of time and supplies, etc., can be made on the books against each project as they are incurred.

Commercial organizations will have to include in these charges appropriate items for over-head cost, building mainte-

nance and service, amortization of equipment, and related items, beyond the obvious day-to-day dollar expenditures. These are a true part of the research cost; they should be considered at all times as an essential and important part of the total expense picture. It probably is desirable to charge off to current operations at the time of purchase materials which are consumed or destroyed in the course of the studies. Included in this naturally are such items as animals, chemical supplies, glassware, and related articles. Cost of equipment which is used over and over again can probably be considered as a permanent capital expenditure to be amortized as part of the over-head costs of the laboratory. Balances, refractometers, electric furnaces, incubators, and similar equipment are examples of items of this type.

Whatever the accounting system may be, it should be developed in such a way that the demands on the time of the scientific laboratory staff to operate it are reduced to a minimum. It is not economical to ask the laboratory head to carry out any more bookkeeping than is necessary to provide the minimum information needed by the accounting office to carry out its functions. This may be put differently by saying that the cost accounting system must not be made so laborious that the time spent on it is out of proportion to the possible benefits which might accrue from the use of the information.

SCIENTIFIC CONTRIBUTIONS

A scientific or research worker lives and satisfies his fundamental instincts by winning the approval of his scientific colleagues. He obtains this recognition by participating in the activities of scientific societies, through attendance at their meetings, working on their committees, and discussing papers in which he has special knowledge and interest. The worker who is really productive also has material of his own to contribute in the form of scientific papers, reports, or reviews. Such writings should be stimulated, because it is through such appearances that the scientific prestige of the organization is advanced and that the discoveries of the laboratory become

available for use by others to the general benefit and public welfare. Therefore, every scientific worker should be given the opportunity of attending and participating in scientific society activities and in the presentation of papers at the meetings or in publications to the full extent which his scientific training may render possible. For this purpose the laboratory must provide financial support in the form of traveling expenses and living costs while at such meetings.

The frequency of attendance will depend upon the special circumstances in each case; it ought, however, be at short enough intervals to make each worker feel that he is not kept secluded from contact with fellow workers in his field. The same type of situation applies to the meetings of various trade associations, since in these are discussed matters of industry-wide importance, which are unlikely to come before the more scientific discussions of research societies.

To some the opportunity will be provided of participating in *United States Pharmacopoeia* or *National Formulary* deliberations.[1] These are an invaluable part of the scientific activities of the organization, and should be fostered by every available means. Those not in commercial organizations may also be called on to assist in various professional and semi-legal affairs, such as those of the Council on Pharmacy and Chemistry of the American Medical Association, the Therapeutic Trials Committee of the American Medical Association, the Council on Dental Therapeutics of the American Dental Association, and other organizations of like interest. Participation in these activities is an honor which should be welcomed by everyone working in the field of medicinals. Every laboratory should encourage such work to the maximum.

Table 1

DRUGS LISTED IN THE UNITED STATES PHARMACOPEIA XIII AND NATIONAL FORMULARY VIII, FOR WHICH USE OF LIVING ANIMALS IS REQUIRED FOR THE PRODUCTION OR STANDARDIZATION

Drug	*Living animal from which normally obtained*	*Living animal used for potency test*	*Living animal used for safety test*
Serums and Specific Biologicals			
1. Diphtheria Antitoxin	Horse	Rabbit Guinea pig	Guinea pig Mouse
2. Diphtheria Toxoid	—	Guinea pig	Guinea pig Mouse
3. Diagnostic Diphtheria Toxin	—	Rabbit Guinea pig	—
4. Scarlet Fever Streptococcus Antitoxin	Horse	Human Rabbit	Guinea pig Mouse
5. Scarlet Fever Streptococcus Toxin	—	Human Rabbit	—
6. Citrated Normal Human Plasma	Human	—	Guinea pig Mouse Rabbit
7. Human Immune Globulin	Human	—	Guinea pig Mouse Rabbit
8. Normal Human Serum	Human	—	Guinea pig Mouse Rabbit
9. Human Measles Immune Serum	Human	—	Guinea pig Mouse Rabbit
10. Human Scarlet Fever Immune Serum	Human	—	Guinea pig Mouse Rabbit
11. Tetanus Antitoxin	Horse	Guinea pig Mouse	Guinea pig Mouse Rabbit
12. Tetanus Toxoid	—	Guinea pig Mouse	Guinea pig Mouse Rabbit
13. Antimeningococcic Serum	Horse	Mouse	Guinea pig Mouse Rabbit

Drug	*Living animal from which normally obtained*	*Living animal used for potency test*	*Living animal used for safety test*
Serums and Specific Biologicals			
14. Antipneumococcic Serum	Horse Rabbit	Mouse	Guinea pig Mouse Rabbit
15. Typhoid Vaccine	—	Mouse	Guinea pig Mouse Rabbit
16. Typhoid and Paratyphoid Vaccine	—	Mouse	Guinea pig Mouse Rabbit
17. Rabies Vaccine	Rabbit	Mouse	Guinea pig Mouse Rabbit
18. Smallpox Vaccine	Calf	Rabbit	Guinea pig Mouse Rabbit
19. Old Tuberculin	—	Human Guinea pig	Guinea pig Mouse Rabbit
Gland and Organ Derivatives			
20. Liver Extract	—	Human	—
21. Suprarenal	—	Dog	—
22. Epinephrine Injection, and Solution	—	Dog	—
23. Insulin Injection	—	Rabbit	—
24. Parathyroid Injection	—	Dog	—
25. Posterior Pituitary Injection	—	Guinea pig	
26. Powdered Stomach	—	Human	—
Vitamin Preparations			
27. Cod Liver Oil	—	Rat	—
28. Halibut Liver Oil Capsules	—	Rat	—
29. Oleo Vitamin A Capsules	—	Rat	—
30. Synthetic Oleo Vitamin D	—	Rat	—
31. Concentrated Oleo Vitamin A & D Capsules	—	Rat	—
32. Rice Polishings Extract	—	Rat	—
33. Hexavitamin Capsules	—	Rat	—

Drug	*Living animal from which normally obtained*	*Living animal used for potency test*	*Living animal used for safety test*
Parenteral Fluids			
34. Water for Injection	—	—	Guinea pig Rabbit
35. Isotonic Sodium Chloride Solution	—	—	Rabbit Guinea pig
36. Ringer's Solution	—	—	Rabbit
37. Dextrose Injection	—	—	Rabbit
38. Dextrose and Sodium Chloride Injection	—	—	Rabbit
39. Anticoagulant Sodium Citrate Solution	—	—	Rabbit
Arsenicals			
40. Arsphenamine	—	—	Rat Rabbit
41. Neoarsphenamine	—	—	Rat Rabbit
42. Sulfarsphenamine	—	—	Rat Rabbit
43. Tryparsamide	—	—	Rat Rabbit
Cardio-Vascular and Muscular Agents			
44. Ergot, Fluidextract, Extract	—	Rooster	—
45. Digitalis, Capsules, Powdered, Injection, Extract, Tablets, Tincture	—	Cat	—
46. Ouabain Injection	—	Frog	—
47. Strophanthin Injection	—	Frog	—
48. Strophanthus Tincture	—	Frog	—
49. Apocynum	—	Cat	—
50. Convallaria	—	Cat	—
51. Aconite, Fluidextract, Tincture	—	Guinea pig	—
Antibiotic Agents			
52. Penicillin	—	—	Rabbit Mouse
53. Streptomycin	—	—	Mouse Rabbit

5

Development of Biologicals

CHARLES R. LINEGAR

THE history of the search for the means of treating the ills of man presents interesting chapters in the book of life. In olden days the treatment of pain and discomforts lacked rationale because the basis of the malady was only dimly, if at all, comprehended; hence practices, such as witchery, black magic, and sorcery to drive the evil spirit from the body of the afflicted, the mysterious art of alchemy, appeasement of supposedly angry idols or divine gods, and blood letting dominated ancient therapeutic practices. But, interestingly enough, throughout the ages, various potions, concoctions, and mixtures from plants and minerals were employed for external or oral administration by various peoples. Knowledge of these preparations was usually handed down through families and tribes and was gradually disseminated as civilizations spread. With the advent of chemistry and pharmacy, many new preparations, notably new galenicals, were added to the armamentarium of the therapeutist. Yet treatment remained largely empirical, because the action of these drugs was obscure and the causation of most diseases was still unknown. Those preparations, later discovered to have a scientific basis for use, have stood the test of time; indeed, they are still used in therapeutics.

The development of the science of bacteriology and the remarkable advances made in the other medical sciences, many within the last few decades, have uncovered a mass of scientific facts about the etiology, symptomatology, effects, and treatment of most diseases. Even to the layman it is evident that the civilized world has made great strides in the knowledge and distribution of useful medicinal agents. A considerable share of this

is attributed to our ever-increasing understanding of normal physiological functions and processes, of the changes wrought by physiological imbalance, improper nutrition, infection and other diseased conditions, and of the action of drugs upon certain tissues of the body in both the normal and the pathological state. Yet, despite these acknowledged advances, daily progress still makes it evident that many gaps remain in our present knowledge. Little is known, for example, about the actual processes within the various cells, how disease brings about changes in their function or form, or, in fact, precisely how drugs act upon them. Hypotheses and beliefs about certain diseases are repeatedly revised with new advances. Notwithstanding, the etiology of some currently recognized diseases is unknown; nor has an effective prophylactic or therapeutic agent yet been discovered for their treatment. Indeed, it is not too much to say that although many drugs and therapeutic practices of today will be utilized for years to come, nevertheless, a number that are popular today will be discarded in the future; others will be modified, either gradually or rapidly, in pace with developments in scientific thinking and understanding.

Botanists have traveled to all parts of the earth in quest for natural drugs of plant origin; indeed, remedies are still being sought in the almost inaccessible jungles and realms uninhabited by the white race. As plants were identified, chemists have analyzed them for natural active principles. In addition, they have made and are continuing the synthesis of thousands of man-conceived compounds to find therapeutically valuable agents. Similarly, mineralogists have searched the waters and ventured over the face of the earth for nature's contribution to materials for the treatment of disease. As the search goes on, hitherto neglected sources have come belatedly to the front.

It has been known for a long time, moreover, that parts of the animal bodies have curative properties. Despite this knowledge, certain tissues of animals, such as pituitary, thyroid and suprarenal glands, lungs, and stomach, were, until recently, discarded as waste and scraps at the abattoirs. Today these serve as impor-

tant raw materials for biological preparations, great care being taken in their selection and preservation. Equally well known was bacterial antagonism or antibiosis, but it was not until the recent application of the antibiotic action of penicillin in therapeutics that this field of endeavor really gained impetus. Antibiotic agents, however, were antedated some years by the production of certain antiserums, vaccines and other immunizing agents, still employed against specific infectious diseases. Also of recent origin has been the discovery of vitamins which are of great value for the treatment of certain deficiency diseases, such as beri-beri, scurvy, and pellagra. The tremendous concentrated work fostered during World War II on blood products, and various other therapeutic agents, is to be heralded as another triumph of scientific investigation. Other equally fundamental studies, albeit at a somewhat slower pace, are being continued as science marches forward.

DEFINITION OF BIOLOGICALS

"Biologicals" may be regarded in a very broad sense as prophylactic, diagnostic, and therapeutic organic medicinal preparations derived from or elaborated by cells or tissues of animal or plant origin, the latter class including products of viral, bacterial, or fungal sources and therapeutic serums prepared by use of such materials. Some authors also classify in the biological group those chemical substances, such as arsenicals, that are evaluated for their potency or toxicity in animals.

This group of medicinals is usually marketed in a semi-purified state, but it may also be represented by completely or highly purified organic substances or by materials which have been practically unaltered from the raw material stage to the finished package. They are prepared either in a dry form or dissolved or suspended in a suitable liquid or semi-solid medium, usually containing a preservative. Most of them require parenteral (*i.e.*, subcutaneous, intramuscular, intravenous, or intradermal) administration, although some are suitable for enteral (oral) usage and others for topical application. The

active ingredients thus far identified constitute a wide variety of organic compounds; others have not been identified or even classified as to type.

THE DEVELOPMENT PROCESS

The purpose of this chapter is to present briefly a number of the general problems of biological development and to list some of the test and control procedures utilized in evaluating and standardizing representative biological preparations rather than to discuss the development of all known biologicals.

"Biological Development" * comprises not only the introduction of entirely new biological products but also includes the modification, refinement, or improvement of products now marketed, in order to extend their application or to better their appearance, stability, or efficacy. This involves sufficient testing of raw materials, intermediates, and final products by various means to assure their safety, stability, and performance; it is concerned with the choice of dosage form and size as well as suitable containers and preservatives for the final product.

Development is, in the main, a long and tedious process, requiring imagination, ingenuity, integrity, rational and clear thinking, and basic scientific knowledge; it can be speeded up, but it cannot be rushed; nor seldom do great discoveries result from fortunate accidents. Regardless of the complexity or simplicity of the various problems, the development of each new or modified product encompasses certain fundamental processes or investigations which must be considered for each preparation depending upon its nature and intended use. If satisfactory information is available regarding parts of or some of the steps in the following general schema it may be accepted without further investigation; otherwise the biological investigator must:

* The terms "development" and "research" have caused confusion and can be explained simply as follows:—The directive of development is the production of a drug for sale while that of research is to study drugs from an academic point of view with no regard to saleability. In both, the same basic methods of study are employed and the terms can be used interchangeably if the directive is kept in mind.

(*a*) conceive the idea for the new or modified preparation;
(*b*) select the best source for the ingredients or ingredient of the tentative preparation;
(*c*) find ways and means for obtaining the active principle in usable form by various procedures, such as bacteriological, chemical, physico-chemical, or biochemical, and, if possible, identify it by chemical, biological, immunological, therapeutic, or other means;
(*d*) investigate acute and chronic toxic signs and symptoms, local irritative effects, duration of action, rate and manner of elimination, cumulative tendencies, sensitivity reactions, amount of tissue damage following varying dosage levels, and, if the preparation is inherently toxic, the cause of death from overdosage;
(*e*) determine the mode of action and efficacy of the active materials;
(*f*) compound the preparation and determine its proper dispensing form (including container) and learn its stability under various conditions;
(*g*) institute and develop adequate tests on the preparation for potency, toxicity, pyrogenicity, etc., to acclaim it safe for clinical trial, and prepare labels for it in keeping with known regulations or practices; and
(*h*) initiate clinical trial, and aid in evaluating the results.

The experimental group should plan its general project in detail, making a tentative outline of different phases of the problem and constantly realigning its perspective as new data are accrued. Since most developmental problems require the application of scientific procedures from diversified fields, the investigator ordinarily collaborates with other specialists unless the job is a comparatively simple one.

THE ORIGIN OF THE DEVELOPMENTAL PROBLEM

It is obvious that the forerunner of a developmental project is the idea, *i.e.*, the problem under consideration and the vari-

ous approaches to it. Although the useful application of the idea cannot always be ascertained at once, a fairly good conception of its potentialities should be formulated before the work is started.

The origin of the developmental projects comes about in various and sundry ways. Dabbling with primitive notions and superficially examining various materials in a trial and error fashion is not a scientific method of development; however, despite this fact good products occasionally have been discovered this way. Extraordinary unexpected discoveries have been made during planned experiments by investigators keen enough to note and appreciate the importance of unusual or irregular results. In some instances, a clinician or a fellow worker, who is interested in or has need for a new or modified product, but does not have time or facilities to complete the work, makes the suggestion. In certain cases the rights for undeveloped or semi-finished potential products are bought and development is completed. A number of ideas are gleaned by careful review of published articles on various subjects. Some are obtained by furthering a fellow scientist's chance remark or counsel, and others are pure and simple hunches based on a small amount of factual information. Probably the most fruitful source of developmental problems comes as part of a carefully planned general program which, as it is developed, leads from the original goal to one side issue after another and then to other entirely new developmental projects.

Regardless of how the idea for the problem is born, the developmentalist usually saves his enthusiasm until he finds that it gives promise, for there is ordinarily a long and frequently a rocky road between the origin and completion of most projects. It is a wise move to record the names of the individuals responsible for, and the date of the suggestion of, each problem in order to clarify the inventorship for possible future patent rights.

SOURCE OF MATERIALS

The raw material for the manufacture of biological products usually comes from animal tissues, blood, urine, and milk; human tissues (placenta), blood and urine; plant material, micro-organisms and products formed by them; or chick embryo cultures. Most of these materials may be found domestically; some, however, are cheaper and more readily obtainable, or, indeed, are found only in foreign markets. Other materials in frequent use, such as preservatives, stabilizers, buffers and agents for adjusting tonicity and acidity, are generally available.

The final selection of the source of raw materials should take into consideration not only relative cost, availability, and active principle content, but also ease of recovering the active ingredient, its solubility, stability, and toxicity, and the side actions of impurities carried along with it by different methods of preparation. The latter factors are usually not ascertained until a considerable number of chemical, biological and other tests have been made on material from various sources.

IDENTITY AND PURIFICATION OF THE ACTIVE PRINCIPLE

When investigating the potentialities of a new preparation, as much chemical and physical knowledge as possible is obtained at an early stage in its development. Thus, an attempt should be made to isolate the active ingredient so that it can be identified into a chemical class. Since the raw materials used for the manufacture of biologicals are generally rather complex in composition and frequently the active ingredient may be easily destroyed, the individuals attacking the problem of separating essential from inert substances must be highly trained in the handling of such materials. The methods employed vary with different materials and usually involve known or specially devised chemical, physical, physico-chemical, biochemical, or bacteriological procedures.

By the use of these methods it is sometimes possible to isolate in pure form the active principle of a new raw material, and even to ascertain its empirical formula or to determine its chemical structure. In other instances, methods may be discovered for partial but not complete purification of the active ingredient. Many such partially purified biological preparations have been satisfactorily used in therapeutics even though chemical identification of their active substances may not have been accomplished. Sometimes all attempts at purification fail because the original activity of the material is almost completely lost by deterioration of the active substance. In this case the material has to be used in the original state, or if for some reason its use is unsatisfactory, further development is stalled pending determination of new methods of purification.

When published methods of purification of the active principle of a raw material exist, of course, the primary task is to verify these, or to determine whether they are suitable for the degree of purification needed for the type of preparation under consideration. Regardless of whether methods of recovering the active ingredient are previously known or are newly worked out, preparations from available raw materials are made and must be subjected to considerable animal investigation before any one of them can be finally accepted as suitable for clinical trial.

When an active material is purified there is, in many instances, a decrease in local irritation or pain upon injection, sensitivity or side reactions, and toxicity. Likewise, studies of toxicity, effective dosage, mode of action, irritative effects, and safety are sometimes more accurate and usually more reproducible from batch to batch on fairly pure material showing good activity. Even though a partially purified preparation appears to be usable, a high degree of purification is often attempted for comparative studies. If parallel experimental investigations on the materials of high and low purity exhibit decided differences in favor of the former type, greater purification is definitely indicated.

Although the tendency in therapeutic preparations is toward

greater purity, this may be limited by increased cost due either to a longer processing time, to the necessity of using more equipment and agents for processing, or to a considerable loss in total activity. It may occasionally be undesirable to purify beyond a certain stage because of decreased solubility or efficacy of the final preparation. Again, if the cost of high purification is prohibitive and less pure preparations are proved by therapeutic use to be as efficacious and stable without causing objectionable side reactions or sensitivity, a high degree of purification is not warranted.

The steady improvement in the marketed product penicillin during a short period clearly illustrates what can be accomplished by intense and continued effort on the part of developmental groups. The first crude penicillin manufactured had a potency of about 50 units per mg.; it was used clinically before appreciable knowledge of its chemical properties and constitution existed. Now it is known that at least four penicillins, predominately G, F, K, or X, can be made by different manufacturing processes and each in pure form has a different potency in units per mg. Penicillin has been manufactured on a large scale and distributed as sodium, potassium or calcium salts at a potency representing over fifty per cent of total purity. Penicillin "G" has now been synthesized although it was first crystallized in the laboratory some time previously. Today highly purified crystalline penicillin "G," of which the sodium salt has a potency of 1500 to 1667 units per mg., is being produced commercially. With this remarkable increase in purity of the manufactured product, there has been a decided improvement in its stability, and a decrease in the number and degree of irritative reactions following its therapeutic use. The story of improvement in the quality of certain other biological drugs is equally dramatic.

SOME GENERAL PHARMACOLOGICAL METHODS OF TESTING

Although the effects of drugs on man are not always the same as those on the lower animals, experiments on the latter are

necessary and useful in screening harmful preparations, in evaluating the relative toxicity and effectiveness of new therapeutic agents, and in discovering their mode of action. Before animal experimentation is begun, the material, insofar as its properties permit, should be prepared for injection, oral usage, or surface application in a convenient, uniform, and practical form by use of solvents or dispersing media of low toxicity and minimal irritative action. The procedures followed in the biological studies depend upon the nature and form of the preparation and, in part, upon its intended therapeutic use. These include studies of local surface applications, and of systemic effects following oral, intravenous, subcutaneous, intramuscular, or intraperitoneal administration, even though the last method is rarely employed clinically. The oral route of administration is, in fact, usually preferred by the clinician for preparations that have a uniform and predictable action by mouth, hence a study is made of the relative effectiveness of practically all new preparations by the oral versus the parenteral routes in animals.

Many biological preparations are ineffective orally because they are poorly absorbed or are inactivated to a great extent by the stomach acidity, intestinal alkalinity, or enzymatic activity and therefore have to be given by one of the parenteral routes. The choice of injection route is usually indicated by the results of the biological studies, e.g., *(a)* if the drug is peculiarly toxic intravenously, causing hemolysis, flocculation, severe fall in blood pressure, etc., it may be given by other parenteral routes, *(b)* if it is too irritant subcutaneously, intravenous or intramuscular administration may be satisfactory, and *(c)* if it is too damaging to the tissues locally by both the subcutaneous and intramuscular methods, sometimes it is possible to give the preparation intravenously. When injected into the blood stream in significant quantity, suspended insoluble material or oil preparations may form emboli, blocking small vessels in various vital organs. Consequently, if such preparations are to be administrated parenterally, intravenous use is not advocated; however, it may be studied experimentally to determine the

effect of an inadvertent intravenous injection. If the medicinal is to be applied topically, for example, to the conjunctiva, upper respiratory tract, bladder, urethra, vagina, abraded skin, or open wounds, its irritative effects on the types of surfaces recommended for clinical use and also the toxicity and the activity of its ingredients are investigated.

If a drug is combined with new materials or vehicles to facilitate its administration, to alter its type of action, change its absorption rate, prolong its effect, or to stabilize the preparation, a study of all untested components is required, as well as of the complete preparation including the active principle. These combinations may be illustrated by such preparations as peanut oil and white wax mixed with penicillin to prolong its therapeutic blood level, or by globin hydrochloride combined with insulin to increase the duration of its blood sugar lowering effect. Even if the principles, penicillin and insulin, have been thoroughly investigated, these combinations constitute new preparations for study.

Although a new drug may be exceedingly toxic, nevertheless it may still be usable in therapeutics if its activity is sufficiently great to provide ample safety. The first experimental investigations on a new drug are therefore directed towards a measurement of its toxicity in short or long-term experiments, including the amount of tissue damage, and of its effectiveness by various routes of administration. The range for toxicity studies covers the dose which produces no detectable reactions *(nontoxic),* that which causes toxic signs or symptoms but no deaths *(tolerated dose),* and that which results in deaths up to 100 per cent of the animals used *(lethal dose).* The effective dose is that quantity of drug just producing a desired physiological response *(minimum effective dose* = MED*),* or cure of a particular disease entity *(minimum curative dose* = MCD*).* The comparison of toxicity and effectiveness of a drug should be studied in more than one species to avoid drawing false conclusions on results obtained in a species showing a high degree of tolerance or sensitivity. The ratio between toxic and effective dosage is the criterion by

which safety of a preparation is measured; the higher this so-called therapeutic ratio, the greater is the safety of the drug.

ACUTE TOXICITY

The onset of mild to severe toxic manifestations in a relatively short period of time following a single or a few repeated doses is considered acute toxicity. It may be exhibited by some drugs in very low dosage; in others moderate dosage brings about these reactions; while in yet others a very high dosage is required. A few substances are nontoxic in the largest dosage feasible to administer by any route. When a common endpoint is used to compare the size of the toxic doses of a particular preparation it is found that these vary according to the route of administration. The intravenous toxic dose is usually the smallest because there is no loss or delay in getting the drug into the blood stream. Conversely, the oral toxic dose is ordinarily the greatest since absorption may be incomplete and hence take longer than by the other routes, and varying degrees of inactivation or destruction of the ingested material may occur. It will be found that the subcutaneous and intramuscular toxic doses are generally between these two in size.

For purposes of uniformity in comparing the toxicity of various drugs, the toxic or lethal doses in different species of animals is expressed on the basis of body weight rather than per animal in order to compensate for variations in weight within a group and between species. In spite of this refinement, however, differences in toxicity are frequently found between species due to variations in metabolic rate and processes, in function or sensitivity of affected tissues, or in elimination and detoxifying mechanisms. Usually the lethal dose (per kg.) for small adult animals, such as mice, rats, and guinea pigs, is somewhat greater than that for larger species, and in general the lethal dose for young animals is ordinarily somewhat less than that for adult animals of the same species. Moreover, the normal variation in sensitivity or resistance causes individuals even of a carefully selected group of animals of the same species to display different

reactions to the administration of a drug although given by the same route and at the same dose level. Therefore, a considerable number of animals of each species is required for accurate determination of the average response to a given dose.

In comparing the acute toxicity of various drugs, the mean or 50 per cent lethal dose (MLD or LD_{50}) obtained in a particular species by the same route of administration is frequently utilized. However, it is obvious that the chance of finding a dose which kills within a limited period exactly 50 per cent of a group of animals is remote. Consequently, this dose has to be estimated or calculated from dose-mortality data covering the range usually of 10 to 90 per cent deaths. Ordinarily zero and 100 per cent mortality values cannot be used for calculation of the LD_{50} because several low dosage levels may cause no deaths while doses surpassing the level causing 100 per cent deaths should kill all animals. For statistical evaluation of the LD_{50}, the per cent deaths as an arithmetic or probit value * is plotted against or correlated with the arithmetic or, usually better, log-arithmetic dose per kg.

The type of graph chosen for this evaluation is the one giving the straightest line for the data obtained and the best line of fit for the points plotted is calculated using the "least squares" method or determined by inspection. The mean lethal dose (LD_{50}) is then read from this line by estimation or is determined by calculation. In like manner the minimum lethal dose, such as LD_0, LD_1, or LD_5, or the maximum lethal dose, such as LD_{99} or LD_{100}, are determined by extension of this line, provided points were obtained within a reasonable distance of the values sought. For adequate evaluation of the results the variation of the group response must also be expressed. The reliability of any desired value, moreover, is not only dependent upon the number of animals used, but also upon the correlation between dose and effect, and it is usually expressed as the standard error. The minimum, mean, and 100 per cent toxic doses may be obtained from similar analysis of data in animals receiving doses causing

* For explanation of the latter, see C. I. Bliss, *Ann. Appl. Biol.* 22: 134, 1935.

toxic symptoms but no deaths, for example, insulin convulsions in mice.

Often the toxicity estimation becomes a method of bioassay for certain preparations. For example, a special adaptation of this is found in the assay of potency of such products as antitoxins and digitalis preparations. Thus, the potency of an antitoxin is found from its ability to neutralize the toxicity of a definite amount of its specific standardized toxin. For the standardization of official toxins, a slight excess of toxin is mixed with its respective standard antitoxin so that following injections of the mixtures into animals a definite endpoint is obtained. The L+ test dose, in the case of standard tetanus or diphtheria toxin, is that amount of toxin which when mixed with a specified amount (0.1 or 1.0 unit respectively) of standard antitoxin and given subcutaneously will kill guinea pigs within a specified time. The mean lethal dose (LD_{50}), used for standardization of gas gangrene toxins (oedematiens, perfringens, and vibrion septique), is that amount of each toxin which when mixed with a designated amount (0.02, 0.2 or 0.5 units respectively) of its specific standard antitoxin and injected will kill one-half of a group of mice within a fixed period. Varying amounts of an unknown serum, containing the particular antitoxin to be evaluated, are then mixed with one L+ or LD_{50} dose of its specific standard toxin for injection into the animals to find that amount of serum giving the same endpoint and hence containing the same number of units as the standard antitoxin. In the assay of digitalis and like cardiac drugs, the amount of unknown drug which just causes cardiac arrhythmia and death in cats, when given intravenously as a diluted tincture at a fixed rate, is compared with the amount of standard reference powder having the same result in a similar group of animals.

It is of major importance in toxicity studies to realize that different species of animals and various strains of the same species may differ widely in sensitivity to drugs. Likewise shifts of tolerance even of the same strain may occur, due to changes in diet, individual caging, feeding times, methods of handling, humidity, light and temperature, and sometimes to increased

noise and confusion in the quarters. Consequently these factors not only call for careful control, but must be considered when toxicity data are evaluated. In addition, they emphasize the importance of the parallel treatment of a similar group of animals with a suitable control material so that cross comparisons can be made when new animals or conditions are employed in subsequent toxicity studies on other lots of the same material.

Aside from recording the amount of a drug required to produce a particular reaction in, or to kill, a certain percentage of the animals, it is essential to note the type, time of onset, severity, and duration of all toxic signs or symptoms at each dosage level in all species employed as an aid in determining the mode of action of the drug. The degree of pallor, erythema or cyanosis of the conjunctiva, pupillary reaction, pulse regularity and rate, respiratory type and rate, and general activity of the animal should also be watched. Gasping, salivation, anorexia, micturition, vomiting, defecation, and abnormal posture should be recorded if they occur. Where the animal died, it is important to know whether the respiration or heart failed first. Data of this character prove of considerable value in interpreting toxic effects in humans, particularly when similar reactions are observed.

Of course, the therapeutic effect of a drug itself may be merely a milder manifestation of its primary mode of action. In such instances, if unduly accentuated by greater dosage the preparation may give rise to severe reactions or even fatal outcome. These modes of action may be exemplified by blood sugar reduction by insulin, cardioinhibition by digitalis, blood coagulation by thromboplastin, delayed blood clotting by dicumarol, and skeletal muscle paralysis by curare alkaloids. Many biological drugs can, however, be administered in a rather wide dosage range without appearance of untoward reactions. Yet in cases of over-dosage or unusual susceptibility, human reactions of a similar nature to those occurring in animals may be encountered. Although these types of reactions are not usually associated with the mechanism of therapeutic action of the drug, nevertheless careful observations and analysis of the toxic action

in animals are needed to give the clinician some idea of the kind of untoward reaction to watch for when using a new drug in the human.

Some of the animal signs or reactions, having particular significance in interpreting or predicting toxic effects of drugs, should be mentioned. Thus, the signs of flaccid paralysis usually denote central or peripheral nervous system depression, or acute shock. Excitement or convulsions generally indicates direct or indirect central nervous system stimulation whereas tremors may be due to central or peripheral stimulation. Gait changes or abnormal posture are customarily caused by higher neurological involvements although they may be lower in locale in animals. Acute shock or collapse marks severe vasodilation or extreme cardiac depression. Various pain responses may also be exhibited by the animals and the irritant action of a drug detected by erythema or swelling at such sites of administration as mucous membranes, superficial veins, subcutaneous tissues, or skin.

The rate of elimination, *i.e.,* destruction, excretion, or detoxification, of a drug is important in a study of duration of its effects. Frequently the drug elimination rate may be evaluated by analysis of its concentration in blood or urine at various intervals following its administration. However, it should be pointed out that toxic symptoms may persist much longer than significant blood levels can be demonstrated if irreversible or prolonged reversible tissue disturbances have been caused. Where suitable methods of determining the blood or urinary concentration are not available, elimination rates may be roughly estimated by giving fractions of the toxic or lethal dose sufficient to cause a physiological or toxic reaction. If, after repeated administration of this dose at regular intervals, the reaction increases in intensity without occurrence of irreversible tissue damage this is evidence that the elimination rate has been exceeded and cumulation has occurred. By adjustment of the dose and time interval used, it may be possible to find a dosage schedule which more or less maintains the effect on an even keel; this may be taken as a measure of the elimination rate.

In summary, the acute toxicity studies in animals should be designed to give relative comparisons of the toxicity of biological drugs, to analyze the mechanisms of the observed toxic reactions, to find out the duration of these reactions, and to ascertain if cumulation occurs with a few repeated doses of a drug, or if it has a markedly delayed toxic effect. These studies should be made in more than one species of animals, such as mice, rats, guinea pigs, rabbits, cats, dogs, or monkeys, nor are they to be considered complete without gross and microscopic examination of tissues of the animals which die or are sacrificed. Control groups of animals are utilized *(a)* to detect colonies with abnormal mortality rates from infections, or other causes, which might be misconstrued as drug toxicity, and *(b)* to serve as a basis of comparison of tissue damage resulting from administration of the drug. They are kept under the same environmental conditions, and receive the same treatment (except the drug) and rations as the experimental groups. It may be noted that a similar procedure is followed in chronic toxicity studies described later.

OTHER GENERAL AND SPECIAL METHODS OF TESTING

Drugs acting systematically may exhibit a specific action on skeletal muscle, smooth muscle, cardiac muscle, central or peripheral nervous system, glands, bone marrow, blood, kidney, liver, or other parts. In certain instances, moreover, they may show mixed effects on more than one of these structures. With procedures requiring anesthesia of the animal for the study of the drug action, the choice of the anesthetic agent is important since some anesthetics have decided influences on certain types of physiological responses.

Frequently, blood pressure measurements, together with electrocardiograms and respiratory recordings in unanesthetized or anesthetized animals following administration of drugs, offer valuable information as to the type of drug action or toxicity; this is true particularly when the intravenous route is utilized. Respiratory stimulation or depression usually will be found to

be due to humoral, direct or reflex central nervous system effects. On the other hand, the cardiovascular phenomena, such as vasodepression, vasopression, changes in heart rate and regularity, or shifts in pulse pressure, ordinarily arise from central or reflex vasomotor activity, from direct cardiac or smooth muscle stimulation or depression, or from direct action on the parasympathetic or sympathetic division of the autonomic nervous system. Because of the intricate relationship existing between the respiratory and circulatory systems, and the complexity of their compensatory mechanisms, the exact site or mode of action of a drug on either system is frequently difficult to determine. A single specific action of a drug may sometimes be used to evaluate its potency or to control its purity. The official test for potency of epinephrine is based on its blood pressure elevating effect while the contamination of a drug, such as streptomycin, with histamine-like material is determined by measurements of vasodepression.

Splenic, kidney, and leg volume tests are designed for measurement of local vasodilation or vasoconstriction; often, however, they prove mechanically difficult to perform. Likewise, the recording of intestinal movements, either of mixed pendular (longitudinal muscle) and peristaltic (circular muscle) type, by a balloon inserted into the lumen is sometimes quite troublesome. The latter method records the intestinal motility caused by the systemic or local action of drugs; in general, smooth muscle or parasympathetic stimulants increase the activity of the gut while smooth muscle and parasympathetic depressants and sympathetic stimulants decrease its motility. Uterine motility in animals, as influenced by certain smooth muscle or autonomic drugs, is studied by inserting a balloon into the uterus or by exposing the uterus and recording the movements directly from a horn or segment *in situ*. The action of drugs on the myoneural junction (skeletal muscle) may be determined *in vivo* by recording their effects on contractions of the gastrocnemius muscle of a suitable anesthetized animal following faradic stimulation of the cut sciatic nerve. Similar action may be demonstrated by direct application of the drugs to an isolated

nerve-muscle preparation from the frog. The action of smooth muscle drugs may also be investigated *in vitro* by determining their effect on strips of smooth muscle from the intestine or uterus in suitable bathing fluids. Incidentally, the contraction of guinea pig uterine sections is the basis of the official bioassay of posterior pituitary extracts.

The blood is an important body constituent and hence many informative tests are performed on it, particularly after repeated doses of a drug. Blood volume, determined by the concentration of injected dye or other substances, together with red cell count and volume, plasma protein content, and specific gravity, indicate the relative concentration or dilution of the blood. Red cell counts, hemoglobin estimations, and white and differential counts are determined more frequently in chronic studies but sometimes give valuable information about the activity of certain materials in acute studies. Often clues as to the activity of drugs are found from determination of blood constituents, such as non-protein nitrogen, sugar, serum albumin and globulin, fibrinogen, chlorides, sodium, potassium and calcium, as well as measurement of coagulation time, sedimentation time, prothrombin time, and others. Such tests may also become methods for official determination of potency as, for example, the reduction of blood sugar by insulin in the rabbit or the elevation of blood calcium by parathyroid extract in the dog. Urine analyses, for non-protein nitrogen constituents, inorganic elements, *p*H, volume, and specific gravity, are sometimes made, and especially protein content, red cell and leucocyte counts, and numbers and types of casts if the drug causes kidney damage.

For complete analysis of the action of drugs, there are many other types of experimental tests which may be enumerated, viz., electroencephalograms or brain waves, nerve action potentials, metabolism studies, nitrogen balance experiments, renal and hepatic function, various immunological reactions, and perfusion of various organs for local vascular or other effects. Various animal preparations, such as decortication, high section of the spinal cord, cross circulation, complete and partial sympa-

thectomy, gastrointestinal fistula, hepatectomy, and heart-lung arrangements, are also useful tools in studying drug action.

When these methods are added to those previously mentioned the list is indeed impressive. This does not mean, however, that all new drugs are tested with such completeness. Most of them have a limited pharmacodynamic action and do not affect all of the tissues. It is, therefore, impossible to set up a list of general pharmacological methods of study to apply to each new preparation. The experimentalist first determines the drug's toxicity, then perhaps the blood pressure changes or some other activity indicated by the toxic reactions. Thereafter he has enough information to narrow his field of investigation and concentrate on definite investigative procedures. Of course, he must decide how to change tactics and techniques when investigations are fruitless, how far to proceed in evaluating the primary and secondary actions of the drug, and when the data are sufficient to warrant clinical trial.

IRRITATIVE REACTIONS

The methods available for the study of irritative reactions of injected or topically applied materials in experimental animals are imperfect in that degree and duration of pain, being subjective manifestations, cannot be estimated. It has been demonstrated, for example, that mild irritative reactions may be very painful while severe irritations may cause little pain, depending upon the location of the tissue damage, the type of the irritation, and number and kind of sensory nerves involved. The animal reacts positively to pain by squealing, by drawing up or shaking its injected leg, by attempting to scratch its injected side or abdomen, by shaking its head following ear injections, or by increased general activity, but the investigator has no way of evaluating the severity of the pain response. Nor can one determine whether mild pain is being experienced by the animal when signs or symptoms are absent. Studies of changes in skin temperatures, in electrical resistance through subcutaneous areas, and in brain waves, reflexes, and other neural patterns

have not been sufficiently standardized at present to consider these as generally reliable indices for measurement of the intensity of such pain stimuli.

The type, degree, and duration of local irritative effects of materials, injected or applied topically, can, however, be investigated in various species of animals. To eliminate animal variation, most of these effects can be compared in the same living animal or on the same excised tissue to that of a control material, such as saline or another marketed product having somewhat similar properties or uses. The irritative properties of various concentrations of a preparation are studied by evaluating the local reaction or effect at various intervals following: *(a)* single or repeated application to mucous membranes, such as the conjunctival sac, vagina, bladder, rectum, and upper respiratory tract, *(b)* single intradermal or single or repeated (in the same site) subcutaneous, intraperitoneal, or intramuscular injections, determining the gross and microscopic appearance of the site, and *(c)* single or repeated applications to wounds or abrasions, noting, in addition to the irritative reaction, the healing time. Because of the size of the leg muscles, usually no more than 1.0 cc., total single dose, should be injected intramuscularly in dogs, 0.25 to 0.35 cc. in rabbits, and less in smaller animals because some irritation due to stretching and even rupture of the tissue may be produced mechanically. The intradermal volumes ordinarily should not exceed 0.15 cc., although the quantities by the subcutaneous and intraperitoneal methods need not be so limited.

Other methods of studying irritative effects, using normal saline or other products as a control, are the survival time of cilia from freshly excised tracheas following direct application of the preparation, or the percentage of mortality of the growing chick embryo in incubated fertile eggs following injection of the material into one of its sacs, onto its chorioallantoic membrane, or intravenously into its blood stream. For special use in the neural canal, the preparation may be injected intraspinally or intrathecally in animals to determine its irritant effect on the neural membranes.

CHRONIC TOXICITY

It is a rare drug which is sufficiently efficacious even with nature's help to clear up the ravages of disease by a single administration. Consequently, the possible cumulative or chronic effects of repeated dosage of therapeutic agents should be investigated in animals before they are used repeatedly in humans. For such chronic studies two or more dose levels, *i.e.,* fractions of the mean lethal or maximum tolerated doses, are fed or injected over a period of several weeks or months. The dosage levels and intervals are selected on the basis of results obtained in the acute studies on the time of onset and duration of action, elimination rate, and short term cumulative effects. The material is given to adult animals to find out if their weight is maintained and to young animals to ascertain whether it interferes with normal growth or causes injury to vital organs.

Since it is difficult to store animals for long periods without some deaths from infections and other causes, a fairly large group of animals on each dose level is required. To save time and cost it is best, however, to begin the experiment by making preliminary studies with smaller groups and to add to these after satisfactory dose levels have been determined. Regular tabulations are made of the food intake (if it contains the drug), weight gains or maintenance, injuries, infections, appearance of the coat, and general condition of the animals. If cumulative effects appear, such as weight loss, lack of growth, and other signs of drug toxicity, the dosage for this group is reduced or the dosage interval lengthened, and usually a new group is started at a lower dosage level. Routine blood and urine analyses are generally made at intervals during the observation period but sometimes other tests, such as metabolism and renal or hepatic function, are indicated.

A number of animals from the same group, receiving the same diet and treatment (except the drug), and housed under the same environmental conditions for the same period as the experimental animals serve as controls for evidence of toxicity

and for comparative tissue examinations. Without the control group it would be impossible to know whether the observed changes are due to the materials administered or to a poor colony. In fact, where the number of deaths is rather high in both test and control groups, it is difficult to evaluate the results; the cause of the high mortality should be found and if possible eliminated in the succeeding tests.

The individual groups should be large enough to permit sacrificing some animals at intervals during the prolonged test to determine when tissue damage, if any, occurs. As rather large numbers of animals are used in chronic toxicity experiments and the animals are studied for a long period of time, the cost of such tests is high; therefore it is of utmost importance to plan the experiment carefully and to check the results frequently.

TISSUE DAMAGE

Specific tissue damage may occur when no visible signs of toxicity appear at the particular dosages employed. Consequently toxicity alone is not a safe criterion on which to judge the safety of a drug for human use. Since evaluation of specific tissue damage in humans following administration of drugs during clinical trials is limited, except in the case of biopsies, to signs and symptoms arising from affected organs, it is essential that as much be known about the type and degree of potential tissue damage as possible before the drug is tried on the human subject. Human blood and urine are available for study but alterations in these do not ordinarily indicate the location, type, or degree of pathological changes.

Examination of animal tissues following administration of new preparations include the local site of injection, *i.e.*, intramuscular, subcutaneous and intraperitoneal tissues, and, if given orally, the stomach and duodenum, and also the various organs or tissues which might be affected following systemic absorption. The doses in animals for the tissue studies by the various routes of administration range from those causing no detectable symptoms up to and including lethal doses. Gross and microscopic

tissue examinations are made in a representative number of animals receiving the therapeutic agent in single or repeated doses and in control groups receiving none of the material. The tissues of all animals dying, whether from drug effects or other causes, must be examined. These gross and microscopic studies should be carried out by individuals who thoroughly understand the pathological changes in animal tissues. Two or more species of animals should be employed; a single species may be either abnormally sensitive or tolerant to the drug, or may show extremely atypical pathological changes. The best means of comparing the effects of various drugs on tissues is by using the same strain of a species, such as mice, rats, or rabbits, but this is usually impossible to do with other species, like the dog and cat, unless the experimentalist goes to great expense in raising his own colonies, which very few are in a position to do.

It should be kept in mind that toxic reactions and tissue damage which were not demonstrable at any time during the animal studies may still occur in the human. Moreover, if marked or severe tissue damage of the vital organs appears in animals following effective or therapeutic dosage levels clinical trial is not warranted. Even in the case of moderate tissue damage, clinical trial is not recommended or it should proceed with utmost caution.

ALLERGY

A discussion of the toxic manifestations of any class of drugs, particularly biologicals, is incomplete without mention of those exceptional, much studied but imperfectly explained, series of responses listed as allergic reactions. Allergy, or idiosyncrasy, is an individual, specific, abnormal local or systemic reaction to a foreign substance which in most subjects produces little or no significant reaction. The reaction may occur when the substances are inhaled, ingested, injected, or applied to the skin or mucous membranes. The allergic response should not be confused with a high susceptibility in some individuals in whom the normal pharmacodynamic action of a drug is elicited in even unusually small dosage.

When an invading foreign material, such as proteins contained in serums, bacteriological, and other products, is antigenic, the resulting body response is the formation of antibodies appearing in the globulin fraction of the blood proteins. These may be detected by specific reactions (agglutination, precipitation, neutralization, etc.) with the particular substance causing their production. Administration of these antigenic substances leads in one instance to the development of a condition in which the individual possesses relative freedom from abnormal symptoms upon subsequent invasion of the foreign protein, and may lead in another instance to the development of an abnormally high reactive state. The former condition or immune state may not be permanent; likewise the latter condition or allergic state is usually not static.

It has been demonstrated experimentally that non-protein substances, as iodine, iodoform, diazonium compounds, certain carbohydrates, and formaldehyde, are capable of combining with non-antigenic protein to form antigens, *i.e.*, to cause antibody formation and even sensitization. These substances are called haptens or partial antigens. One hypothesis given for the allergic manifestations so produced is that, after entrance into the body, they combine with the body protein to form a new substance which acts as a foreign protein. After sensitization has been produced by the drug-protein complex, it is conceivable that the drug alone may produce a local or systemic allergic reaction. However, such partial antigen action does not lend explanation to the great number of allergies reported with compounds which do not combine with proteins.

Space does not permit the discussion of the many theories regarding the causes of the allergic versus the immune state, nor the methods of producing immunity, and the treatment of allergy (desensitization, administration of antihistamine substances, sympathetic stimulants, etc.). It is, however, in order to mention some of the abnormal reactions which may be experienced or observed. Included in the many allergic manifestations are such signs and symptoms as various forms of mild or severe skin eruptions, joint involvement, edema, adenopathy,

tissue damage, respiratory, cardiovascular or gastrointestinal disturbances, febrile reactions, headache, malaise, and even neurological involvements.

In practically all cases, the acquisition of allergy necessitates previous exposure to the particular foreign substance. The degree of the resulting allergy depends on the nature of the material, the size and frequency of the sensitizing doses, and the inherent characteristics of the individual developing the conditions. The tendencies towards certain types of allergic reactions may be hereditary; others may be developed by maternal transfer *in utero* or possibly during suckling and thereby occur in infants. The condition in many instances tends to develop more readily when the administration of antigenic material is spaced at fairly wide intervals. Acquired allergy may develop after some months, sometimes even years of intermittent exposure, or this reactive state may appear in days or weeks. There is experimental evidence that the sensitivity which an allergic individual possesses can be temporarily transferred with his serum to a non-allergic person.

Much of our knowledge of anaphylaxis and allied allergic conditions has been obtained from animal experimentation. To produce anaphylaxis in animals a protein material is given by injections usually at two to three week intervals. If the interval between administrations is very short or very long, the reactions are lessened or may even be absent. Anaphylactic reactions can be demonstrated rather easily by proper injection of ordinarily innocuous horse serum into a guinea pig. The first injection (sensitizing dose) produces no ill effects, but following a period of about two to three weeks, readministration (usually intravenously) of the same serum (shock dose) usually causes immediate severe reactions and even death. The various species appear to differ in the mechanism by which death is caused in anaphylaxis and in the ease with which this type of allergy is established. Death in the guinea pig is mainly due to bronchiolar spasm and asphyxiation, while in the dog and rabbit this phenomenon is less marked, the most prominent feature being vascular shock. The highest to lowest suscepti-

bility in animals has been reported in the following order: guinea pig, rabbit, dog, cat, monkey. Serum sickness in humans is an allergic reaction characterized by fever, skin eruptions, swelling of the lymph glands, and other non-fatal manifestations; it differs from the immediate anaphylactic reaction in that it is delayed for about a week and may follow a single injection of a rather large dose of animal serum.

It seems probable that there are no fundamental differences in many instances between the allergic reactions in lower animals and humans to repeated administration of foreign proteins. For example, the Arthus phenomenon observed in animals has its counterpart in humans. This reaction is an inflammatory process which may develop into severe necrotic areas following repeated subcutaneous injections of certain protein materials, such as horse serum, at intervals of several days. The rabbit appears to be more susceptible to this reaction than other animals. Anaphylactic shock has also occurred in humans following injections of protein, although there is little tendency to develop acute generalized shock in man; furthermore, care is usually taken to avoid conditions favoring anaphylaxis. Anaphylactic or subcutaneous tests for degree of antigenicity should be conducted on materials suspected of containing traces of protein, such as protein hydrolysates, as well as on new protein preparations to be reinjected by parenteral routes clinically.

Since human blood is an important therapeutic agent, discussion of allergy is not complete without mention of the recently discovered factor, Rh (or related ones), which is present in the blood of certain individuals although absent in others. Transfusions of Rh-positive blood into an Rh-negative patient produces antibodies similar to injection of other antigenic material. If Rh-positive blood is later given to the same patient severe allergic reactions may arise. This discovery has contributed immensely to an understanding of the frequently fatal allergic manifestation, fetal erythroblastosis, which may develop in the fetus or after birth of a normal appearing child and is characterized by anemia, edema, enlarged spleen and liver, jaundice, pallor, and sometimes stupor, convulsions, and death.

These cases, usually occurring after the first child, appear to depend on the production of Rh antibodies in an Rh-negative mother against the placental-transferred Rh factor from an Rh-positive fetus, these antibodies acting detrimently to the fetus when transferred back through the placenta.

It is noteworthy that some kind of allergic reaction in humans has been described for practically all therapeutic agents in wide use. Many pages have been written on the type, severity, duration, and treatment of allergic reactions but no generally accepted rational explanation of their cause has been universally given. Unfortunately, most human allergies cannot be reproduced in animals; consequently, the developmentalist is unable to predict the particular allergic effects that may be encountered clinically with most new materials.

MODE OF ACTION AND EFFICACY

An ideal biological preparation for the diagnosis, prevention, or treatment of disease has a uniform and predictable therapeutic effect with only slight or no local irritative properties, low relative toxicity, and freedom from side actions and sensitivity. The aim in development is to produce a product which approaches the ideal as nearly as possible; obviously, appreciable deviation in any of these attributes may result in a questionable product for clinical trial and usage. Since differences in the reactivity of the various species are recognized, data should be obtained in more than one species before conclusions on mode of action or effectiveness are drawn.

If the preparation affects all animal species tested in the same basic way physiologically, prophylactically, or therapeutically, it may be concluded that it will usually have a similar action in man. Such similarities, for example, exist in the insulin effect on blood sugar, the action of penicillin on certain common infections, antitoxin reaction with toxins, the use of serum albumin for the treatment of shock and hypoproteinemia, the action of posterior pituitary on the uterus, with protein hydrol-

ysate in protein deficiency, the hemostatic effect of thromboplastin, and the skeletal muscle relaxing effects of curare.

On the other hand, should the preparation produce widely divergent effects in the various species, perhaps explainable by species differences in physiological mechanisms, the effects on man are best judged by a study of the results in that species in which the physiological mechanisms involved most closely resemble those of man. It does not necessarily follow, however, that primates or closely related species should be utilized. A well-known English pharmacologist has pertinently written: "Monkeys are genealogically related to man and are sometimes used for the trial of new remedies, but pharmacologically they are often less human than dogs." Of course, in cases in which the human disease entities or manifestations are not seen in animals, for example, whooping cough, typhoid fever, and gonorrhea, only the safety and uniformity of the product for therapeutic use can be ascertained in the laboratory and its efficacy must be evaluated solely in humans.

The value of the preparation in therapeutics is based on *(a)* whether it works at all, *(b)* the percentage of cases showing improvement or cure, *(c)* the number of relapses following definite improvement or cure, and *(d)* the amount of irreversible tissue damage caused by the preparation. For a new product this requires a large number of case studies, usually over a long period of trial under various conditions, to determine if it deserves a place in the handbag of the clinician. The complete subject of therapeutic efficacy and also of mode of action of individual biologicals is too broad to be discussed here. However, illustrative types of biological studies which are made in connection with various developmental problems, and their relationship in some instances to clinical usefulness of the product, have been described in the previous section.

STABILITY AND DISPENSING FORM OF THE PREPARATION

Instability of a solution, suspension, or solid preparation means undesirable changes from a therapeutic or pharmaceut-

ical point of view. These are caused by chemical reactions (such as oxidation, reduction, and hydrolysis), chemical incompatibilities or interreactions of the ingredients or physical changes (such as *p*H, solubility, phase separation, and moisture content). The results of these chemical and physical transitions may be unsatisfactory changes in color, odor, taste or clarity of solutions, and incapacity for uniform resuspension of colloidal solutions, suspensions, and emulsions. Failure to resuspend thoroughly may be due to coalescence of colloidal particles, increased particle size in suspensions, and irreversible phase separation in emulsions or semi-solid preparations. Changes in potency or activity and in irritative or toxic reactions are other evidences of instability.

Bacterial contamination frequently affects stability by altering *p*H or by various enzymatic reactions. Sterility of the preparation, therefore, is an important problem in stability studies. The methods of handling various biologicals in order to obtain a sterile final product should be carefully investigated. While solid preparations for use on wounds have to be sterile, those for oral use do not need to be, although, even in the latter case, the bacterial count should not be too high since deterioration may occur when traces of moisture are present. On the other hand, for biologicals to be administered parenterally both the solid material to be reconstituted and liquid preparations must be rendered sterile. Solutions which can be sterilized by ordinary filtration or by some form of heat treatment offer no problem, nor do solids that can be heat-treated. However, suspension or emulsion types of preparations, of course, cannot be filtered and, if not thermostable, they are often difficult to prepare in sterile form. These are usually prepared by aseptic combination of sterile components in a suitable mixing apparatus, followed by aseptic filling into final containers. However, the suspension of protamine zinc insulin is made by dissolving the protamine zinc insulin complex in an acid medium and mixing it aseptically in vials with an alkaline buffer in which the complex is insoluble.

Solid or dried materials are usually stable for a longer time

than solutions or suspensions, but this form is less desirable because of the added requirement of reconstitution with a suitable sterile diluent before use. If a liquid preparation exhibits evidence of instability in a relatively short time, it is impractical to dispense it for other than immediate use. However, should the active material be stable in the dry form, it may be weighed directly into suitable containers in that state, or its solution dried in containers in a low temperature, reduced pressure oven, or, if heat labile, lyophylized (frozen and dried in frozen state under very low pressure and temperature). Stability studies are also made on the aseptically reconstituted material so that the user of the product will know how long these can be safely stored and used.

The contents of liquid multiple dose containers or diluents for reconstitution must be maintained mold free and bacteriostatic by use of preservatives which are physically and chemically compatible with all ingredients in order that stability is unaffected. The preservative should be capable of preventing growth of usual contaminants and is tested by determining whether certain micro-organisms grow when innoculated into the preparation. Commonly used preservatives are chlorobutanol, phenolic compounds, mercurials, and anionic or cationic detergents. Knowledge of chemistry of the preparation aids in the choice of preservatives to be added, but, of course, thorough stability studies are required to prove that the correct one was chosen.

The conditions of storage for the preparation and its outdate, *i.e.*, the period beyond which the preparation cannot be expected to yield its specific results, are determined on the basis of prolonged stability studies. Materials labile to prolonged room temperature, as most liquid biological preparations are, must be refrigerated. Some are relatively stable to room or elevated temperatures; needless to say, it is a tremendous advantage in sales and distribution if refrigeration is not required. The usual approach to setting up storage limits is to store each preparation under refrigerated conditions (4 to 10° C.), at room temperature (20 to 28° C.), at body temperature (37° C.), or

higher, for various periods, and to study the changes in activity or potency, appearance, *p*H, toxicity, and irritative properties. Storage above refrigeration temperature is useful for indicating what might happen during shipment in hot weather or into tropical regions where it is not possible, with present facilities, to keep materials refrigerated. Since elevation of temperature usually speeds up chemical reactions and thereby deterioration of a preparation, it may be possible, with products showing a fair degree of thermostability, to predict roughly by using several elevated temperatures how long these preparations might be stable at lower temperatures. It should be noted, however, that because of the protein nature and complex composition of some biological preparations, elevated temperatures may cause markedly accelerated decomposition rates so it is not possible to set up any general formulas.

Biological preparations usually vary somewhat in composition until uniformity of manufacture is established. Consequently, it is good practice to study more than one early lot for stability. These studies are carried out for any reasonable length of time that is required for significant changes in stability to occur. If the material becomes contaminated during storage, the results are uncertain and should be discarded.

The final dispensing form depends upon *(a)* the results of the stability studies on the final product stored in different types of containers (with different types of closures when the material is supplied in vials or bottles), *(b)* the size of the single dose of the final injectable form and *(c)* the number of doses to be included in the container. Ampuls are usually limited in size to a single dose of the product, thus having the advantage of reducing closure difficulties. Moreover, they eliminate deterioration of the liquid forms from the constituents or coatings of the closures, and can be nitrogen filled or flushed for products susceptible to atmospheric oxygen. They also prevent absorption of moisture in hygroscopic solids which may be altered by increased moisture content. Multiple dose containers are usually designed for aseptic removal of part of the contents and consequently require rubber stoppers instead of screw cap clo-

sures. The choice of the proper type of rubber closure, as well as the type of container for use with each product, is an important phase of study of stability and dispensing form.

CONTROL TESTS ON AND LABELING OF THE PREPARATION

Throughout the development of a new product, methods of testing its potency or activity, irritative properties, toxicity, and safety, and its various physical and chemical characteristics are studied. Each lot should be assigned an identification number and all of the results of these tests recorded as part of its control for future reference along with the manufacturing data. This is good practice to follow even with preliminary experimental work in order that all data on a particular material can later be identified and evaluated. It is also important to pay particular and early attention to those general control procedures which might apply to any product. By the time the product is ready for clinical trial all methods of testing should be established so that tentative standards of quality can be set for raw materials, intermediates, finished bulks, filled and labeled products. These standards are necessary to insure that the quality of subsequent manufactured batches of the product is maintained at the level intended by the group responsible for its development.

The finished dry or liquid bulk material intended for filling into smaller containers should be completely tested to ascertain whether it is satisfactory for use; obviously, if it is unsuitable, the cost of filling is eliminated. Likewise, filled material should be tested before labeling and packaging for the same reason. Where the product is relatively unstable in liquid bulk form, it must be converted fairly rapidly into a more stable dry state. Even some solids can be held in bulk for only short periods. With such products selected control tests are performed on the bulk and the other necessary tests on the filled material.

A general list of tests on final products (finished bulks, filled or labeled materials) to be applied according to their particular requirements is as follows:

Color of liquid or solid preparation

Odor and sometimes taste
Bulk volume, melting point and solubility of solid material
Clarity of solutions
Foreign particles in suspensions or solids
Turbidity of suspensions and ability for uniform resuspension
Physical properties of colloidal solutions
pH of liquid preparations and of reconstituted material
Potency or activity
Tonicity or solid content
Irritative properties
Quantitative analyses for essential elements, such as nitrogen, sulfur, sodium, etc.
Heavy metal content (as contaminants)
Other special tests for a particular product, such as cell counts, viscosity, surface tension, absorption spectra, antibacterial characteristics, specific rotation, and refractive index
Preservative content
Sterility
Toxicity or safety
Identity tests
Volume check on filled material

The chemical and physical tests can usually be completed in a relatively short time and therefore serve as a quick means to determine whether a uniform product can be made by duplication of the manufacturing procedures if the same raw materials are used, and to indicate what changes in the product occur with different raw materials or by modification of the manufacturing process. Certain tests, such as nitrogen or solid content, are also useful in checking the precision of liquid bulk dilutions or of preparation of solutions from solid materials.

Accurate assays of potency or activity are important not only for prevention of excessive potency to reduce the cost of manufacture and possible toxic reactions from overdosage, but also as a guarantee of a minimum labeled strength. If the potency or activity of impure or pure substances can be determined by physical or chemical means, the accuracy of such methods is

usually greater than that obtainable by biological means. Bioassay (biological or physiological assay) is the determination of potency, activity, or toxicity, in terms of an arbitrary or officially assigned standard, of any preparation requiring evaluation in intact living animals or upon surviving isolated tissues or upon selected micro-organisms (the so-called microbiological tests). These are used to supplement chemical or physical assays or in the absence of other suitable methods of assay. The endpoints in bioassay include various physiological responses, such as blood pressure elevation, contraction of isolated uterine musculature, estrus induction, uterine or ovarian weight changes, and, in some cases, a certain percentage of toxic symptoms or deaths in the test group.

Some methods of bioassay are surprisingly accurate and reproducible, giving a low standard error, while others, depending on the type of response utilized, exhibit rather wide variations and therefore a large standard error. The accuracy of a bioassay may be increased by using a larger number of animals (the standard error is roughly reduced in proportion to the square root of the number of animals used) but this is limited by cost and facilities when a number of assays are involved. Besides the animal variation of the type of response used in bioassay, the margin of safety of the drug and range of its therapeutic efficacy are other factors to be considered in fixing the accuracy necessary for the biological assay. Sometimes, in order to decide on the final type or the required accuracy of the bioassay method, rather extensive investigational work must be done. From the control or quality point of view, it is best to strive for the highest degree of accuracy commensurate with reasonable cost for the type of preparation under consideration.

Although all methods of testing cannot be described in detail, some brief general remarks about a few of these should be made. Stability tests indicate the most suitable range for *p*H of the preparation and therefore *p*H, in most instances, must be maintained within these limits to prevent more rapid breakdown of the preparation. The solid content or tonicity may be associated in part with irritative properties and accordingly

has to be limited. At times, for parenteral preparations, the body temperature elevating property in animals or the pyrogen content of the medium used, if aqueous, and of diluents, must fulfill requirements of "Water for Injection," and, whenever possible, modified pyrogen standards may be set up for the final product. Although the preservative is not an active ingredient, its content must be sufficient to maintain sterility in multiple dose containers and yet not be excessive for toxicity or incompatibility may result. It is therefore important to control the amount of preservative in the preparation within set limits by accurately checking manufacturing procedures or by direct testing of preservative content.

Various contaminants may markedly alter the over-all toxicity and irritative characteristics. Each lot must be checked for inadvertently included toxic agents of bacterial or chemical origin. The safety, identity, and sterility tests are the final checks on the product. In the safety test, forced feedings or injections of representative samples of the finished (labeled) product are made into animals at several times the human equivalent per kg. dose and the animals are observed for the appearance of toxic symptoms. The identity test should be designed to distinguish one preparation from others having a similar appearance as, for example, insulin and posterior pituitary, to guarantee that it has not been accidentally mislabeled. It involves special biological, chemical, or other tests and should not be applied until the entire lot is labeled.

Each ampul, vial, or bottle for clinical trial should be adequately identified by a typed or printed label bearing the lot number of the preparation, the amount, potency, or concentration of active ingredient, the name of the product, and a caution statement limiting its use to investigational purposes only. Information as to the identity and quantity of other inert ingredients, the amount and kind of preservative, alcohol content, if any, and storage requirements may be on the label or accompany the package. The expiration date may be added to this information although this information is usually not completely established at the time of clinical trial.

CLINICAL TRIAL

Although the subject is discussed at greater length in another chapter, it is not inappropriate to point out at this point that the last chapter in the development of a new preparation is exacting proof by clinical trial of its value in bringing about certain states, such as hypnosis and anesthesia, and in effecting improvement or cure of specific diseased conditions; and whether it brings about the anticipated result without undesirable or undue side actions. Here is the important, difficult, and sometimes courageous task of translating experimental findings in animals to those for therapeutic application. Difficulties are obviously reduced when the condition seen in humans can be reproduced in its entirety in animals; in these instances the animal evaluations are directly transferable to man once human dosages are determined. In many cases, however, the activity or efficacy of the preparation can be ascertained only in man because most human diseases are atypical or cannot be duplicated in animals. Often standards based on certain biological, chemical, or physical tests become useful therapeutically when clinical experience has related these standards, such as units of antibiotics, endocrines, antitoxin and glandular products, to the efficacy of the preparation in humans.

The therapeutist responsible for the trial of a new drug in humans should be acquainted with all details of the experimental animal data on it before he begins his clinical studies. He should thoroughly understand the disease he is treating with the new therapeutic agent and appreciate the wide variation in responses which may be found in different patients. Any experimental knowledge as to the rapidity of onset and duration of action, side effects, toxicity, tissue damage, and mode of action, if discovered, is invaluable information to him. Although these effects may differ widely in animals and man, the clinician will be on firmer ground in spacing doses and discovering when overdoses are being given if he has indications as to the type of toxic or physiological reactions which

may occur. The extent of tissue damage in the human is very difficult to determine since human tissues are not ordinarily available and only signs or symptoms can be studied. Particular attention should be paid to liver and kidney functions, respiratory and cardiovascular changes, and local and allergic reactions. The patient should be under close surveillance as long as untoward reactions from the new drug are possible and be given prompt treatment if they occur.

The human doses of a new preparation are ordinarily small at first, in fact, usually too small to be effective. Usually they are increased gradually to lessen the chances of a toxic level being administered. Animals are ordinarily more tolerant to drugs than humans, yet the differences in sensitivity of animals and humans for a new product are known only by trial. Variations in responses to certain drugs in different species make choice of preliminary human doses of a new drug even more difficult. The only basis for estimation of the initial human dose of a new product is a particular dose obtained in the experimental studies in animals, such as minimum toxic, maximum toxic, or effective dose, but the first trial dose in humans should be smaller than any of these. Some consider one-tenth to one-fifth of the animal tolerated dose (per kg.) as safe for humans by the same route of administration, but any such formula should be used with utmost caution.

Even though the development group may have done an excellent job in preparing the material for clinical trial, it should be remembered that the desired result of their labors, namely, its clinical acceptance and establishment on the market, cannot be expected to follow automatically. Although a new product may be introduced for a newly-discovered disease or for a long known malady, usually it has to compete with other drugs having more or less the same kind of therapeutic action. In either case it has to produce significant results therapeutically and should improve on drugs in current use; in short, it must be more effective or less toxic, or produce fewer sensitivities or side actions.

Certain types of clinical estimation of drug effects, such as

degree of hypnotic, diuretic, cathartic, or mucous membrane irritative action, can be made on normal individuals. Several obstacles, however, stand in the way of an easy, definitive clinical evaluation in the treatment of diseased conditions. The power of suggestion and its role in therapy must be evaluated. Some chronic diseases have misleading spontaneous remissions during which the patient is temporarily better or is free of symptoms. Many acute diseases are improved or cured by rest in bed; it must be determined whether the patient shows recovery in spite of the drug or because of it. Untreated controls are very useful in determining the effects of drugs in mild types of diseases; they cannot, however, be utilized in diseases with a high percentage of mortality. The effect of a drug may be misconstrued by the concurrent administration of another drug which may have produced the change. Comparing the efficacy of a new drug to that of another against a particular disease is difficult because of the task of selecting at random equivalent groups of patients unless the groups are comparatively large, but such controlled studies should be obtained whenever possible.

The crucial clinical test of the preparation therefore requires considerable time, an adequate number of cases for statistical study, sufficient facilities and enough qualified personnel to make the observations and to record with accuracy the objective and subjective findings. Frequent communication should be maintained between the development group and those carrying out the clinical work, particularly when difficulties are encountered. If the preparation is not as effective as anticipated or causes undue reactions, it may be found, by collaboration of the two groups, that certain modifications improve the product. When these modifications have been accomplished and the product is deemed satisfactory, the developmentalist may seek to improve it further; in particular, however, he directs his efforts towards the continuance of his endless quest for new diagnostic, therapeutic, or prophylactic agents to be used for the alleviation of human ills.

6

Clinical Testing

WINDSOR C. CUTTING

ONCE the pharmacologist has demonstrated a new drug to be potent in animals, and not excessively harmful, crucial testing in man is in order. The important questions in the human trials are relatively the same as those in animals, namely, is the new drug active and beneficial, and, secondly, is the margin of safety adequate? It goes without saying, however, that although the criteria are similar, their application is more rigid and critical in clinical tests.

Nor can the necessity of such tests be minimized. One may predict, but seldom guarantee, what the result of the trials in humans may be. Some drugs have been strikingly effective in animals, as, for instance, benzylpenicillin in infections in the mouse, yet ineffective in man, who in this case does not possess enzymes to split the ester to active penicillin. Other drugs have appeared reasonably safe in animals, with proper dosage, only to show entirely unexpected toxic manifestations upon clinical trial. Thus, dinitrophenol, which did not harm the eyes of experimental animals under ordinary conditions, was found to be associated with cataracts in human individuals.

Besides the primary question of efficacy and toxicity, clinical trials must eventually define the procedures for administration. These include dosage, single and total, route of administration, and intervals between treatment. Also, adjuvant or collateral treatment, special indications, or contraindications because of age, type of disease, or complications and means of combatting untoward side effects may be formulated.

Perhaps incidental to the principal objectives, data of considerable assistance to the manufacturer are provided by clini-

cal trials, both in fulfilling the requirements of labeling, and in the preparation of advertising material. Thus, resumés of clinical trials are particularly valuable for the latter purpose; they are, in fact, used extensively and effectively in periodical advertising and in brochures.

TYPES OF CLINICAL TRIALS

As a general rule, clinical trials proceed in two steps, preliminary and then extended. Bearing in mind the information gathered about the drug in the course of laboratory investigation, and particularly animal experimentation, the investigator cautiously tries first small, and then larger, doses, often upon himself, or upon patients ill beyond hope of recovery, and preferably in whom the drug might exert a beneficial effect. As confidence is born, the scope of the trials is extended, for one must bear in mind that only in numbers may one acquire a knowledge of the niceties of effect and the unusual in toxicity.

The extent and length of the preliminary tests are dependent, of course, on the nature of the drug. It is at this point, moreover, that the investigator must determine whether to proceed to further and more extended tests. For example, should the preparation prove to be possessed of considerable toxicity, and the character of the conditions for which it is intended comparatively minor, it is probably advisable to abandon the drug or formula, or return it to the laboratory for further study.

When preliminary and orienting trials appear promising, more extensive tests must be planned to allow an answer of such important questions as to methods of administration, effectiveness, and toxicity. In the following pages these aspects will be discussed in order.

METHODS OF ADMINISTRATION

Although the final answer as to the best method or route of administration may not be obtained until after long clinical experience, a workable method must be established early.

This is usually started with a study of the effect of a single dose of the drug, often along the lines of previous animal trials.

First, there should be a comparison of various routes or methods of administration. By their nature, certain drugs are designed for topical or local application, others are effective only for systemic administration. In case the preparation falls within the former category, the problem is usually simplified to terms of supplying a medium for the drug serving to limit or promote its penetration, as desired, and, perhaps, to determine the length of time that a single application will remain effective.

On the other hand, a study of the routes for systemic administration is often somewhat more complicated. Theoretically, at least, a number of methods are available. Thus, the drug may be given orally, parenterally by subcutaneous, intramuscular, or intravenous injection, or in other ways. Many drugs are effective only when given parenterally; a few must be administered by mouth; others may be given by either route. Ordinarily, the oral route is preferred primarily because of its convenience; however, if absorption of the active principal is incomplete, slow, or variable in comparison to a parenteral route, the latter may be selected. An even more important factor to be given consideration may be the rapidity of action which parenteral injection furnishes.

Comparisons of the administration routes necessitate some yardstick of measuring either the concentration, or the biological effect, of the drug in the body. When the concentration can be determined chemically, and is proportional to the desired effect, the investigation is greatly facilitated. It is fortunate indeed that such methods have been developed for many of the newer drugs. Thus, the sulfonamides are easily estimated in blood and tissues by simple chemical methods, while penicillin is measured, considerably less easily, however, by bacteriological tests. The distribution of a drug in the body may thus be studied as well; information of this nature is obviously important. For instance, a drug to be used in the treatment of meningitis may be relatively ineffective if it does not penetrate into

the spinal fluid. Incidentally, many tissues are inaccessible in man; consequently, considerable reliance must be put on results of studies of distribution in animals.

After the characteristics of a single dose are determined, the study of multiple doses must often be considered. Some drugs, such as analgesics or antispasmodics, may not ordinarily be given in serial doses, but others, like the chemotherapeutic drugs, digitalis, or quinidine, require repeated administration for effectiveness. The latter is usually resolved into the determination of the amount necessary for an initial dose, yet sufficiently large to assure quick saturation of the patient to the desired extent, and then for a smaller maintenance dose which will preserve the effect; also material is the ascertainment of the interval at which the maintenance doses must be administered.

EFFECTIVENESS

Ordinarily a much more difficult problem than determining the best route and method of administration is that of determining just how effective the drug may be in a therapeutic sense. Both the nature of the disease and the availability of medical cases often impose limitations of varying degree on obtaining evidence and assessing value. Generally speaking, there are four types of clinical tests for effectiveness.

First, evidence of the most crucial and decisive nature is derived from the successful treatment of even a small number of patients who suffer from a disease which is otherwise *uniformly fatal.* Two examples of this near-perfection spring to mind at once. After the lives of less than a dozen patients with hemolytic streptococcus meningitis were successively saved with the use of sulfanilamide, it became immediately evident that here was a drug which was uniquely effective in this formerly fatal condition. Likewise, patients with subacute bacterial endocarditis, for the first time in history, proved subject to cure by adequate and prolonged penicillin therapy. In the case of such effective specific drugs, the number of cases which need be studied be-

fore a definitive opinion can be reached as to its value is comparatively small—easily within twenty-five.

However, when comparisons of a finer degree are necessary, as with two drugs, each of which may save life in an otherwise fatal condition, then more evidence becomes essential. Here the endpoint becomes not life or death, but the duration of the illness, the degree of involvement, the incidence of complications, or some other less tangible and exact criterion. In such instances, the number of trials must be large enough to allow statistical analysis. If the end point is a matter of definite recognition, relatively few—perhaps fifty to one hundred cases—may give significant statistical proof. On the other hand, if one must decide on the basis of vague symptoms or those of infrequent occurrence, as many as a thousand cases may have to be collected for conclusiveness in analysis.

Drugs which are not specific for the cure of a disease, but rather constitute symptomatic treatment, that is, being capable of only controlling a symptom incident to the disease, are less frequently prone to critical assessment on the basis of only a few trials. However, were morphine a new drug today, the demonstration of striking relief of pain in a score of intensely suffering patients would be adequate to assure its effectiveness. While it is true that similar results may still be demonstrable with new analgesics, as with the specifics, when there are competing drugs in a field, the mere demonstration of such action does not in itself permit a conclusive evaluation of the drug. Thus, isonipecaine relieves pain, but critical comparison with morphine or other analgesics in perhaps hundreds of cases was necessary to establish its relative potency and its probable usefulness.

Secondly, evidence may be obtained from *alternate cases.* In such tests, every *other* patient is given the drug under investigation, the alternate patients remaining untreated, or administered some more usual drug or method. Indeed, for most drugs, whether they be specific or symptomatic, this method is the most favorable system of analysis. As a matter of fact, of course, most common illnesses are not uniformly fatal; and unless the ex-

pected fatality is 100 per cent, the previously described small series tests are not applicable. This is not to say that the finding upon which the study is based may not still be based on deaths, but death, for instance, in 20 per cent as against 80 per cent of the patients. However, in most instances it is not deaths which are considered; instead such minor variable criteria as number of days in hospital, amount of weight lost, or estimated degree of relief of symptoms serve as the governing factors.

Effects are calculated, in this method, not so much from direct remedial results but rather on a comparison basis with the untreated cases, known as the control series which of course are as nearly as possible identical with the series under test except for the treatment afforded. One important safeguard must have strict attention if the calculations are to possess any value. This is due to the fact that while most data based on biological reactions vary, the variability of symptoms inherent in the "control series" is many times that of the "uniform fatality" of the first type of tests considered. Therefore, it will be found that numerically many more trials are necessary under this method, and indeed some amount of statistical analysis is valuable. Of course, when, in a series of 100 patients, mortality is halved compared to an alternate series, one may have no doubt of the general significance of the result; they are evident to the most skeptical and critical. On the other hand, when differences in results are less striking, statistical calculations at times prove of considerable help. Such computation, for example, may show that the result observed had, perhaps, only one possibility in a thousand of occurring by chance alone. It is up to the investigator then to decide whether he is satisfied with a ratio of one in ten or one in one thousand, so far as this element is concerned, to make the results acceptable to him. At this point, admittedly, statistical analysis veers from mathematical certainty to something of an art calling for careful judgment and evaluation in reaching a final interpretation.

As we have pointed out, biological data, particularly in man, are highly variable and complex. Investigators have frequently had a feeling that while one trial was a perfect test, another

possessed some flaw or fault affecting its reliability; yet the latter results are far too close to reality to be discarded or discounted. In such instance, only with a large series indeed, and a high apparent statistical significance, can an investigator of human individuals have any sense of finality and assurance.

Oftentimes a study of alternate cases may be additionally refined as a "blind test." Such tests are devised by first having the drug under trial prepared in the same form and appearance as an inert substance to be used as the control. Neither patient nor physician is informed as to whether the inactive or potent article is being tried in any individual subject. Moreover, records are kept by another person who does not see the patients, thus helping to prevent bias by either patient or observer. The method is particularly useful where some minor or subjective symptom is under test. To give an important example of its value, vaccines for the common "cold" had been reported to have great benefit. It was suspected, however, that the patients and physician not only anticipated that relief might occur but hoped for it. Put to a "blind test" cold vaccines have been proved valueless. Indeed, in some of the trials persons being administered material which served as the inert control enthusiastically reported great relief. Unreliable responses of this sort serve as an additional indication of the caution necessary when dealing with endpoints which are not objective or obvious, but are measured by subjective reaction.

A third method of test involves the use of *alternate or selected series.* Here the comparison is of results found in different groups rather than individual patients. Thus, one group of patients may be compared with another treated perhaps the year before or treated by another investigator. The two groups may, on the other hand, be treated simultaneously, but the patients selected in some other manner than by simple alternation of serial cases.

The results from this method are obviously less critical and precise than for alternate cases because of the many variable factors implicit in such a selection. Thus, the characteristics of diseases change from year to year; nursing attention may be

greatly different in various localities; and enthusiasms are harder to control when some of the evidence is not immediately at hand. Nevertheless, humanitarian aspects often necessitate trials of this character despite their reduced significance. Especially if lives are at stake, one is reluctant to deny any suffering patient the possibility of a cure by a new drug. Thus, it is often pointed out that had the early investigators of diphtheria antitoxin resolutely withheld the remedy from alternate children, the value of their work in an absolute state would have been more definitive and the evidence more helpful today in view of the present grave form of the disease. However, no one seriously censures these early investigators; their course would no doubt be repeated today. Nevertheless, there can be no question that both immediate and long-term evidence are greatly desired.

A modern example of a carefully selected series which served to establish a new drug's reliability is seen in Colebrook's trials of sulfonamides in puerperal fever. But in this instance the comparison was with the results of many previous years, and the observer, moreover, a deep student of the infection having the ability to evaluate results. Also, the endpoint could be expressed absolutely, in percentage mortality and hence with more precision. Another illustration, concerned with a drug more symptomatic than specific, may be seen in the study of the effects of heparin and dicoumarin in phlebitis. The incidence of complications has been reliably compared with that expected from previous experience with other medical treatment, although more difficult comparison with surgical ligation of veins is not entirely satisfactory. The latter exemplifies the difficulty with selected series—the investigators are likely to be of different temperament and in different hospitals, and a defendable answer is not forthcoming without the highest degree of cooperation between all engaged in the work.

The fourth and poorest means of clinical assessment is by trial on a *single case*. Of course, it may not be possible to study diseases of extraordinary rarity otherwise, although the majority of illnesses are not so limited. But even with rare diseases this evaluation is acceptable only because it is the only alternative.

It may be assumed, therefore, that rarity does not lend decisiveness to a trial; indeed, the results will ordinarily be as erratic as with single cases of more common diseases.

The variations already discussed, inherent in biological phenomena, natural and planned, can be evened out only by number of cases. Indeed, a report of recovery in a single case of a disease so uniformly and presumably absolutely fatal as rabies should be suspect. Not only would there be suspicion as to correct diagnosis, which, of course, must be positive, but one must be prepared for occasional completely unexpected and unrepeatable recoveries, purely coincidental to current therapy. In this class are the rare, but genuine, regressions of malignant tumors.

TOXICITY

The dangers of a drug are, in a way, as important as its therapeutic effectiveness. Ordinarily, they are considered during the same clinical trials which test for efficacy in the drug, but the two subjects may be discussed separately for the sake of clarity.

Toxicity is of two general sorts. First is the ordinary expected toxicity which appears when the dose is excessive. Naturally, what is excessive in one person may not prove so in another, although in the second the same symptoms will appear when his tolerance is reached. Thus, 10 mg. of amphetamine taken at noon ordinarily will not produce undue wakefulness that night; 20 mg., however, may produce this expected symptom. Another person, though, may take 20 mg. at noon without insomnia, but a still larger dose will be found which does produce this symptom.

It may be noted that evident toxicity in itself is not necessarily a contraindication to the use of a drug. Thus, tinnitus often appears during the administration of quinine, but it is usually tolerable, and is looked on as an unpleasant side effect, rather than dangerous toxicity. The same is true of the use of colchicine for gout, where indeed relief is coincident with the appearance of toxicity, usually nausea and diarrhea.

The second type of toxicity differs strikingly from the first.

Instead of being expected upon reaching a certain dose, it appears, without anticipation, and sometimes at low dosage levels. Moreover, it is seldom demonstrable in lower animals. Usually only a minority of patients exhibit this state, often called sensitiveness or idiosyncrasy. The symptoms are not like those of overdosage; rather, they resemble a type of allergic reaction. Indeed, it is conceivable that all idiosyncratic reactions are indicative of sensitiveness in the specific allergic sense, although such a connection has not always been demonstrated. The more common of these manifestations are dermatitis and urticaria of various types, the Arthus phenomenon, hay fever, asthma, bone marrow depression, and visceral degenerations. Phenobarbital may be mentioned as an example of a drug which ordinarily produces somnolence and coma; in the rare sensitive person, however, it may give rise to a macular eruption on the skin. Aspirin is an excellent example of a drug widely used and ordinarily considered safe but which is capable of producing alarming symptoms in those sensitive to this drug.

The first type of toxicity, namely, that caused by over-dosage, is much the less to be feared. If doses are gauged carefully, accidents may be foreseen in their incipiency and thus prevented. The second type, however, may appear without warning and is often of much greater potential danger, indeed of such serious impact that every new drug must be explored fully in this connection. With the background of animal experience, one usually has an adequate knowledge of ordinary toxicity by the time 100 patients have been treated. Perhaps a thousand, or even several thousand, patients must be observed, however, before one can have any surety that all likely sensitivity manifestations have been observed and their rate of incidence determined. For example, thiouracil and propylthiouracil are drugs that required considerable study before their ability to cause changes in blood cell formation was observed.

When assurance of reasonable safety and satisfactory effectiveness under acceptable means of administration are presented, the new drug may be considered ready for general use from the clinical point of view.

ADAPTATION OF PRINCIPLES OF TESTING BY THE MANUFACTURER

Usually the pharmaceutical manufacturer has neither the facilities nor the personnel for extensive clinical trials with new drugs. Even should these be available, confirmation from entirely unbiased sources is not only desirable, but also a matter almost of necessity. Accordingly, when a product appears to possess merit from pharmacological or preliminary clinical tests, the producer faces the immediate problem of choosing reliable investigators, experienced in the particular field, to conduct further inquiries into the properties of the new drug. Experience in the field, however, is not the only requisite; the investigator must also have access to adequate clinical material, including untreated, or otherwise treated, patients as controls.

Adequate clinical material further includes patients willing to cooperate in the tests, in a position to be accurately diagnosed and who may be kept under suitable observation before, during, and following the trials. Moreover, the outside investigator must have the necessary facilities, not only to examine expected developments, but any leads incidental to the trials as well. Thus, many drugs, during the course of their tests require repeated physical examinations of patients, laboratory measurement of physiological constants (chemical or physical) and functions and often actual measurement of the concentration of the drug in the body tissues. X-ray examinations may be needed; experienced consultants, particularly pathologists, should also be available. These many facilities and skills are essential if one is to obtain a reliable estimate of effectiveness, toxicity, and procedures for administration. One requirement in the investigator is an independent mind; he should even be somewhat skeptical in his attitude. But above all he must be capable of careful planning and of objective estimate of the actions of the drug.

Where is the manufacturer to find investigators of these qualifications? Unfortunately, many practicing physicians lack the necessary skill, facilities, and experience to be helpful in un-

dertaking the work. The busy private practitioner, moreover, often has neither time, training, nor inclination for the patient and systematic collection of the necessary data. His services are generally limited to reporting unusual reactions or toxic manifestations. But he should not be entrusted with the task of verifying clinical toxicity or efficacy unless he is fully qualified to undertake this type of activity. Sometimes, however, there are such men who are active in research; who are qualified by formal training and experience; who have an insatiable curiosity and a critical mind; and who have the necessary facilities for controlled studies.

On the other hand, the academic clinician connected with a medical school or occasionally a hospital is freely consulted by those with new drugs for trial. His very position makes him an obvious consultant for research. His primary function is not to treat the individual patient, but rather to impart knowledge to others. His approach is both critical and impartial. He has, moreover, the time, the disposition, and the mental qualifications to undertake and carry out crucial clinical trials; from men of his type usually come the definitive answers.

In the past, contact between the manufacturer and the academic-minded clinician has been haphazard. While mutual interests were occasionally discovered and developed, oftentimes the investigations themselves were not carried out by the best qualified investigators. Again, geography frequently determined the selection of the investigator, with the result that certain observers were overburdened with investigations, which suffered accordingly, while others, with perhaps even better opportunities for carrying them out, were not interested in the problem by the manufacturer. The loss was a mutual one.

In an attempt to remedy this inequitable procedure, as well as to improve the quality of research generally, the Council on Pharmacy and Chemistry of the American Medical Association in 1946 organized the Therapeutic Trials Committee. This group stands ready to assist manufacturer and investigator alike in promoting the development of new drugs from the clinical view. One of the objectives of the Committee is to bring to-

gether the investigator, having proper facilities, with the manufacturer of a new product. Incidentally, it hopes to assist and guide such trials in the most promising directions. It lends the experience of its members to the planning of the trials and assists in the preparation of the results for publication. It may also aid in locating sources of clinical material, for example, in prisons or other State institutions, for appropriate investigations.

The Committe also may lend assistance in answering the sometimes difficult question of the number of investigators who should handle a particular problem, and in correlating their work whenever this is advantageous. Obviously, however, this correlation and assistance must be such as will not diminish the independence of the investigators. Indeed, without free personal initiative the stimulus to do other than routine and unimaginative work may be sacrificed.

The costs of the investigations must be considered by both the pharmaceutical manufacturer and the investigator. Where only a few trials and tests may be needed, expense may not constitute a major item, but for the most part clinical trials, like the original chemical and pharmacological investigations, are drawn out and expensive. In fact, clinical trials on hospitalized patients are exceedingly costly. This means that the number, extent, and variety of tests, and the number of investigators to be financed, must be carefully considered and rigorously planned. In the case of large programs, financial support almost of a necessity must be raised outside the investigator's institution. Thus, it may come from private individuals, foundations, the Government, or from a group of interested manufacturers. Here again the Therapeutic Trials Committee may assist in planning the trials to simplify their scope critically and to avoid needless duplication, as well as in obtaining financial support for worthy projects from the sponsors of the drug or treatment, and occasionally from other sources.

When a drug firm supports clinical investigations, it must be prepared to give the clinician a free hand in the final design of the trials and publication of results. Otherwise, more able investigators will refuse to cooperate and the firm will thus

fail to get truthful and unprejudiced answers which are vital to long term profitable production. Of course, the company in subsequent advertising material may refer to the publications of the investigator in the same manner as other bibliography. Ordinarily, also, there should be no confidential aspects to the agreement between manufacturer and investigator. The firm may use the published reports, or the unpublished findings if the investigator permits, in support of new drug applications to the Food and Drug Administration, but should not use unpublished reports or the investigator's name in promotional material except by his express permission. Except in wartime, when such reports were frequently given to governmental agencies, investigators should not, however, be expected to give such permission.

The purpose and objectives of the Therapeutic Trials Committee are not dissimilar to those of anyone interested in sound research and the advance of rational therapeutics. They reflect a trend in the thinking of those who today are research minded. Since there will be an increasing use of this type of investigative facility, part of a published statement by the Committee is reproduced from *The Journal of the American Medical Association* (June 15, 1946, p. 596):

Purpose.—The Committee has been formed to encourage and aid sound research on medicinal agents and to promote therapeutics through an adequate understanding of the usefulness and limitations of drug products. In particular, the Committee (on its own decision) will organize impartial clinical trials of biologic and pharmaceutic agents which offer promise in the prevention, treatment or diagnosis of disease.

The fundamental objective of the Committee is to stimulate progress in the control and treatment of disease through facilitating investigations to establish the usefulness and limitations of diagnostic, preventive and therapeutic agents. The critical clinical appraisal of such agents and the dissemination of information about them will be accomplished by the voluntary cooperative effort of pharmaceutical manufacturers, laboratory investigators, clinical investigators and the medical profession.

Procedure.—1. The Committee will initiate or receive from outside sources suggestions regarding problems which offer promise of better means for preventing or curing disease or regarding particu-

lar products which are offered for the diagnosis, prevention or treatment of disease.

Requests for the investigation of theories, methods and means for controlling disease may be addressed to the Committee. Forms for the purpose of submitting requests to the Committee for clinical trials may be obtained from the Secretary. If the Committee deems a project desirable and feasible, steps will be taken to interest sponsors and investigators in conducting a cooperative project under Committee sponsorship.

2. The Committee will seek and receive and analyze information and suggestions with reference to university departments, hospitals, research institutes and other suitable agencies for conducting clinical trials, with special reference to their fields of particular interest and competence. The Committee will welcome information concerning available investigators.

3. The Committee will provide a medium whereby investigators interested in particular therapeutic problems may coordinate their efforts and seek advice from others working in the same field.

On its own initiative, or at the request of one or more investigators, the Committee may arrange at a suitable time and place a conference on a therapeutic problem of interest. The purpose of conferences will be to provide a mechanism for the prompt exchange of information on problems in which investigation is proceeding rapidly and simultaneously in a number of different centers. By such conferences, investigators may compare ideas and coordinate their efforts, thus preventing waste of time and duplication of effort. In addition the Committee may arrange for a rapid interchange of information on therapeutic investigations through a central clearing house. It will assist clinical investigators in securing competent advice on the conduct of their investigations.

4. When the Committee is convinced that a product or problem merits investigation and knows of a competent agency potentially interested in the investigation, steps shall be taken toward bringing the two together.

If more than one sponsor may be interested in a product, efforts will be made to secure their cooperation by inviting them to participate in the project.

5. Before a product shall be subjected to clinical trial, information must be available as to its nature, standardization, pharmacologic actions and toxic effects.

Items on which information should be furnished to the Committee are the following:

(*a*) Full data concerning the composition of the agent.

(*b*) Physical and chemical properties, including methods of assay, particularly those applicable to *in vivo* studies.
(*c*) Pharmacology (actions, toxicity and fate).
(*d*) Results of any preliminary clinical studies.
(*e*) Conditions for which the drug is believed to be of value.
(*f*) Proposed dosage and method of administration.
(*g*) Any other relevant information.

6. The Committee shall be under no obligation to initiate or participate in any investigation unless the Committee deems such investigation promising and feasible.

7. The Therapeutic Trials Committee may serve as an agency whereby the sponsors of a problem or product are brought in contact with suitable hospitals or testing agencies so that an independent contract may be concluded in each instance between the sponsors and the agencies conducting the clinical trials. The Committee will subscribe to such contracts provided it is satisfied that the plan of investigation, financial arrangements, means of reporting and other factors are such as will insure an adequate and unbiased clinical trial. On request, suggestions regarding the technic of the proposed trial will be offered.

Prospective investigators will be requested to submit to the Committee, as part of a proposed contract, their general views on the following:

(*a*) A proposed plan of investigation.
(*b*) An estimate of the cost of the investigation.
(*c*) An estimate of the time required to complete the investigation.
(*d*) An estimate of supplies or special equipment which they would wish to be supplied by the applicant.
(*e*) A statement of the direct contacts they wish to have with the sponsor.
(*f*) A statement as to the frequency with which they wish to make progress reports to the Committee.

It is understood that these statements are only tentative.

The Committee will not undertake to direct the method by which an investigator shall pursue a problem. If a proposed plan of investigation appears unsatisfactory to the Committee, the investigator will be given the opportunity to modify his plan. If he does not care to do so, the problem may be offered to other investigators. The Committee will, if requested by the investigator, offer advice regarding the proposed plan of investigation, but it desires to assure at all times the freedom of the investigator.

8. If the contract so provides, the investigator may avail himself of the cooperation of the sponsors in supplying technical information related to the investigation.

9. Reports shall not be offered for publication until reviewed by the Committee. Investigators are free to publish their results in any manner they see fit. However, no mention of the Therapeutic Trials Committee may be made in any publication unless the report has been specifically authorized by the Committee.

If, after consultation between the Committee and the investigator, publication appears desirable, the investigator will be authorized to publish the results under his own name in a suitable professional periodical as a report to the Council on Pharmacy and Chemistry. Before the report is published, the sponsor will be informed confidentially of the results.

10. The mutual obligations shall be considered as completed with the termination of the individual contract, and further investigation with the cooperation of the Committee must be subject to further contracts.

Of additional interest are the forms for the application for clinical investigation, the proposal for contract, and the actual contracts suggested by the Committee. They might well be used as a guide by any group of individuals interested in research projects.

Application for Clinical Investigation

The undersigned hereby requests the Therapeutic Trials Committee of the Council on Pharmacy and Chemistry of the American Medical Association to arrange for a clinical investigation of

.....

Attached to and submitted as part of this application is the available scientific information regarding this agent, including the following:

1. Composition.
   (If a single substance, give structural formula, if known; if a mixture, name each ingredient and indicate quantity of each in a given quantity of the drug. In the case of biologic products or similar agents, state source and method of preparation.)
2. Properties.
   (Include both physical and chemical properties, method of assay and, if known, a method for detection of the agent in body fluids and tissues.)

3. Pharmacology.
   (Include data on actions, toxicity and fate of agent.)
4. Other relevant laboratory data.
   (Include, where applicable, data on biochemistry, bacteriology, immunology and the like.)
5. Results of preliminary clinical studies.
   (If preliminary clinical trials of the agent have been made, the methods and results should be described and the names and affiliations of the investigators given.)
6. Conditions for which agent is believed to be of value.
7. Proposed dosage and method of administration.

It is understood that this information will be transmitted to the Committee for consideration and, if a decision is reached to sponsor an investigation, the information will be transmitted to the prospective investigators.

....
Date *Applicant*

.....
Affiliation

.....
Official Title

PROPOSAL FOR CONTRACT

Date:

This proposal is to be prepared by the investigator to enable the Committee to understand the investigation and its implications. The information may be submitted in other form if the investigator prefers, but it should cover the subjects suggested by the headings. It is understood that all statements are tentative and do not preclude adaptations as the project develops, provided the total sum is not exceeded without specific concurrence of the sponsors and notification of the Committee.

1. Name, official position and address of responsible investigator:
2. Subject of investigation:
   a. Name or description of product or products:
   b. Field of investigation:
3. Questions to be answered by investigation:
4. Plan of investigation:

5. Requirements for investigation:
   a. Personnel (professional, technical and clerical assistants and approximate annual salaries):
   b. Materials (equipment and supplies):
6. Funds desired from sponsors:
   a. Professional assistants .....$
   b. Technical assistants .....
   c. Clerical and stenographic assistants .....
   d. Expense of patients .....
   e. Equipment .....
   f. Supplies .....
   g. Project overhead .....
   h. Contingent fund (not to include overhead).

   TOTAL $
7. Nature of any institutional collaboration in this work:
8. Concise description of facilities available for the investigation:
9. Suggest frequency and extent to which you would furnish progress reports to the Committee:
10. Indicate the extent or limitations you wish to place on amount of direct contact between you and the sponsor:
11. Statement of expected time of beginning work and estimate of its duration:

Signature.....
Responsible Investigator

Approved:

.....
Therapeutic Trials Committee

.....
Official Title

.....
Sponsor

....
Official Title *Date*

CONTRACT NO. .....

This agreement made this ..... day of ..... 194..., between ..... hereinafter referred to as THE SPONSOR, and ..... hereinafter referred to as THE INVESTIGATOR, WITNESSETH:

1. THE SPONSOR agrees to grant $..... to THE INVESTIGATOR, and THE INVESTIGATOR agrees to conduct under .....immediate direction an investigation of ..... in accordance with the plan of investigation contained in the Proposal for Contract No. ..... dated ..... and approved ..... which is made a part of this contract and attached hereto as Appendix A.
2. On the termination of this contract, any unexpended balance of said grant shall be returned to THE SPONSOR by THE INVESTIGATOR.
3. THE SPONSOR agrees to furnish the following equipment and supplies to THE INVESTIGATOR:.....
4. On the termination of this contract, the following equipment and supplies shall be returned to THE SPONSOR by THE INVESTIGATOR: .....
5. THE INVESTIGATOR shall make reports of progress to the Therapeutic Trials Committee of the Council on Pharmacy and Chemistry of the American Medical Association, hereinafter referred to as THE COMMITTEE, at the following intervals:....
6. No publication of the results of the investigation contemplated by this contract shall be made by either party until after the proposed publication has been submitted for the consideration of THE COMMITTEE. In the event that THE COMMITTEE does not approve of the proposed publication, any future publication shall make no reference to or mention of THE COMMITTEE.
7. THE SPONSOR shall communicate with THE INVESTIGATOR only through THE COMMITTEE except as hereinafter provided: ....

8. Unless extended by mutual agreement among THE SPONSOR, THE INVESTIGATOR and THE COMMITTEE, this contract shall terminate on .....

Signed.....
THE SPONSOR

.....
Official Title

.....
THE INVESTIGATOR

.....
Official Title

Approved.....
Therapeutic Trials Committee
by the Secretary

.....
Date

(This contract takes effect when approved by the Therapeutic Trials Committee of the Council on Pharmacy and Chemistry.)

This definition of correct procedure may make the investigator appear to be a prima donna who lays down all the rules. However, it must be remembered that his only profit from the undertaking lies in the satisfaction of having discovered new facts which may advance knowledge, and in the recognition of his accomplishments by his colleagues and others. It must be borne in mind that he receives no direct financial benefit, except to the extent that academic promotions may depend, in part, on productive research; he, therefore, will not be influenced in the performance of his investigations nor as to their manner of presentation to the public. This independence, however, has considerable value for the pharmaceutical manufacturer, for in lack of commercialism rest the foundations of objective evaluation of the merits of his products.

Adequate clinical evaluation of a new drug is usually dependent on the services of experienced researchers with sufficient time to conduct investigations. At times it can be done at one medical center with one or several investigators participating. At other times, however, it may be necessary for a large group

to enter into the research project and perhaps to divide the work so that the research will be thorough with a minimum of overlapping. Such was the case for the evaluation of penicillin in the treatment of syphilis and of streptomycin for tuberculosis. Normally these extensive projects are not necessary; the drug can be more simply evaluated. Nevertheless, regardless of the scope of the research project or the number of researchers involved, there is always the need for information sufficiently complete to meet the questions raised by the medical profession. There is no detailed plan to elicit this information; it must be devised as the needs, which will depend on the drug, arise. However, a general plan was outlined by representatives of the Food and Drug Administration and of the Council on Pharmacy and Chemistry and was published in *The Journal of the American Medical Association* (December 9, 1944, pp. 958-961).

Briefly, the authors propose studies on biochemistry, pharmacodynamics, experimental functional pathology and chemotherapy as test procedures in laboratory animals to determine the probable usefulness and limitations of the new drug. Then, questions on acute toxicity, subacute toxicity, chronic toxicity, local effects, and special problems, such as reproduction, should be answered. After which, the following questions may be posed:

1. Has the drug definite and desirable pharmacodynamic or chemotherapeutic actions?
2. Are its actions constant and reproducible?
3. Are these actions observed in different species of animals?
4. Is the mechanism by which its actions are produced a desirable one, or are the actions the result of an ultimately undesirable reaction of the animal?
5. Are the effects obtained in animals in which experimentally produced pathologic or functional changes have been made comparable to effects obtained in human diseases?
6. What is the therapeutic index of the compound (ratio of effective dose to toxic dose: ED_{50}/LD_{50})?
7. Are the undesirable side actions of sufficient importance and severity to militate against its clinical use?
8. Is there an adequate margin of safety in its use?

These same authors sum up the primary objectives in clinical investigations thus:

(1) to determine the therapeutic efficacy and (2) to detect all signs of clinical intolerance or toxicity. The secondary, but nevertheless important, objectives are (1) to establish the effective dosage range for different age groups and conditions, (2) to determine the type and extent of collateral treatment necessary to obtain the maximum benefit from the drug, (3) to determine the best method of minimizing any undesirable side actions incident to the use of the drug and (4) to determine the contraindications and precautions to be observed in the use of the drug.

As a result of considering the above and other factors one is then able to ask and answer the following questions to the satisfaction of all mutually interested parties:

1. For what conditions is the drug to be offered?
2. How effective is it in these conditions?
3. Is it superior to other drugs and methods of treatment?
4. What is its inherent toxicity?
5. Does its toxicity outweigh the therapeutic advantages, keeping in mind the seriousness of the conditions for which it is being offered?
6. If there are other drugs equally or more effective in the same conditions, is the new drug less toxic or does it offer advantages in ease of administration, duration of action and so on?
7. How extensive will the use of the drug be; are its applications limited?

In summary, when the therapeutist is presented with a new drug for clinical trial, he must determine the best means of administration, the effectiveness, as exactly as possible, and the dangers, before it may be passed on to the practitioner for general use. This assessment is seldom an easy task. It requires considerable planning, objectivity of mind, and willing and available patients.

The manufacturer with a new product for clinical trial must work in cooperation with the research investigator and may provide financial support without assurance of favorable reports and without any immediate or direct participation in the direction of the investigation. But regardless of the outcome of an

investigation, research is absolutely necessary to satisfy the medical profession, Federal agencies, such as the Food and Drug Administration and the National Institute of Health, and, of course, that part of drug manufacturing concerned with profit. For the good of the industry, as well as humanity, a product must be thoroughly explored before it is offered in commerce. And if there is any question concerning its efficacy the drug will be best kept off the market until all uncertainty is removed. Lack of confidence by the medical profession, generated by lack of efficacy on the part of the product, and damage to the patient caused by toxicity that would have been apparent if proper research had been conducted, can be costly.

Development of Facilities and Controls

EDGAR B. CARTER

IT is one thing to produce a new pharmaceutical formula or a new chemical compound successful in the laboratory; it is another, however, to manufacture it on a large scale in the plant. Consequently, after the formula of the new product has been perfected, its pharmacology investigated, and its clinical efficacy and safety demonstrated, it still is often necessary to extend consideration to the development of proper and adequate facilities and controls for its production on a commercial scale.

The development of facilities need not, however, have overattention in a work of this nature. Ordinarily, the equipment available in the plant will be utilized for the production of the drug. Thus, where the company is already manufacturing parenteral solutions, the ampul cleaning, filling, and finishing facilities are simply adapted to the making of a new parenteral drug.

We may, however, take this opportunity to emphasize one important aspect of production facilities. Generally, it is good policy to install the best equipment that the organization can afford. It should also be borne in mind that, for the manufacture of standard dosage forms, such as ampuls, tablets, capsules, syrups, and elixirs, highly specialized machines have been developed and are readily available. Not only is it wholly unnecessary, in the usual processes, to design and build new equipment, generally speaking, but it will ordinarily be found that equipment on the market is free of the complications that frequently de-

velop in the case of so-called special equipment. Indeed, the use of these facilities is not only economical in the long run but makes a better and more uniform product, serves to protect the preparation from contamination, and minimizes the possibility of errors in its manufacture, packaging, and labeling.

Similarly brief comment may be made so far as the plant arrangement and design are concerned. It will be found that the flow of materials through the establishment will be far more satisfactory if these are originally planned by one having considerable experience in pharmaceutical manufacture. It is hardly possible, in a work of this nature, to give more than this suggestion toward a most intricate and important subject.

Nor is it practicable to attempt to describe the equipment that may in a particular instance be required for the manufacture of the new drug product. For example, an organic synthesis may require special types of equipment depending upon the processing involved, e.g., hydrolysis, esterification, alkylation, amination, nitration, or high-pressure catalytic reduction. Even in the production of galenicals and ointments the equipment depends upon the particular type of product to be made, and particularly, the size of the batches involved. Again, for certain types of parenteral solutions, all-glass equipment becomes essential; for others, glass-lined steel may be used; and for yet other solutions, stainless steel will be found to give the best results. Similarly, filtering devices must be selected with particular solutions in mind; here, too, the equipment will vary with the size of the batch.

In brief, equipment should be tailored to the drug product to be made. However, so many are the pitfalls that may be encountered in converting a laboratory process to a plant process that it is accepted practice, both economically and logically, to take the laboratory process first to a *pilot plant* to determine the proper methods before attempting to manufacture the product in large scale equipment.

For the production of organic medicinal chemicals in quantity, as a matter of fact, pilot plant operation is an absolute prerequisite. While it may not be quite so essential in the manu-

facture of pharmaceutical dosage forms, even in such instances the use of a pharmaceutical pilot laboratory will contribute much to future operations. This becomes evident when we recognize that, in working with new drug products in dosage forms, it is impossible to foresee all the conditions that may arise in the manufacture which may affect the end product.

What is a "pilot plant" in drug operations? Briefly, it may be described as nothing more than a small manufacturing plant in which the equipment consists of small scale models of that which will be used when the product is in full production. It should not, however, be viewed as a laboratory table operation. Usually, the successful manufacture of batches one-tenth the size of the expected commercial quantities will give a fairly representative idea of what may be looked for in large scale production. For example, if the product is to be made commercially in batches of 1,000 gallons or 1,000 pounds, a batch of 50 or 100 gallons or pounds will usually suffice for pilot plant operation. Where regular production will be in fifty gallon batches, five gallon trial runs in the pilot plant should disclose the problems that may be encountered at a later time. Needless to say, if the production is to be in very small batches, the pilot operation may well be the production unit.

CONTROLS IN GENERAL

Unlike facilities, controls are never static, involving, as they do, a pattern of constant and continuous supervision over the processing, packaging, and labeling of the drug. Indeed, it frequently becomes essential to develop and plan special types of controls for a particular drug. But even if this be unnecessary, existing control methods must still be affirmatively adapted to the production problems involved. In the following pages the usual protective measures prevailing in all well-operated and supervised pharmaceutical plants will be discussed.

However, a quick impression of the care and detail that necessarily go into the establishment of proper controls may be gathered from the few questions put by the Food and Drug

Administration in its new drug application regarding the subject:

1. Precautions employed to insure adequate and proper identity, strength, and purity of raw materials;
2. Whether or not each lot of raw materials is given a serial number, and the use made of these numbers in subsequent plant operations;
3. The method in which the formula card is prepared, and the way in which it is utilized;
4. The number of individuals checking the weight or volume of each ingredient entering into each batch of the drug;
5. Whether or not the total weight or volume of each batch is determined at any stage of the manufacturing process, subsequent to making up a batch according to the formula card, and at what stage, and by whom, this is done;
6. The precautions taken to check the total number of finished packages produced from a batch of the drug with the theoretical yield;
7. The precautions taken to insure that the proper labels are placed on the drug for the particular lot;
8. The analytical controls employed during the different stages of the manufacturing, processing, and packing of the drug, including a detailed description of the collection of samples and the analytical procedures to which they are subjected. Similarly, if the product is one which is represented as sterile, the same information should be given for sterility controls;
9. An explanation of the exact significance of any control numbers utilized in the production and packing of the drug, including any code numbers that may appear on the label of the finished article. It should also be stated whether or not any of the numbers appear on invoices;
10. Any additional procedures that may be employed, designed to prevent contamination and otherwise insure proper control of the product.

PERSONNEL

It must be constantly borne in mind that facilities include more than equipment and plant arrangement. Perhaps its most important single component is personnel. In pharmaceutical manufacture and control, the responsible individuals in each department must be selected and trained with much care and forethought. Nor must they possess merely the desirable attributes of good foremen, such as honor, integrity, and leadership. More important, they must have a comprehensive knowledge of the art and science of pharmacy.

Although for the manufacture of chemicals, generally chemists and chemical engineers are desirable, the manufacture of pharmaceutical formulas—the dosage forms in which medicines are dispensed to patients—calls for every phase of the production to be supervised by men trained in pharmacy. This is because it is not enough to be able to see to it that all the ingredients of a formula are carefully weighed and added to the mixture; it is also necessary to be certain that nothing be permitted at any stage of production which may affect, modify, change, or precipitate any of the active ingredients in the preparation.

In the early years of manufacturing pharmacy, before analytical control became customary (or, we may say, compulsory), it was not unusual to find products on the market wholly lacking some of the active ingredients declared on the labels. Yet such active ingredients—often, indeed, the most expensive ones —had been carefully weighed and incorporated into the formula, to be lost, not through dishonesty, but through ignorance of the laws of pharmacy involved. Sometimes the active ingredients were destroyed in the manufacturing process. More often, they were precipitated in processing or were removed by the filter-aids used for clarification and discarded with the filter papers.

In emphasizing the need of trained pharmacists in supervisory positions we do not intend to imply that it is answered by

the general class of so-called graduate registered pharmacists, legalized to fill prescriptions after completion of the customary courses. Actually, we have in mind men highly trained in pharmacy and the related sciences.

Even the rank and file of the workers should, moreover, be selected with great care and these should be inculcated with the thought that theirs is an important part in an important undertaking. The nature of the work should appeal to the more fastidious, and special efforts may well be made to attract and hold the higher type of worker.

CONTROL ORGANIZATION

Control is intimately related to production. It is a truism in the manufacture of any article that adequate control must be exercised if the quality and uniformity of the end product is to be maintained. In the production of pharmaceuticals, however, control is paramount. Medicines are made for the sick, and the well-being of people everywhere may be profoundly affected by the product of the pharmaceutical manufacturer. Indeed, the lives of multitudes can be jeopardized by a little carelessness or thoughtlessness on the part of those engaged in this work.

To many, control in a pharmaceutical plant suggests chemical or analytical control. But this is only one part of a broad subject. Control starts with the writing of the manufacturing work-order. This is the working formula, the step-by-step instructions for the process. Also included, in addition, is factory control and laboratory control. Thus, the responsibility for the approval of all finished merchandise is vested in the control manager, who is independent of the factory and responsible only to the general manager. Except for certain special inspectors, who, in some plants, are responsible to the control manager, the responsibility for factory control rests entirely on the plant superintendent. Both factory and laboratory control are indispensable; laboratory control without factory control,

or vice versa, will never suffice to protect the merchandise or the patients to whom it is administered.

In the following pages the various control procedures are discussed. These include *(a)* the manufacturing order, *(b)* factory control, *(c)* inspection at the production center, *(d)* samples for inspection and approval, *(e)* laboratory control, *(f)* the bioassay laboratory, *(g)* micro-bioassay of dietary supplements, *(h)* checks on stocks of ingredients and finished materials, *(i)* control of packaging materials, *(j)* control of labeling materials, *(k)* control of label copy, and *(l)* plant sanitation in general.

THE MANUFACTURING ORDER

The manufacturing order—known in some plants as the "work-order," and in others as the "formula card"—may be broadly described as the pattern to be followed in the manufacture, processing, packaging, and labeling of the drug product.

Thus, the manufacturing procedure to be followed is outlined precisely in the work-order. A further part of the master manufacturing work-order are the requisitions for all ingredients to be used, with their proper code numbers. Even the exact pieces of equipment to be utilized in production are specified. The work-order, moreover, requires that the batch be weighed or measured and checked or adjusted against the theoretical values given in the outline at certain points in the manufacture. It directs the taking of samples for laboratory examination at other stages in the operation. Spaces are left for the initials of the workmen completing each step in the procedure, as well as for the date on which each operation was started and was completed. Certain operations may call for the ticket to be stamped with a time clock when started and terminated as an additional assurance of accuracy.

Usually there is a separate sheet or packaging work-order giving standard specifications for packaging and labeling and providing for a final count of all finished packages and a check against the theoretical yield stated in the outline.

In some establishments, the writing of the master work-order

is a function of the control department or of a chief pharmacist. In others it is done in a separate planning department also vested with the responsibility of scheduling the work through the plant. Copies of the master work-order are then prepared for each batch to be manufactured by blue-printing, photostating, or some other process which gives replicate copies to prevent typographical errors. In some plants, the work-order issued for each batch includes the requisition for all packaging and all labeling supplies. On the other hand, when the formula will be a long time in work, the finishing work-order may not be issued until later so that the order for different size packages will provide for the immediate stock needs. In such a case, the finishing work-order catches up with the manufacturing work-order in the finishing room, and the two are attached before delivery of the merchandise to the stockroom.

FACTORY CONTROL

Factory control is the system organized to minimize human error and to detect it if and when it does occur. The system will, of course, vary for each type of product. Many of the patterns of control are quite similar among the different manufacturers; indeed, there has been a laudable exchange of information on the subject among competitors. Again, many of the systems have been the direct outgrowth of an error, either in the establishment or in the plant of another manufacturer. For example, when it became known that two potent drugs were accidentally mixed in one establishment, in practically every pharmaceutical house in the country the superintendent called together some of his department managers and asked, "Could it happen here?" There can be no doubt that every responsible head immediately reviewed and, where necessary, revised his system so that it would be virtually impossible for the drugs for one manufacturing work-order to become mixed with those for another.

It would in one chapter be impossible to outline all the methods and systems that comprise factory control for the vari-

ous types of pharmaceutical products. A few examples, however, will be given to emphasize the basic principles and practices.

One cardinal rule is that no two ingredients should ever be placed on the weighing bench at one time. Moreover, all weights must be verified by another workman, and both weigher and checker responsible for the operation must affix their initials at the proper place on the requisition. Another is that no two tablets of similar shape and color should ever be made at the same time on adjacent tablet machines; in a similar connection, unless absolutely necessary, sulfanilamide and sulfadiazine tablets should not be scheduled through the tablet department simultaneously. In tablet-making, furthermore, good practice dictates that the total weight of granulation for a batch of tablets be determined when it is removed from the drier and mixed. This weight is recorded and checked against the theoretical weight stated on the work-order. The total weight of all the tablets is likewise recorded on the work-order and, when added to the weight of the "tailings" or "siftings" plus that of any imperfect tablets, must substantially check with the theoretical weight specified on the work-order.

Some establishments have counting devices attached to the tablet machines and fill the tablets into bottles just as they come from the machines. Others make use of counting boards. These are usually made of highly polished wood with cavities of the proper size; each cavity thus holds one tablet. The total number of cavities in the board hold the number for each individual bottle, and the whole, when filled, may conveniently be dumped through a filling device into the container. There is no excuse, other than carelessness, to pack more or less than the exact number of tablets required for each bottle. To preclude errors some plants require the operator filling the tablets into the bottles to place in each a slip showing the serial number of the batch and the number of the operator. When an operator realizes that she individually is expressly responsible for the number of tablets in the bottle, there are fewer mistakes. Once the tablets are packaged, the total count in each size bot-

tle must check with the theoretical count on the work-order. Any appreciable deviation calls for an immediate investigation.

Ordinarily a solution for ampuls is made up to a definite volume. A sample is sent to the control laboratory for assay, although the plant may make a rough check by determining the specific gravity, which should agree with the stated figures on the ticket. The solution is filled into ampuls, each receiving a measured volume sufficient to provide the excess specified in the *National Formulary*. All broken ampuls should be counted and recorded, and all ampuls rejected by the inspectors likewise recorded. The total count must closely approximate the theoretical yield. The final packages are also counted; the total ampuls in all boxes must, of course, agree with the final filling count.

Autoclaves for sterilization are equipped with recording temperature gauges which record the sterilization temperature (not just steam pressure) and the elapsed time. This record becomes a part of the permanent manufacturing record for that particular lot of ampuls. In large autoclaves it is desirable to have several thermocouples located at different points throughout the sterilization chamber.

Narcotics, extremely poisonous, and very valuable drugs all call for special systems of handling. Indeed, in many plants, the "narcotic men" will personally deliver and check the dilution of the weighed and checked narcotic and its addition to the mixture of the partially completed formula. The same practice may be installed for other drugs over which close supervision must be maintained.

In the case of a parenteral solution of dextrose and alcohol, two or three men qualified to withdraw alcohol from the alcohol storeroom should collect the weighed amount in large Pyrex flasks. Together they should pour the contents into the dextrose solution and return the empty flasks. The chemical laboratory determines the percentage of alcohol in the finished bottles. This percentage of the total volume in the number of finished bottles should agree with the total amount of alcohol added to the batch.

At all times, containers holding mixtures of unfinished or finished products must be tagged with the list number, work-order number, and the name of the product.

INSPECTION AT THE PRODUCTION CENTER

Certain work done routinely in the plant requires the presence of an inspector. In manufacturing operations, the foremen usually act as their own inspectors; but on bottling and finishing lines, several special inspectors may be necessary to detect errors should they occur. Sometimes labels for another product may have been mixed inadvertently with the labels for the drug being finished. Although these should be removed by the inspector when the labels are issued, inspectors on a labeling line must catch the error if it slips through the first inspection. Since it is impossible for an inspector to stop and read each label on each package, it is customary to pick a numeral or a short combination of a few letters on some particular part of the label which distinguishes that particular dosage form from any other. The inspector then watches for this abbreviated code. The combination selected should, of course, be in prominent type and easily recognized.

In some plants, inspectors are paid an inspection bonus. The bonus is in addition to the regular salary and is, in fact, a premium for not making mistakes. If a mistake is passed by an inspector, a fine is levied against the bonus, not against the basic salary. It is not unusual for a foreman or a supervisor of inspectors to slip a package improperly labeled into the finishing line to see if it will be caught by the responsible inspector. Mistakes occur so rarely that it is necessary to have some means of keeping inspectors alert at all times.

Occasionally, inspectors work under the superintendent and the foremen in the particular department. In other establishments, the inspectors work for the control department; they are not responsible to the superintendent of the factory.

SAMPLES FOR EXAMINATION AND APPROVAL

Samples should be taken by one who understands the principles of sampling in order that they be truly representative of the batch. In most instances this sampler will be an employee of the control department, or at least he will have been trained by that department.

Most chemists have been trained in the principles of sampling and are acquainted with the responsibility involved. A number of books treat on the subject; and the *United States Pharmacopeia,* under its section on General Tests, Processes, and Apparatus, discusses the sampling of original containers of vegetable and animal drugs. The *National Formulary* has similarly specified the number of ampuls that shall be selected to represent a lot used for the official sterility test. These schedules give a general idea of samples to be taken from large batches as representative.

In the purchase of chemicals in large containers and when the shipment contains a number of units, someone acquainted with the nature of the chemical should open each container for a general inspection of the contents. Some control men advocate an identity test on a sample from each container and an assay on samples from a representative number. Although manufacturers of chemicals usually have good control systems, they, like the pharmaceutical manufacturer, must depend on the integrity and care exercised by human beings. They make mistakes and even though this occurs in rare instances, the processor can hardly afford to assume that every container in the shipment is properly labeled as to identity and purity. Moreover, the processor is legally responsible for the identity and purity of the product he makes from purchased materials, nor can he shift that responsibility even though he himself may have grounds for a damage suit.

LABORATORY CONTROL

The final approval comes from the control laboratory. The chemist determines the amount of the active ingredients in a sample of the final product; this must be within the limits of the tolerances of the *United States Pharmacopeia,* the *National Formulary,* or some other recognized standard. Otherwise, the product is rejected and must be reworked or destroyed. This laboratory examination is made on a *sample.* As indicated, it is important that it be truly representative, otherwise the examination means nothing.

The control laboratory does not limit its work to the examination of final samples. Indeed, it begins to function when the first of the basic ingredients is received. Thus, a shipment of such an ingredient is unloaded at the receiving department. The receiving clerk counts and checks the number of packages, inspecting the shipment generally to see that the containers are all in good order and that there is no evidence of faulty packaging or damage in transportation. The gross weight of the shipment is verified, an identifying number is assigned, and a record made of the lot numbers of the manufacturer which may appear either on the containers themselves or on the invoices; thereupon the merchandise is placed in quarantine. A representative sample is prepared by an inspector for the control laboratory. This is placed in an appropriate container supplied by the control laboratory and is labeled to show the name of the product, the name of the shipper, the code number indicating the specified quality, the manufacturers' lot number, the receiving identification number, the quantity represented in the shipment, the date, and any other pertinent information, along with the initials of the man responsible for the sample.

In the laboratory, the sample is examined and tested to see that it complies with all of the established specifications for that code number; and, if found to be satisfactory, the shipment is approved for use. In many plants the control laboratory will issue special stickers or tags, one for each container, indicating

that the batch has been tested and approved for use. Only when so approved is the material removed from quarantine. At this time, the data concerning the shipment are entered on the perpetual inventory in the planning department. Special systems are set up for small shipments of very valuable drugs or for materials received in tank car lots, but always with the view of withholding the material from use until approved by the control laboratory. The serial number assigned to the shipment in the receiving department is retained as an identifying number as long as any of the merchandise remains in the warehouse, and the number is entered on each manufacturing work-order for which it is used. Likewise, the perpetual inventory control records show each work-order to which the particular shipment is assigned.

Manufactured pharmaceuticals are customarily examined three times by the control laboratory. Thus, a process sample is assayed before filling, another after finishing, and a final check is made before the goods go to the stockroom.

In the manufacture of galenicals, the dilution to the required volume is usually stopped short of the required amount and is later adjusted on the basis of the assay of the process sample. Alcohol content may likewise be determined on the process sample so that it, too, may be adjusted in bringing the batch to the calculated volume. In the preparation of tablets of very potent medicaments, it may be desirable to assay the dry granulation and to adjust the weights of the tablets so as to give as nearly as possible the exact amount of the active ingredients in each tablet.

In the case of tablets or capsules to be coated, the assays for active ingredients are made before coating, and the final check on the coated product usually includes only an examination for identity, color, solubility, or insolubility in artificial gastric juice (when tablets are enteric coated), and uniformity.

Final samples of other products are checked for physical properties and for content of active ingredients. Ampuls are subjected to a special inspection for the presence of undissolved particles and for color. The volume of the solution in the

ampuls must be correct and the dose must contain a labeled amount of the drug.

Liquids, such as elixirs, syrups, tinctures, etc., are checked for color, taste, odor, consistency, clarity, and are assayed for activity. Ointments, in addition to the ordinary tests, are ordinarily checked microscopically for uniformity of dispersion and for the size of the particles of ingredients insoluble in the ointment base. Ophthalmic ointments will usually be tested by the bacteriologist to determine the number of bacteria per gram of ointment. To market *sterile* ophthalmic ointments would require procedures far too expensive for practicality, but with good sanitary practice it is easy to make ointments virtually free of bacteria.

A bacteriological laboratory may be a part of the control department or it may be a separate department doing a certain amount of control work on a service basis. All reports on sterility or bacterial count, as well as the reports from the bioassay department and pyrogen laboratories, are sent to the control department to be filed with its own reports and used as a basis for issuing a final sample approval. The bacteriological laboratory will likewise render routine reports on antiseptic tests of certain types of preparations and report on bacterial, mold, or yeast contamination of products subject to spoilage from microorganisms.

When antibiotics, such as tryrothricin, penicillin, and streptomycin, are made, special laboratories are required for their assay and sterility tests. The chemical laboratory will be required to make moisture determinations and other physical and chemical examinations. Here again all laboratory reports are collected by the control department and become a part of the permanent record of that department, as well as a basis for issuing final sample approvals. The approvals are sent out from this office either on separate slips which are attached to the manufacturing and finishing work-orders, or they may be entered directly on the work-order records by the control manager. Only when approved by the control manager may a product be released to the stockroom for distribution. The stockroom man-

ager may not receipt the work-order for the stock unless it bears the release from the control manager.

The sample of a medicament sent to the control laboratory must be more than adequate for at least two separate sets of all the tests required to control the identity, quality, and purity of the product. The unused portion is set aside in the sample room where it is kept for reference for a period of years.

Not only may the samples in the control file be reexamined if a complaint is received on the particular serial or batch, but they should also be examined from time to time to see if each serial is standing up well. Such an examination serves to indicate the condition of that particular batch as it may exist on the druggists' shelves when stored at ordinary room temperatures.

The equipment of the control laboratory must be adequate for the number and types of products made in the plant, and the complement of trained chemists must be sufficient to render prompt service in the examination of all the process and final samples. If the facilities of the laboratory are inadequate to handle this task, it is evident that either the laboratory facilities must be expanded or the number of products manufactured must be reduced. If a small pharmaceutical manufacturer attempts to make the same number of items as a large manufacturer, he will have to have just as large a control laboratory. Indeed, it obviously requires just as much work to test a sample representing ten gallons of a product as it does to test a sample representing 1,000 gallons, or more.

Control work can be speeded up by the use of the most modern equipment. In some instances, micro methods and semi-micro determinations give more accurate results in less time than do the customary macro methods. Microbiological methods, where applicable, make vitamin assays possible in two or three days that required ten to thirty days when rats were used for the standardization. The use of the spectrograph, spectrophotometer, and the fluorophotometer is worthwhile since these instruments provide greater accuracy in much less time than the older methods of testing. The new infra-red

spectrophotometer appears to offer still greater advantages in the control laboratory.

To make use of all these modern tools of the analytical laboratory, better trained chemists are essential and, in order to attract the better trained men, a satisfactory future must be provided for them. Either the control laboratory must be a stepping stone to a position of greater responsibility in the plant or administrative branch of the business, or the ability of a productive and dependable control chemist has to be recognized and recompensed properly. Certainly, a man capable of producing accurate assays on pharmaceutical products in a reasonably short time is a valuable man in any control organization. If, in addition, he can supervise several technicians for assays and determinations of simple nature, then he becomes still more valuable in this very important work, and a satisfactory future should be provided for him in the laboratory.

THE BIOASSAY LABORATORY

There are a number of drugs that do not lend themselves to a chemical assay for determining their activity. These must be standardized by the effect of measured doses on laboratory animals or on living, excised animal tissue. In some plants, the bioassay laboratory responsible for such work is a separate service laboratory working under the control division. In other establishments, bioassay work is a separate unit of the pharmacology department. In either case, it is desirable that the work be under the immediate supervision of an adequately trained pharmacologist, since most of the methods employed in biostandardization are pharmacological methods.

For example, the official method for the standardization of digitalis is the cat assay method, although recently a new chemical method has been proposed for the standardization of digitalis and possibly for the standardization of digitoxin; the method appears to be promising. Strophanthin preparations are assayed in the same manner. Pituitary solutions are standardized by measuring the amplitude of the contractions produced on the

uterine tissue of virgin guinea pigs. Epinephrine solutions give measurable increases in the blood pressure of dogs, while the amount of histamine in injectable preparations is measured by its blood pressure-lowering effect on animals. From the time they were first discovered, vitamins have been standardized on laboratory animals. Today, vitamins A and D are assayed on white rats. The activity of vitamin K is measured by its effect on the clotting time of the blood of young chicks. In the case of hormones, the activity of estrone is determined by its effects on the epithelial cells of the vaginal mucosa of ovariectomized mice. The luteinizing and follicle-stimulating properties of anterior pituitary products are estimated by their specific effects on mice.

All bioassays, and, indeed, all animal tests, to be reliable, must be made on healthy animals. To keep animals in the proper condition, sanitary animal quarters must be provided. diets must be adequately supervised and complete, and trained caretakers be hired. Furthermore, for vitamin assays on white rats, it is important that animals be kept in air-conditioned rooms.

Because of these elaborate requirements for satisfactory laboratory work on small animals, it is customary to place all such animal work under one head. Routine safety tests, pyrogen tests, toxicity tests, tests for histamine-like substances, tests for anaphylactic properties, and tests for immunizing effects can well be performed by the staff of the bioassay laboratory. By concentrating all of this work in one unit, the necessity for duplicating animal quarters and facilities is obviated.

There are many times in the operation of a pharmaceutical plant when the quick, qualitative demonstration of certain pharmacologic activities is required, such as the mydriatic effect of a drug or the local anesthetic properties of a mixture. These may properly be referred to the bioassay department. With new drugs requiring the development of special pharmacological tests for their control, the procedures are perfected by the pharmacologist, and then, when the tests become routine control

procedures, may be delegated to the supervised technicians of the bioassay laboratory.

MICRO-BIOASSAY OF DIETARY SUPPLEMENTS

One of the most interesting developments in recent years has been the assay of some of the vitamin preparations by bacteriological methods. Instead of determining the effects of measured quantities of the vitamins on the growth of white rats, the bacteriologist has devised methods of measuring the effects of definite quantities of vitamins on the growth of micro-organisms. Results just as accurate are obtained in a much shorter time and at considerable less expense than by the classic assays on rats. This has been a most fortunate development for the pharmaceutical manufacturer of vitamin products, since much of the vitamin assay work may now be sent to a bacteriological laboratory, with the release of bioassay laboratory space for the additional, ever-increasing amount of testing that must be done on laboratory animals.

So far these micro-bioassay methods have been applied only to water-soluble vitamins; and, since good chemical methods are available for thiamine, ascorbic acid, and folic acid, the bacteriologic procedures are used chiefly for the other B-complex factors, pantothenic acid, riboflavin, pyridoxine, nicotinic acid, biotin, and inositol. With the development of interest in amino acid preparations, the same micro-organism methods have been adapted to the determination of all of the essential amino acids. Many micro-organisms may be used for this type of work, but so far the interest has centered largely on the use of *Streptococcus lactis R, Lactobacillus casei, Lactobacillus arabinosus,* and some of the yeasts.

CHECKS ON STOCKS OF INGREDIENTS AND FINISHED MATERIALS

A well-managed control department will not be content with checking merely incoming ingredients and finished stocks. In addition, a periodic check of the warehouse stocks must be made

to see that they are still in perfect condition. Thus, a shipment of a basic ingredient may have been acceptable when received, but if it has not been properly protected, the product may no longer be suitable for use. For example, crude drugs are prone to absorb moisture and odors from other drugs stored nearby, and thus deteriorate.

Finished goods in the stockroom may well be checked at regular intervals. There probably is not a pharmaceutical manufacturing establishment in the country that does not have a definite rule that new stocks must be placed in the back of the shelves or stacks and that older goods must be removed first. There are probably few such establishments that do not find at times that the newer stocks have been placed in front and are being sold before some of the older preparations. Similarly, steam pipes in stockrooms are usually always well insulated, but sometimes insulation may be removed for repairs; finished goods pushed against the hot pipes suffer considerable damage. It is good practice to extend the control department inspection service to include these periodical checks on the condition of all merchandise.

The problem of returned goods will be commented on briefly. Every pharmaceutical manufacturer has to contend with it. It is an unpleasant subject at best. If there is the least question about the satisfactory condition of the returned merchandise, it may usually be handled most economically by destroying it altogether. Even with products containing ingredients of high value, there is seldom a sufficient quantity available to pay for a recovery program. Merchandise in apparently good condition, returned from dealers, branches, or customers, should always be carefully inspected by someone trained in the control laboratory. If it is in perfect condition, it may be returned to the stockroom. Even if it is not, it serves as an interesting index of what may happen to the product under certain abnormal circumstances in the trade. Thus, vitamins, epinephrine, digitalis, and similar products may well be assayed for the information to be gained about their stability under conditions of storage or

shipment. A study of the packaging of returned goods may also give valuable information about proper packaging.

CONTROL OF PACKAGING MATERIALS

Good pharmaceuticals may be quickly spoiled by the use of improper containers, poor caps, or by cap-liners that are attacked by the product. Rubber closures have always presented a problem, especially in the packaging of multiple-dose containers of injectable solutions. Rubber "breathes" air; in doing so it takes up moisture which it in turn imparts to any anhydrous substance in the vial. It should be borne in mind that "rubber" closures are not pure rubber. Even the so-called "pure gum" is not; more properly it should be called "rubber compound." During the war period these compounds were made of various substances. Even in normal times, however, rubber compounds contain pigments, accelerators, antioxidants, and other ingredients, some of which may be quite reactive with the substances that are to be packed.

A good packaging department will exercise the same control over all packaging supplies that the control laboratory exercises over ingredients and finished pharmaceuticals. It is even advisable to test the ink used in printing the labels, especially the colored inks. It is exceedingly embarrassing to devise a striking colored label only to learn that the preparation will change the color if a little of it comes in contact with the label, or that the latter may fade or change when exposed to light. While there are alcohol- and alkali-fast red printing inks, others will fade quickly if the ampuls, for example, bearing the red labels, are immersed in alcohol or compound cresol solution.

CONTROL OF LABELING MATERIALS

Even if an establishment manufactures only fifty items, a very small specialty line indeed, and each item is offered in only two different size packages, it would have to stock 100 different kinds of labels and cartons. A plant, manufacturing a thousand

or more items, which is more nearly representative of the average pharmaceutical line, offered in from two to six different size packages, is faced with a real problem in arranging a suitable stockroom for ordering, storing, and issuing labels and cartons. Obviously, great harm may result if just one label or carton is erroneously used on a product different from the proper one.

A considerable amount of competence is required of personnel supervising and issuing labels and cartons. The finishing work-order is accompanied by requisitions for a specified number of labels and cartons of each required size. Only the exact number should, of course, be issued so that there will never be any remaining to cause possible trouble. Material spoiled or mutilated in stamping the serial number or in the labeling process must be returned and exchanged for others. It should then be mutilated or burned. While this procedure causes some work, excess labels and cartons issued to take care of spoilage, even with the understanding that they will be destroyed if not used, sooner or later appear at the wrong time and place; and, unless the inspection is perfect, they may be used on the wrong packages.

No matter what controls are adopted, errors are apt to occur in the label and carton room, and eternal vigilance is required on the part of the inspectors to detect wrong labeling. Much of the time the mistakes happen at the printing establishment. Labels are usually printed in sheets of ten or twenty different kinds of labels. If one or two sheets become turned half-way around in the stack before they are cut apart, there will be some wrong labels in all the piles unless the printer is warned to plan his forms so that any sheet of printed labels turned from its proper position will give labels that are imperfectly trimmed or so badly cut that they will be readily detected.

Some pharmaceutical houses that use many cartons of the same size adopt a series of rule markings printed so as to appear on one edge of the folded cartons. One, two, or three marks may be used, and are spaced differently on the cartons for each product. The mark or marks on the edge of a stack of folded cartons will make a continuous line or lines down the stack;

any break or lack of continuity in the lines indicates a carton which does not belong in the stack.

CONTROL OF LABEL COPY

It would be a wonderful experience in the pharmaceutical manufacturing business to have an entirely new and perfect set of beautifully designed labels and cartons and to feel that that phase of the work was settled for a good many years. Unfortunately, label copy is in a continual process of revision. A new revision or a supplement to the *United States Pharmacopeia* or the *National Formulary,* for example, may make a formula change imperative; new labeling must be obtained to correspond. On unofficial specialties, improvements are made from time to time, and each formula change usually calls for new labeling. Newer knowledge about the drug also may necessitate a modification in dosage or warning statements. Thus, a new drug may have required a rather drastic warning statement at the time it was first marketed. Subsequently, experience demonstrates that the warning is unnecessary, and an amendment to the new drug application is approved to permit its modification in the labeling. Again, the Council on Pharmacy and Chemistry of the American Medical Association may adopt new rules requiring other labeling statements. Of course, many changes may be deferred until the labels and cartons are to be reprinted.

Someone must be responsible for a master file of labeling where all changes, past, present, or future, are recorded. Usually, when a new label is to be reordered from the printer, a copy is pasted on an appropriate order form and circulated to several experts in certain fields. For instance, the proposed copy may go first to a pharmaceutical expert who checks the printed formula with the catalogue copy and the work-order, which have already been verified as correct. He is responsible for all pharmaceutical aspects of the labeling. Then it goes to a member of the medical department to verify that the dosage statements and warnings are proper. The copy must be finally checked by

one who is familiar with the requirements of Federal and State drug laws and the rules and recommendations of the Council on Pharmacy and Chemistry of the American Medical Association or the Council on Dental Therapeutics of the American Dental Association. If any changes have been made by the previous reviewers which are not in accord with the actions of the Food and Drug Administration on the new drug applications or Council actions, he makes the required corrections. This last reviewer should likewise be familiar with the informal rulings emanating from the Food and Drug Administration. He should, in addition, keep informed of court actions under the Federal Food, Drug, and Cosmetic Act as published in the "Notices of Judgment" and elsewhere. Proofs from the printer must be compared with the latest revisions in the master label file.

PLANT SANITATION

Sanitation is an essential condition for good pharmaceutical manufacturing. Certainly it is important as an aesthetic consideration, but under the Federal Food, Drug, and Cosmetic Act it becomes compulsory. Section 501 states:

> A drug . . . shall be deemed to be adulterated—(a) (1) If it contains in whole or *in part of any filthy,* putrid, or decomposed substances; or (2) if it has been prepared, packed, or held under insanitary conditions whereby it *may have been* contaminated with filth, or whereby it *may have been* rendered injurious to health. . . .

Literally interpreted, this section would set up a standard impossible to attain. Dr. Charles E. Vanderkleed has said in connection with this section, "The mere presence of an ordinary house fly *(Musca domestica)* in a factory room in which a drug is being manufactured, definitely and positively renders the entire output of that room, for the time being, adulterated." Obviously, no one could be expected to comply with a literal interpretation of this portion of the law, but good housekeeping and special attention to cleanliness should satisfy government inspectors and aid materially in the production of pharmaceuticals. The time will probably come when the pharmaceutical manu-

facturer will employ a full-time sanitation or sanitary officer just as many of them employ safety engineers today.

The problem of maintaining sanitary conditions within the pharmaceutical plant is not as difficult as in the food industry because not so many of the raw materials used attract and nourish insects and rodents. Nevertheless, the drug manufacturer must cope with exactly the same types of problems. He, too, must eliminate the chances for contamination by rats and mice, from such insects as flies, cockroaches, moths, beetles, and weevils, and from micro-organisms including yeast, molds, and bacteria.

In the construction of pharmaceutical plants in the future, special emphasis will be placed on structural details for preventing the entrance of rodents and insects. No doubt special fumigation chambers will be installed for the treatment of incoming shipments of crude drugs or other commodities which may harbor vectors of contamination. In such idealistic factories of the future, the air-conditioning systems will serve to prevent the entrance from the outside of flying or crawling insects.

The pharmaceutical manufacturer who cannot build an entirely new plant may have to consider making many little changes in the buildings which he now occupies. Much can be done with the application of brick, cement, and steel to existing walls to prevent the entrance of rats and mice. Floor drains and ventilators, as well as all other openings to the outside, should be protected with screening or grating to prevent the entrance of unwanted visitors. One pharmaceutical manufacturer, not many years ago, turned into the sewer the contents of a large tank of milk of magnesia after a bird had dropped through a ventilator into the tank. It was a costly lesson, but he made certain that such an accident could never occur in the future.

When everything possible has been done to render a building rodent-proof, there is still the problem of coping with the casual entrance of rats and mice into the building. This often occurs when doors are opened for incoming shipments at night; frequently the rodents are within the shipments themselves, for example, in bales of crude drugs. The problem of getting rid

of the rodents once they are in the building is best handled by the professional exterminator. If he is not available, the company may well delegate some employee to take over the responsibility. There is sufficient literature available to enable one to become very proficient in this field, and information on new rodenticides is readily available from the manufacturers.

To safeguard pharmaceuticals from insect contamination calls for equal vigilance. To screen completely and effectually an entire pharmaceutical plant is practically impossible, but rooms for the handling of products which attract insects should be screened. At best, screening can only prevent the entrance of mature insects; there is no barrier sufficient to prevent the entrance of insect eggs or larvae. These enter on packaging materials, of which glued cartons are the worst offenders, and in bales of roots, bark, and various crude drugs. Here again a professional exterminator is helpful; but, unless he is one with special experience in food or drug manufacturing plants, he may introduce toxic substances of greater potential dangers to the final product than any insect excreta or moth webbing that might be present.

Molds, yeasts, and bacteria, at times, present problems which may only be solved by one with training and experience in industrial bacteriology, but most of the ordinary difficulties that arise from micro-organisms can be prevented by good housekeeping methods.

Parenteral solutions must be sterile and, if offered in multiple dose vials, must contain bacteriostatic agents sufficient to prevent the growth of micro-organisms incidentally introduced with the air admitted for the withdrawal of the first doses. On the other hand, the great majority of pharmaceutical products for oral or topical use are not susceptible to spoilage from the accidental introduction of micro-organisms. They are offered in containers which are opened frequently and must be so formulated as to discourage the growth of yeast, molds, or bacteria. For the protection of such products, ordinary, commonsense cleanliness is usually adequate.

A cough syrup, because of its high sugar content, will not support the growth of fermenting bacteria or yeasts due to a moderate degree of accidental contamination; but, if some of the syrup is diluted with tap water and is allowed to stand in pipe lines, pumps, or tanks through inadequate washing, a fermenting mass mixture may result which can bring about serious trouble in a product later introduced into the same pipes, pumps, and tanks.

Good housekeeping requires not only clean work rooms, but the thorough cleaning of all equipment and utensils and convenient facilities for washing the hands of employees. Clean clothing for workers lessens the chances for contamination of products and gives the workers a consciousness of cleanliness. The effect of clean, white clothes on the general attitude of workers is far more valuable to the company than the impression created on visitors. It is interesting, too, to note that in most factories the trouble and expense of showing visitors through the plant at frequent intervals is rated, not for its advertising value so much, as for the general effect on personnel in maintaining a continuing consciousness of plant cleanliness.

Control in the pharmaceutical establishment is not just the responsibility of a control manager or a control department. It is the responsibility of the plant superintendent and of every employee from the top management to the janitors. It is good business to make satisfactory and uniform products. It is good business to avoid or detect human errors. But every employee should be encouraged to feel that to have a part in the manufacture and distribution of medicines is a privilege as well as a responsibility; each should be encouraged to use every possible precaution to assure that no medicinal product will ever leave the establishment that is not as nearly perfect as it can possibly be made.

Human errors will occur; but they occur only rarely, and thus there is a tendency to feel that everything will be all right. Control is established to prevent errors or to discover them when they do occur. A good system will disclose them, provided that someone detecting an error does not proceed to hide it lest

it be embarrassing to himself or others. Proper relationship between foremen and workers will assure the prompt reporting of detected errors. Employees should be told that mistakes will be forgiven, but the concealment or disregard of one will not be overlooked and justifies immediate dismissal.

8

Labels and Labeling

JOHN G. SEARLE

PRELIMINARY research and development having been completed, the new drug product must be readied for its market. At this point, at least, this refers to the planning of the container—both the immediate one and the carrying carton, if any—and the preparation of the label and other printed matter, such as a circular, brochure, or direction sheet, to be used both in its promotion and its application.

Of these two aspects, the preparation of the "labeling"—a comprehensive word-of-art denoting, as we shall see, all printed matter on or accompanying the drug—is indisputably the more important. Obviously, the complex scheme of modern merchandising practices usually prevents the manufacturer from explaining verbally and directly to the final consumer the nature of the product and its purpose and the manner of its use; the duty of conveying this information is necessarily delegated to the printed word. The obligation, moreover, is, on the one hand, prescribed, and, on the other, circumscribed, by requirements imposed by statute, particularly the Federal Food, Drug, and Cosmetic Act. Indeed, in discussing the subject in this chapter, the approach is primarily from this viewpoint.

It must not be concluded that the preparation of labeling material for a drug is an independent operation, performed perhaps in the privacy of the advertising copywriter's office. On the contrary, it is, as shall be shown, intimately related to the research and development work that has gone before. Indeed, it is not too much to describe labeling as the sum of all the prior investigations into the nature and characteristics of the product, crystallized, so to speak, into a form in which it is palatable to

the person for whom the preparation is intended. This is not to say that all data, previously accumulated, are to be passed on in this way. But if we picture labeling as a distillation of all the pertinent facts learned about the product, we will, at least, acquire a better appreciation, first, of its source and origin, and, secondly, of its general purposes.

DEFINITION OF LABELING

Labeling of a pharmaceutical product has developed a long way from the single act of attaching a bit of paper proclaiming the name of the product. It has become a science and an art, and may from time to time require the services of the physician, pharmacist, chemist, lawyer, artist, sales and advertising executives, and perhaps other specialists. Closely circumscribed by regulations it must, nevertheless, provide a considerable variety of information to many who will handle the package while it is en route from manufacturer to consumer.

Generally speaking, the printed matter accompanying a drug to be distributed throughout the United States is governed by the provisions of the Federal Food, Drug, and Cosmetic Act. This statute employs the all-inclusive term *labeling,* defining it to mean "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." A *label* is described as "a display of written, printed or graphic matter upon the immediate container of any article." The definition of labeling has been further clarified and, to some degree, extended by Regulation §2.2 to include "all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce, or held for sale after shipment or delivery in interstate commerce." Since a very considerable portion of the authority of the Food and Drug Administration is derived through its power to regulate labeling, it is not strange that the exact meaning of these words has been the subject of considerable controversy which has extended through a number of court decisions in various jurisdictions.

Most of this controversy has been focused upon the meaning of the phrase "accompanying such article" in the statutory definition of labeling. While it seems to be conceded as obvious that printed matter, such as circulars or leaflets, that are a part of the drug package, that is, in or on the container, constitute labeling, the Government has taken the position that the concept is much broader. Thus, it has contended in certain cases that counter and window displays and advertising leaflets may also be considered as labeling when both they and the drug have a common origin (*i.e.,* the manufacturer or distributor) and reach the consumer more or less simultaneously. This position has been broadly sustained in lower court decisions, though very recently there have been conflicting rulings among the different circuits of the U. S. Circuit Court of Appeals. However the final meaning of the word "accompanying" may be settled, the general tenor of interpretation of the entire statute seems to be quite broad, and is perhaps aptly summarized in a statement from one of the above decisions:

> It was enacted to protect the public health and to prevent fraud, and it ought to be given a liberal construction. Consequently, we are impelled to the conclusion that misbranding is cognizable under the Act if it occurs while the articles are being held for sale. This conclusion is sustained by the legislative history of the Act, from which it appears that it was not the purpose of Congress to limit the scope of the phrase "accompanying such articles" to printed matter placed in the carton in which the article is contained.

It is thus apparent that, with respect to the applicability of Federal regulations and the hazard of misbranding, the concept of labeling is indeed a broad one. As was pointed out in some detail in one of the decisions referred to above, the current interpretation represents a marked change from that prevailing under the 1906 law, a change, however, quite in harmony with the fundamental purpose of the law and the intent of Congress to protect the consuming public from dangerous medication or fraudulent or misleading claims. However, while everyone concerned with the promotion of pharmaceutical products should constantly bear in mind the broadened application of the term,

the scope of the present discussion must necessarily be limited to consideration of the more conventionally accepted phases of labeling, such as container and carton labels and package inserts.

It is interesting to note, at the outset, that much of the text of the Federal Food, Drug, and Cosmetic Act, applied to drugs, deals with defining the offense of *misbranding.* That this is quite in keeping with the historical purpose of the Act is evident from our discussion above. For example, the first provision of the section on misbranding, emphasizing that a drug or device shall be deemed misbranded if its labeling is *false or misleading in any particular,* sets a comprehensive standard for the law, and establishes a guiding principle upon which its enforcement is based. At the same time, it constitutes another important departure from the 1906 Act, wherein drugs were deemed to be misbranded with respect to certain particulars only if their labeling was false and fraudulent. This change affords statutory acceptance of the philosophy clearly expressed by the Supreme Court many years before the enactment of the present law:

> Deception may result from the use of statements not technically false or which may be literally true. The aim of the statute is to prevent that resulting from indirection and ambiguity, as well as from statements which are false. It is not difficult to choose statements . . . which will not deceive.

Consequently, it need not be further emphasized that in designing labeling for a pharmaceutical product the regulation exerted by the Food and Drug Administration becomes a major factor to be considered.

PURPOSE OF LABELING

Labeling is obviously utilitarian, its primary function being to convey information. However, that it may serve as well as a medium for customer eye-appeal is equally apparent. Indeed, it frequently is designed with its advertising value in mind, although all of this is to no avail if the labeling does not clearly, truthfully, and completely tell its story. Nor should this be

viewed as a simple task. In fact, it must at times tell that story to so many people representing many different interests and backgrounds, and to people so far divergent in ability to comprehend it that in some instances a serious question is raised whether any label for a particular preparation can be devised which will satisfactorily accomplish the many purposes required of it.

Thus, the labeling of a drug must, in general, meet the needs of, and therefore be comprehensible to, the ultimate consumer, a series of distributors, the enforcement agencies, and of course, the manufacturer. The consumer may, in any instance, be a lay person without understanding of medical or pharmaceutical terms, or he may be a doctor or a pharmacist. The doctor and pharmacist will also appear in the capacity of distributing agents, in connection with various other recognized commercial channels, including, in more recent times, such outlets as department and food stores. All labeling must, furthermore, withstand the scrutiny of the Food and Drug Administration, and perhaps of various State and municipal health boards; and in many instances it is reviewed by the American Medical Association through its Council on Pharmacy and Chemistry. As we have noted, too, label statements are also prescribed by law, in many instances to be followed with literal accuracy; indeed, much that appears on the average label is there in fulfillment of some legal requirement.

Primarily, the purpose of any label is to identify the contents of the package, though even this simple and obvious function must be done according to law. Thus, the statute requires that the label bear "the common or usual name of the drug, if such there be" and that it give an accurate statement of the quantity of contents of the package, together with the name and address of the manufacturer, packer, or distributor as the case may be. As a matter of fact, the statement of quantity of contents is the subject of considerable lineage of regulations, prescribing units, and other terms (to illustrate, one may not state "16 fluid ounces" in place of "1 pint") in its effort to prevent possible deception of the public. Of a slightly different nature although

to the same purpose is the requirement in *United States Pharmacopoeia* XIII that the vitamin content of preparations be stated in United States Pharmacopoeial units (for Vitamins A and D) or milligrams (for the other vitamins). Its avowed purpose is to prevent the appearance on labels of statements claiming the presence of impressively large numbers of micrograms in a way calculated to give a consumer, unacquainted with the extreme smallness of the unit involved, an unwarranted impression of high potency.

In addition to the name of the drug, the law requires that there be stated "in case it is fabricated from two or more ingredients, the common or usual name of each active ingredient . . ." and further calls for a *quantitative* statement of the presence of any alcohol and of a specified list of potent drugs, whether they are active or not. The statute thus does not specifically require a quantitative statement concerning the declared active ingredients, other than the eighteen named potent drugs and their derivatives. However, there is an interesting regulation promulgated under this section of the statute, but also reaching back for authority to the provision forbidding false or misleading labeling and to still another relating to the *failure* to reveal all material facts. The regulation in point states:

> A label of a drug may be misleading by reason (among other reasons) of . . . (2) its failure to reveal the proportion of . . . an ingredient . . . when such proportion or other fact is material in the light of the representation that such ingredient . . . is a constituent of such drug.

DECLARATION OF ACTIVE INGREDIENTS

That this regulation frequently poses a formidable problem in labeling becomes evident when we realize that there is no reliable standard by which one can measure in every instance whether the proportion of an active ingredient *is* a material fact in the light of the representation that it is a constituent of the preparation. It is ordinarily obvious that in the case of a tablet, sold under a coined and unofficial trade name and containing

one or more specifically active and potent chemicals, the quantities or proportions of these ingredients will in most instances be material and thus be required to be stated on the label. However, it is far from obvious, in the case of some more complex mixtures of rather less potent drugs, whether such a quantitative statement is a material fact as defined in the regulation to be required on the label. There are some who argue that when we consider that the only real protection from imitation available to the manufacturer may lie in the concealment of the exact amounts of the active ingredients in his product, there is reason to believe that the proportion of the active ingredient is not, in fact, material. However, modern chemistry has made such secrecy almost impossible. Perhaps one may also reasonably question whether any statement of quantitative proportion means very much to the lay public, for one characteristically takes a dosage form rather than a precise grainage, such as an analgesic tablet or two—not five or ten grains—or a tablespoon of cough mixture—not an amount furnishing a particular dose of some ingredient. Reliance, moreover, is placed too often on the directions on the label, the advice of a drug clerk, the experience of a neighbor—or almost anything except the declared strength of the preparation.

While the omission of the quantity or proportion of an active ingredient from the label may in such instances be a reasonable and defensible policy under this regulation, the situation is quite changed when a product has, or may reasonably be expected to attain, an appreciable measure of professional acceptance. In fact, when the use of the product is specifically restricted to professional or prescription demand by use of the so-called Rx legend, the label is required to state the quantity or proportion of each active ingredient. Unlike the lay public, a physician is trained to know and appreciate dosages and concentrations, and to evaluate these in terms of the condition he is treating. While he may, and frequently should, rely on dosage recommendations of the manufacturer, as expressed in a brochure or elsewhere in the labeling, he must necessarily assume a real measure of responsibility to his patient in using

the preparation in question. And this is true even though it be conventionally considered harmless. Consequently, he should be provided directly with the data upon which he can intelligently assume that responsiblity. Whether or not he does so may be for him to decide, but under any circumstances the manufacturer should, by stating the quantitative formula in his label, be in the position of helping his professional customer practice his art, rather than of expecting him to do so blindly.

Perhaps this position can be summarized in the general principle that the consumer, whatever his status may be, is entitled to as much information concerning the formula of a product as he can intelligently appreciate in its use, and application of such a premise would appear to be in general harmony with the intent of the Congress in passing the present Act and with the enforcement policies developed under it; honest adherence to it will lead no one too far astray.

OTHER DECLARATIONS

While it seems obvious that the label should state the form of the product (tablet, ointment, etc.), nonetheless, the Council on Pharmacy and Chemistry of the American Medical Association found it necessary a few years ago to call attention to ampul preparations labeled conventionally, though inaccurately, only with the name of the chemical ingredient without stating that the contents was actually a solution, suspension, or whatever might be the case, of the drug in some medium. The use of a name alone can only be wholly correct where the ampul contains the pure drug, or, perhaps, where the name is a trade name applied to the solution as a whole rather than to the solute alone. It should be remarked, of course, that a ruling of the Council, while indicative of proper practice, does not result in misbranding under the law.

The requirement of the statute that the name and address of the "manufacturer, packer, or distributor" appear on the label normally is obvious in its significance; indeed, compliance is ordinarily a point of pride rather than of insistence. A gen-

uine question may arise, however, as to who is legally to be considered the manufacturer in the case where one firm utilizes facilities of another for a special operation on the product. The Food and Drug Administration stated its position in such cases in part as follows:

> . . . we have concluded that ordinarily the party who completed the manufacturing operation should be regarded as the manufacturer . . . If "A" manufactures the drug, owns it, and delivers it to "B" for the sole purpose of packaging, whether in capsules, bottles, or otherwise, obviously "B's" name could appear on the label only as packer, and we will not be disposed to consider the appearance of "A's" name on the label as manufacturer in conflict with section 502 (b).

This letter goes on to state that where ingredients are mixed and assayed by one firm, shipped to another merely for compression into tablets, and returned to the first firm for assay, packaging, and marketing, the first firm is the manufacturer. However, if the tablet maker adds ingredients or a coating of his own fabrication, he then becomes the manufacturer, and the name of the first firm can appear on the label only as the "distributor." In another ruling on this same subject, the Administration has ruled that when a drug is manufactured by a wholly-owned subsidiary of another corporation, the parent corporation is not in fact the manufacturer, and it may not be so stated on the label.

The foregoing simple facts—title, quantity, formula, and sponsor—constitute, primarily, identification of the product and its manufacturer or distributor. The remaining contents of the labeling serve, on the other hand, to satisfy the needs for information of the various persons handling the package. Foremost among these, of course, is the consumer. Though it has been stated above, it is worthy of repetition that one of the fundamental and avowed purposes of the Federal Food, Drug, and Cosmetic Act is to protect the ultimate consumer from injury by others, and where possible, even from injury by himself. To this end, the law requires the labeling to provide adequate directions for use and adequate warnings against dan-

gerous use, with the Administrator empowered to make exemptions from the requirement for directions in cases where they are "not necessary for the protection of the public health." No exemption from the requirement for warnings is permitted, it is to be noted.

DIRECTIONS FOR USE

In accord with the authority of the statute, certain conditions have been established, fulfillment of which exempts the manufacturer's labeling of a product from the necessity of stating directions for use. Thus, all products can be divided into two broad classes: (1) those complying with the requirement for providing directions, known as "over-the-counter" preparations, and (2) the prescription group, so-called since one of the conditions for exemption from the requirement that adequate directions be provided is that sale of the product be limited to professional and prescription demand.

In general, where the product falls into the first of these broad classes and adequate directions are provided in the labeling, the product is eligible for direct sale to the consuming public on demand without any professional authorization. In these instances the directions provided by the manufacturer will normally be the only information available to the consumer concerning proper use of the product. With this in mind, the Food and Drug Administration has provided in its regulations that these directions must cover use in *all* conditions for which the manufacturer, packer, or distributor recommends the preparation in either his labeling or his advertising, and also for any other conditions in which it is commonly and effectively used. The directions may be required further to state the dose (including variations for age and physical condition) and the frequency, duration, time, and route of administration, and any preparation of the drug that may be necessary for use. In writing these directions, one must bear continually in mind that they are addressed to a lay consumer, rather than to a doctor, and that this consumer will ordinarily have no previous knowledge of, or experience with, the product.

In the art of medical treatment, a skilled practitioner must of necessity treat either symptoms, or fundamental underlying conditions, or both. In many instances his skill is measured as much by the way in which he chooses between these alternatives as by his ability to recognize correctly the situation confronting him and the action that he takes. On the other hand, the person buying medicine over the counter takes upon himself all of these functions. He must, of course, first be aware that something is wrong; this, however, is ordinarily not too difficult. But he must also decide *what* is wrong, a task which on occasion puzzles some of our best medical minds. Finally, with no more guide than advertising, or at best, the advice of a clerk (who may be merely an apprentice), he selects a remedy. The labeling accordingly must answer his implied query whether it is good for what he thinks may ail him, and how he must use it to insure safe and effective treatment. It must further couch these answers in language comprehensible to him. In the case of any but the simplest of remedies, a complete and literal compliance with this requirement for adequate directions would probably require a small treatise on medicine. Indeed, with the wrap-around labels and package inserts supplied with some packages of well-known home remedies, this is not far from the case. In many other instances, however, the directions have been streamlined to a few terse statements of practical information.

It is apparently well established that, among the freedoms so far guaranteed by this country, is the freedom, within certain limits, of a man to treat himself for his own ills. Indeed, the right of self-medication has been explicitly recognized by the Food and Drug Administration with respect to drugs or devices not considered inherently dangerous, and it has been upheld in at least some instances by the courts. The Congressional Committee Report recommending passage of the bill specifically pointed out that "the bill is not intended to restrict in way the availability of drugs for self-medication. On the contrary, it is intended to make self-medication safer and more effective."

However, it has long been the custom of distributors of certain types of home remedies to provide, on enclosures or back labels, directions so complete, so comprehensive, and so lengthy as to be in danger of confusing the average lay customer, or at least discouraging his careful reading. Thus they contribute toward perpetuating the well-known, though insidious, pattern of following the "prescriptions" of a neighbor in promoting promiscuous sale of the product. While this verbosity may provide satisfactory compliance with the requirement for "adequate directions," it is unfortunate that some means cannot be found to require that such directions be simplified to the point that they remain adequate, but are at the same time more completely useful to the consuming lay public.

PRESCRIPTION LEGEND

Prior to the revision (which became effective in the fall of 1945) of the regulations establishing exemptions from the requirement of furnishing adequate directions, the manufacturer of a product considered appropriate for self-medication might freely choose whether he would permit it to come within the class available for unrestricted distribution over the counter, or whether he would market it for professional or prescription use only. To accomplish the latter, he had merely to comply with all the regulations permitting exemption from the need for supplying directions. These provided, in brief, that the drug be exclusively for professional use; that directions be available in the literature; that no directions or indications appear in labeling; that the so-called prescription legend and a quantitative statement of the active ingredients appear on the label.

Thus, without regard to the nature of the product and merely at the expense of losing all direct over-the-counter business in the item, the manufacturer could refuse the responsibility of playing doctor to the public, placing that obligation upon the licensed practitioners of the community. It made no difference whether or not medical experts agreed that the preparation was inherently suited for self-medication; if he were

willing to accept the restriction on sale, the manufacturer could choose, for no better reason than personal fancy, to fill only a prescription or professional demand, and at the same time, to assume no responsibility for directions other than seeing to it that they were available "in scientific publications or otherwise."

In the revisions of regulations, made effective on October 10, 1945, the privilege of a manufacturer to decide whether an item should be sold under the prescription legend or otherwise was effectively abolished by the introduction of a new qualification which must be met before a drug can be exempt from bearing adequate directions in its labeling. This qualification is that:

> Such drug or device, because of its toxicity or other potentiality for harmful effect or the method of its use or the collateral measures necessary to its use, is not generally recognized among experts qualified by scientific training and experience to evaluate its safety and efficacy, as safe and efficacious for use except by or under the supervision of a physician, dentist, or veterinarian.

In other words, only when a drug is generally recognized as unsafe or ineffective unless used under professional guidance may it be sold under the so-called prescription legend. Since another section of the statute, in effect, requires the use of the "prescription legend" or a statement of similar import on unsafe drugs by declaring a drug misbranded "if it is dangerous to health when used in the dosage, or with the frequency or duration prescribed, recommended or suggested in the labeling thereof," it seems evident that the nature of the direction is largely controlled by the nature of the drug. For example, a manufacturer who, for reasons of ethical principles, commercial policy, or even personal preference, may choose to do a purely prescription-type of business is not allowed to do so unless he confines himself to certain products. There are some who argue that even if the statement of policy with respect to self-medication quoted above is accepted as an entirely proper position for an agency such as the Food and Drug Administration to assume, it is questionable whether it justifies the present regulation.

The statutory requirement for adequate directions has also

occasionally been used by the Food and Drug Administration to provide an effective bar to the marketing of certain preparations. For example, concerning tablets or pills containing small amounts of ferrous carbonate and one or more of certain potent drugs (strychnine sulfate, nux vomica extract, arsenic trioxide, mercuric chloride, aloin) it wrote:

> It is the opinion of the Food and Drug Administration that such items are irrational *and that it is impossible to provide adequate directions for their use as required by the law.* [emphasis supplied]

Similar statements were made concerning glandular products which scientific evidence had shown to be therapeutically useless.

AMPUL PREPARATIONS

Another important change with respect to the requirement for adequate directions in the labeling was made effective in October, 1945, when it was stipulated that no exemption from this requirement shall apply to "drugs intended for administration by iontophoresis or by injection into or through the skin or mucous membrane." It was explained that even though the use of these preparations is obviously generally limited to the medical profession or under its direction, their harmful potentialities, if improperly used, and the impossibility of correcting mistakes resulting from misuse, made it advisable that directions be furnished to the physician with each shipment of the drug. However, ampul preparations for injection are normally marketed in interstate commerce in packages containing a number of relatively small individual containers. Since the necessary directions and warnings for such products are often somewhat lengthy, even though it is recognized that they are addressed only to persons with professional background, it is impossible in most instances, to place them on the ultimate container. Consequently, the regulation is satisfied by including this information upon the outside package label or, more frequently, in a circular enclosed within.

While the question has apparently not been raised or an-

swered directly, this practice appears to have been accepted by the Food and Drug Administration as satisfactory. However, it is not infrequent practice in normal distribution for a pharmacist to purchase a large package of such ampuls, provided ordinarily with only one set of directions, and to sell these individually to physician customers. It is an interesting question whether, in so doing, the pharmacist is not technically guilty of misbranding, even though in so selling the ampuls he is performing an act normally accepted as proper by all concerned.

Incidentally, the regulations concerning the labeling of penicillin products specifically require as many circulars to be enclosed within the package as there are immediate containers. Such a procedure might be practical and justifiable where it is common trade custom to pack at most a few containers in a given package, but it could become not only burdensome but also ridiculous were the requirement for directions on ordinary ampul preparations to be interpreted as requiring 100 package circulars in a carton of 100 ampuls.

WARNINGS

Since a warning against improper or unsafe use may be regarded as a form of negative direction, it is logical that much that has been said above concerning directions should apply equally to warnings. This is especially so with regard to the type of warning, on products for lay distribution, which specifies pathological or disease conditions as contraindications to the use of the drug. These statements are clearly required by the statute, and a list of suggested warnings has been issued by the Food and Drug Administration, certain of which, unfortunately, involve knowledge of disease conditions which the average consumer is unable to determine for himself. Thus, the well-known laxative warning, cautioning against use in the presence of abdominal pain, nausea, vomiting, or *other symptoms of appendicitis,* is a case in point. Who, other than a physician, can diagnose the "other symptoms of appendicitis"? Other warnings which name heart disease, lung disease, dia-

betes, high blood pressure, etc., can likewise have adequate meaning only if the prospective consumer has previously consulted a physician and been informed of such a condition. While it might well be considered improper policy for the Government to attempt to keep from the self-medicating public any preparation concerning which such a warning is appropriate but which the consensus has considered safe and efficacious for such unsupervised lay use, nonetheless, there are many who believe it would seem entirely reasonable and proper for the manufacturer to be allowed to offer such a product for prescription use only if he so chooses.

The law regarding warnings in labeling differs materially from that concerning adequate directions in that no exemption is allowed in the case of warnings. They *must* be provided, regardless of whether a prescription legend is used or not. This point has recently been emphasized by the ruling of the Food and Drug Administration that the warning which appears on thiouracil labels must be placed on each prescription container regardless of the nature of the label directed by the doctor. The warning which the Administration regards as satisfactory for thiouracil and propylthiouracil reads:

WARNING: THIS DRUG MAY CAUSE UNFAVORABLE REACTIONS IN SOME INDIVIDUALS. YOUR PHYSICIAN HAS EXPLAINED OR WILL EXPLAIN TO YOU THE SYMPTOMS WHICH MUST BE WATCHED FOR AND PRECAUTIONS WHICH MUST BE TAKEN TO GUARD AGAINST ILL EFFECTS. DO NOT TAKE IN LARGER DOSES, OR MORE FREQUENTLY, OR FOR A LONGER TIME THAN SPECIFICALLY DIRECTED BY THE PHYSICIAN.

Subsequent correspondence has made it clear that this ruling does not apply to all warnings placed on packages of prescription items, but only to the relatively few instances where placement of such warnings on the prescription package may be "necessary for the protection of the patient." While this incident has little or no bearing on the original labeling of a drug, it does serve as a graphic illustration of the ultimate breadth of the control over warnings claimed to be vested in the Food and Drug Administration by the statute.

Though most drug warnings are thus generally covered in

the provision concerning directions, one alone has been singled out for specific treatment in a separate subsection of the Act. This is the statement, "WARNING—MAY BE HABIT FORMING" required to follow immediately after the name and quantity of any narcotic or hypnotic substance in a specified list in the text of this subsection. From a strictly scientific point of view, it is perhaps unfortunate that a single warning has been set up to guard against both of the possibilities of physical addiction to a narcotic and psychic dependence upon a hypnotic drug. It would be an inappropriate digression to review here the whole subject of addiction *versus* habit formation, save to point out that habit formation, in the strict sense of the word, is by no means limited to hypnotic drugs. Any drug—or any experience in living, for that matter—which satisfactorily fills a chronic and annoying need can become the subject of a habit which may be more or less difficult to break, in accordance with the well-known laws of psychology. Indeed, this is recognized in the suggested warning against dependence required on various types of laxatives.

It is also unfortunate that the habit forming warning is required following the declaration of *any* quantity of a hypnotic drug. For when such a warning appears on the label of a product containing a small fractional dose of a barbiturate, for instance, along with other more important potent ingredients, the consumer, professional or lay, tends to ignore it completely. Thus, we may develop a modern counterpart to the boy calling "Wolf," and a most worthy and important warning may lose force in other situations where such emphasis is necessary. In the same way that certain exemptions accrue to narcotic preparations which contain subminimal concentrations of the drug, so might an exemption from the habit forming warning be permitted for the hypnotic drugs when provided in subminimal doses or concentrations, in order to add emphasis to the instances in which its use is required.

IDENTIFICATION MARKS

While the needs of the ultimate consumer for information to be contained in the labeling are thus obviously complex, and while these may be particularly difficult to appraise and satisfy completely because of the widely varying backgrounds of many potential customers, the interests of other groups in the labeling of a pharmaceutical product must also be considered. Prominent among these is the pharmacist. He is called upon to handle a myriad of products from the most harmless to the most poisonous, from undisguised quack nostrums to highly ethical specialties, from the item in everyday demand to one that is called for rarely. He must stock popular competing brands and must know wherein they are alike and how they differ. He must be able to assist the physician and his lay customer. While his professional training, his current journals, and his friends in medical detail service will aid him considerably in these responsibilities, he, too, must look often to the labeling of his pharmaceuticals for guidance.

Identity is of prime importance in prescription practice. The presence of all of the elements necessary to establish identity is of course prescribed by law; it is frequently desirable, however, to go beyond the minimum requirements in emphasizing differences between products which are readily confused. The distinctive label designs and various seals and trademarks which manufacturers have adopted for an entire line may be considered one phase of such identification, by differentiating various brands of standard items one from another. The far greater need for emphatically distinguishing similar and potentially confusable items within a firm's line has been brought into focus in at least two instances in recent years. In the first of these, ampuls containing crystalline "Doryl," packaged and labeled to indicate that they were not for intravenous use but for ophthalmologic use only, were mistakenly used intravenously with fatal results. Despite the informative label statement, the manufacturer was fined for not having sufficiently differen-

tiated both the label and container of the ophthalmologic product from the intravenous one. In the other case, a quinine-containing home remedy for malaria had been sold under the trade name "666" in considerable quantity in certain parts of the country. Due to wartime quinine restrictions, its sale had been discontinued and a new product, free of quinine and recommended for the symptomatic relief of colds, headaches, and like conditions, offered under the same designation, "666." Even though the labeling of this new product was correct with respect to both ingredients and indications, the product was held to be misbranded in that it tended to mislead the consuming public into believing it to be the drug formerly sold under the same trade name.

The well-known incidents arising from the confusion of boric acid and dextrose solutions in certain hospitals further illustrate the same point, and have resulted in the requirement of a special warning on boric acid sold in New York City. Granting that most of such errors involve inexcusable carelessness on somebody's part, nonetheless the manufacturer is placed under a definite and inescapable obligation to do all within his power to make these errors so improbable as to be virtually impossible. Different colored bands on labels have frequently been employed to emphasize such differences in products, but the designer has many other factors upon which to exercise his ingenuity in arriving at a practical and at the same time aesthetic solution.

Adequate directions for storage and expiration dates constitute a matter of particular interest to the pharmacist on some packages. Both of these are required on the labels of certain products by the *United States Pharmacopoeia* or *National Formulary* or the National Institute of Health. Advisory directions for storage are voluntarily supplied by the manufacturer in other instances where aesthetic, rather than therapeutic, deterioration may occur under adverse conditions, in order to insure that the customer receives the product in perfect condition. The presence of a certified color with poor resistance to sunlight or the tendency of a tablet to discolor in the presence of

excessive heat or humidity are instances where such advisory directions are commonly and properly employed.

Since the pharmacist is often regarded as a fountainhead of knowledge, not only by his lay customers but by his medical friends as well, he is interested in all manner of collateral information concerning the products which he handles, particularly those which he might be called upon to alter in some way in filling a prescription. Part of this information is available in the statement of formula and in the directions and warnings; the balance is ordinarily supplied in separate brochures, which may technically be labeling, or through individual correspondence with the manufacturer or his field representatives. The latter course is ordinarily necessitated, not by an unwillingness to provide the data in the labeling, but purely by lack of space or inability to foresee all details which may at some time become germane to the use of the product.

The interests of the wholesaler or distributor in the labeling of a drug are almost entirely confined to ready identity and necessary instructions for storage. It is chiefly to their attention that the labeling on the outside of cases is directed; they would be happy indeed if that were the only labeling they ever had to see in their business! Generally speaking, labeling that meets the needs of other users will suffice for the distributor.

The concern of the physician for the labeling on a pharmaceutical package may range from nothing at all to an interest exceeding the pharmacist's. Some practitioners seldom see or handle the actual package of a drug; others spend considerable time dispensing and administering its contents. In order to use the product intelligently they may, however, require more information than can ordinarily be contained in the directions or warnings on the package label. This need is normally met in a separate brochure, or publication of some sort, prepared by the manufacturer. This brochure is usually supplied to the physician by the manufacturer or distributor, either on the physician's written request or through sales or service representatives as part of a promotional effort. Unhampered by any space limitations, it affords an opportunity to

present truly complete data concerning the nature of the product, its history (to the extent that it is interesting or material) and all the details of dosage, indications, contraindications, technics, precautions, antidotes or restorative measures, and collateral clinical tests that might be helpful or desirable. In contrast to some types of labeling, where lengthy and complicated directions addressed to the lay public may tend to confuse, a complete and scholarly dissertation on the entire therapeutic scope of the product is clearly indicated in a brochure addressed to the physician. It frequently takes the form of a miniature well-documented medical paper, though it is naturally of a promotional nature. The necessity, under the new Food and Drug Administration regulations, of including "adequate directions" addressed to the physician as part of the labeling of all medication intended for injection, has been discussed earlier in this chapter, and in practice has generally resulted in inclusion of such a brochure with each package.

ENFORCEMENT OF LABELING REQUIREMENTS

Over all of this maze of law and regulation stands the Food and Drug Administration as the enforcing agency. Its avowed interest with respect to labeling is to enforce the statute in accordance with the expressed intent of the Congress, to prevent fraud and deception of the public and to safeguard it. The regulations have been drawn with that goal in mind, and the enforcement policy and record have consistently demonstrated such a purpose. Members of the Administration have a standing invitation to the pharmaceutical industry to discuss informally with them mutual problems as they arise, and its series of Trade Correspondence, written in answer to specific inquiries on all manner of topics, is an informative guide to the industry in interpreting the law. It is only natural that much of its activity is concerned with misbranding, at least, so far as drugs are concerned.

Except for a few prescribed phrases required in certain instances, the Food and Drug Administration makes no attempt

to compose or control the composition of any label in detail. By way of illustration, it has ruled that certain warnings must appear on certain classes of drugs, and has issued a series of suggested warnings for such use. However, it was made clear that these warnings are merely suggested, and that any other statement which clearly conveys the same meaning is acceptable. Changes may therefore normally be made in any portion of the labeling so long as the change does not conflict with any existing regulation. However, in the case of drugs for which a new drug application has become effective, it may become necessary to file a supplemental new drug application when such changes are made. In Section 505(e) of the statute, the Administrator, moreover, is required to suspend the effectiveness of a new drug application if he finds, among other things, that it contains any untrue statement.

A new regulation, made effective in October, 1946, states that changes in conditions of use recommended for the drug, or changes in labeling, as compared to that contained in the new drug application, are among the reasons why a new drug application may contain an untrue statement of a material fact. Since the Food and Drug Administration is called upon to pass upon the safety of any new drug, and since this safety must necessarily be a function of the conditions of use and directions provided in the labeling (in its broadest legal sense), this regulation closes a loophole whereby a previously safe drug might be made unsafe through altered labeling, and yet the manufacturer have a new drug application effective.

Standing as another semi-policing agency of a somewhat different nature, the American Medical Association is interested in pharmaceutical labeling through the operations of its Council on Pharmacy and Chemistry. Both the labeling and the advertising of any article submitted to the Council for acceptance are given a most thorough scrutiny. While the purpose of this scrutiny is somewhat similar to that of the Food and Drug Administration, the viewpoint of the Council differs importantly in that it is governed by the high standard of ethical principles which has long been maintained by the American

Medical Association. Consequently, each product which it is called upon to consider is examined primarily in the light of these ideals, rather than in a legalistic sense. In contrast to the complex regulations of practically all Government agencies, the broad principles upon which the Council operates have been formulated into a few simple rules, affording wide powers of interpretation. The findings of the Council under these rules are always subject to review and cannot be considered arbitrary. There is no compulsion for anyone to submit a product for acceptance, and rejection or suspension of a product by the Council cannot bar that product from the market.

The chief effects of the Council rules upon labeling are twofold. In the first place, the Council will not accept "preparations promoted to the public for use in the treatment of disease except as specified in the following explanatory comments," the comments listing (with certain restrictions) such items as antiseptics, laxatives, and "other preparations . . . which in the opinion of the Council could be safely used by the public for the relief of symptoms (such as antacids and analgesics)." This rule, banning in effect from promotion to the public all items except those judged safe, is in interesting contrast to the corresponding one of the Food and Drug Administration requiring, in effect, availability to the public of all items except those judged unsafe! Since both rules will require a good deal of interpretation in the future, one can merely presume that no serious conflict will arise. The situation well illustrates, however, the difference in point of view of the two agencies with respect to labeling of pharmaceutical products.

The other Council requirement that frequently affects labeling is the rule concerning protected names. Such a name will be recognized by the Council for a new remedy where it is not considered in any way harmful to health, and where a generic, non-protected name is not unduly subordinated to the protected name on the package. The practice of merchandizing the "protected" brand of "non-protected" drug has become fairly common in recent years in an attempt to safeguard trademark rights, so this rule will presumably merely serve to make

more widespread among Council accepted products a practice which already enjoys a reasonably common use.

The control that the Council exercises over therapeutic claims made with respect to accepted products may in some instances affect package labeling; more often, however, it is concerned with promotional literature and advertising. While certain of this material is labeling under the broad definition in the statute, it is beyond the proper scope of this chapter.

SPECIAL INTEREST OF THE MANUFACTURER

Having considered the needs and interests of all other parties in the labeling of a drug, we come now to those of the manufacturer. Since he obviously wants to sell the product, the satisfaction of all the needs discussed above is automatically a prime necessity for him. In addition, he is becoming increasingly conscious of the desirability of dressing his package in an attractive fashion to aid in making it pleasing to the customer. While it is inconceivable that anyone—doctor, pharmacist, or patient—would consciously buy an inferior article because of its pretty package, many may unconsciously do so, and many others may be influenced in deciding between items of highly competitive quality by appearance. With all the restrictions and requirements that have been discussed, the label designer's task is not easy, but it is becoming increasingly important.

One of the possibilities of design *per se* being functionally useful was indicated above in discussing ready differentiation between similar products whose possible confusion is potentially dangerous. A comparable opportunity frequently arises in the preparation of labels designed so that part or all may be easily removed when the entire package is dispensed on prescription. An expenditure of considerable ingenuity and money may be justified in some instances in preparing a label which can be equally satisfactory for dispensing or over-the-counter sale.

The manufacturer has one need in his labeling that is not shared by anyone else. This is the identification of individual

batches of a product. Such identification, usually accomplished by a lot number of some sort, is normally an integral part of the producer's system of quality control, and serves to extend that control throughout the market life of the product. Lot numbers are probably set up on about as many different bases as there are manufacturers using them, and are frequently designed to indicate to one who knows the code other information in addition to a mere batch number. The *United States Pharmacopoeia* requires that control numbers appear on each individual container of an injection solution to identify the method and date of sterilization; aside from this one instance, however, there is no other legal requirement for the use of such numbers.

Finally, it sometimes happens that a manufacturer can do a bit of legitimate advertising in his labeling. Having met all the requirements enumerated above, there may still remain space in his labeling for him to stress points of superiority on which he hopes to base sales appeal. To be sure, he is not free of regulation in doing so, for he is specifically enjoined from making any false or misleading representations with respect to any other drug or device. And, of course, he must in no way interfere with the degree of prominence demanded for the statements specifically required in his labeling. Nonetheless, there still frequently remains a legitimate opportunity to add material to the labeling that will be both truthful and dignified, as well as distinctly promotional in nature.

Closely akin to this is the attention paid by many manufacturers to their over-all label design and appearance, purely from the viewpoint of aesthetics. The American public is known to be responsive to smart and attractive dress, whether upon person or product, and pharmaceuticals are no exception. Even in the case of prescription items, where neither the physician who prescribes nor the patient who takes the medicine may see the original labeling, there is an increasing tendency to supply well-groomed packages. Of course, this attention to over-all label design is not entirely predicated upon aesthetics alone, since such design is frequently expected to serve also in the manner

of a trade-mark in distinguishing the product of one manufacturer from that of his competitor.

As Hamlet once impatiently said "The play's the thing," so we, too, in the drug industry may be inclined to consider the discovery of a new drug product to be practically synonymous with its development. Such is far from the case, as the many chapters in this book will testify. In spite of some of the complexities discussed in the preceding pages, labeling need not be, and ordinarily is not, a serious problem in product development. Unlike some others that may arise, it can always be solved for the honestly promoted product. But in common with so many other phases of modern industry, labeling has come of age; it has matured to a stature that demands a place of its own in a pharmaceutical establishment. Failure to accord it proper recognition can lead to unfortunate consequences, but competent and intelligent handling will serve further to embellish even the most outstanding product.

9

Packaging and Storage

R. H. RHODEHAMEL

THE selection of the proper package is a vital step in the development of a pharmaceutical or biological product. A package which protects the product and insures that it reaches the consumer in original form, which has merchandising appeal in its utility and appearance, and which is so designed to permit economical production, will contribute substantially to the successful marketing of the product.

This chapter will attempt to present the major problems associated with packaging of drug products and the most likely approach in overcoming these problems. The importance of a packaging factor will vary in relation to the size of the organization and the number of products involved, but it will be the purpose of this discussion to treat the subject in such a manner that it will apply to the development of a package for one product or for an entire line of products. In several places the term "package designer" has been used in a general sense to refer to the individual or group in an organization who holds the responsibility for the development and control of a package.

DEVELOPMENT OF THE PACKAGE

The basic function of a package is to contain the product in a satisfactory manner. The first consideration in package development, therefore, is to study the product in an effort to anticipate the requirements of the package and the manner in which it will be marketed.

The chemistry of the drug to be packed has an important bearing upon the type of packaging employed, particularly as

regards the degree of protection the package must afford. The chemical nature of a solution may determine if ordinary glass is satisfactory or whether borosilicate glass resistant to chemical attack should be employed. The same type of factor will influence the selection of a liner for the bottle closure or the rubber stopper should a parenteral-type product be involved. The hygroscopicity of a product or its susceptibility to evaporation will determine how efficient the closure must be. There have been observations of product deterioration based on chemical interaction between a parenteral product and ingredients normally found in rubber closures. Chemical reactions can be anticipated between certain types of products and certain plastics used as packaging materials. The foregoing are cited merely as examples to emphasize the importance of carefully studying the chemistry of a product and recognizing its relation to the development of a package.

Considerable attention must be given to the aging characteristics of the product since many of the chemical reactions cited above will occur only on aging. In other cases there are normal product changes which take place on aging. The package designer should recognize these and take whatever protective measures are possible in the package, some of which are discussed in later sections. A study of the average and maximum shelf-life of a product is essential.

There are certain obvious physical characteristics which should be observed before a package can be developed. The pharmaceutical form must of course be known. If the product is a unit dosage form, such as a capsule or tablet, the thickness and width dimension, and the limits thereof, must be determined before a container of proper capacity can be selected. The density of a powder will also determine capacity. The specific gravity of a liquid or semi-solid to be packaged by weight will determine the container capacity. The viscosity of a liquid will influence its pouring qualities, and the design of the shoulder and neck opening of the bottle should take this factor into consideration and permit the contents to flow freely. If a product must be shaken before being dispensed, provision

must be made for adequate headspace in the bottle. It is not uncommon to find a suspension type of product with contents settled to the bottom which, on long standing as an original package on the drugstore shelf, is very difficult to shake into suspension. The selection of a closure must take into account the type of product, and an oily vehicle, for example, will require a different closure than an aqueous vehicle. These are but a few selected examples cited to show the attention the package designer must give to physical characteristics of a product.

The individual responsible for package development should acquaint himself with the marketing plans for a product. He should know the channels through which it will be distributed, how it will be sold and by whom, and whether it will reach the consumer in the original package. As indicated, consideration of the factors affecting shelf-life is also important.

CRITERIA AFFECTING PACKAGE DEVELOPMENT

In the preceding section the need for accumulating complete information on all aspects of a product has been stressed. It is believed that this information should be applied in the light of several criteria which will be present in the development of practically any package for drug products.

The primary function of a package is to protect the product it contains. This protection should be considered from several standpoints, perhaps the most important of which is protection against atmospheric conditions—namely, air and moisture—to which the package will be exposed.

The *United States Pharmacopoeia* has recognized the need for maintaining the stability of a product through proper packaging and storage and has established definitions for containers which provide varying degrees of protection. As a basic definition, a container has been stated to be the device which holds the drug and which is or may be in direct contact with the drug. The closure of the container is a part of the container.

The *United States Pharmacopoeia* has defined a *well closed*

container as one which shall protect the contents from extraneous solids or from loss of the drug under the ordinary or customary conditions of handling, storage, shipment, or sale. Most formulary monographs on individual drugs designate the approved method of packaging and storage. It would not be practicable to quote the type of container specified for individual products, but a review of these monographs is an excellent guide to the relative degree of protection required by various types of products. It will be found, however, that a well closed container has been designated for those products which are relatively stable.

A *tight container,* specified for drugs needing a somewhat greater degree of protection, has been defined as one which protects the contents from contamination by extraneous solids or moisture, from loss of the drug, and from efflorescence, deliquescence, or evaporation under the ordinary conditions of handling, shipment, storage, or sale, and shall be capable of tight reclosure. Where a tight container is specified, it may be replaced by a hermetic container for a single dose of a drug.

A *hermetic container* is defined as one which shall be impervious to air or any other gas under ordinary conditions. In some instances a secondary specification provides that air be excluded from a container either by the production of a vacuum or by displacement with a non-oxidizing gas.

In considering the application of the above definitions to more common types of materials, if the package is a bottle, vial, or jar, and a screw-cap type of closure is employed, attention should be directed to the liner which is in contact with the top of the bottle finish. The use of a liner which serves as a moisture barrier will answer most protection problems. Tight application of the closure is usually a requisite to its efficiency, and the package designer should be certain that instructions governing proper application are given package production units. Many firms have found it desirable, in the case of hygroscopic drugs shipped to tropical areas where prolonged exposure to high humidity is encountered, to employ a double closure consisting either of a cork beneath a screw cap, or a

secondary film-type moisture barrier over the bottle finish beneath a screw cap. The problem of reclosure is particularly important to many drug products and if a material is capable of deteriorating in the period in which a package is being consumed by the user, special attention should be given this reclosure factor.

If the package is a metal container, selection should be made of types with body and closure construction which provide efficient protection against moisture penetration. With this type of container there is an opportunity to use an interior bag consisting of plastic films, metal foils, or laminates of the two.

Paper or other wood-product packages seem to be contraindicated for products which must be protected against atmospheric conditions, but if they are used it should be in conjunction with films or foils which serve as moisture-vapor barriers.

Protection against light is a function of the package in specialized instances. *United States Pharmacopoeia* monographs designate the use of *light resistant containers* for certain products, and this type of container is defined as one which is opaque, or designed to prevent photo-chemical deterioration of the contents beyond the official limits of strength, quality, or purity, under ordinary conditions. Unless otherwise specified, a light resistant container should be composed of a substance which in a thickness of two mm. shall not transmit more than ten per cent of the incident radiation of any wave length between 2900 and 4500 Ångströms. The procedure to determine if a container meets this specification is outlined in *United States Pharmacopoeia XIII,* page 634.

If a container is not light resistant, it must be provided with an opaque covering, or be in an opaque outer container. The use of standard amber glass for bottles, jars, and other glass containers will provide the answer for most light protection problems.

Protection against temperature extremes cannot be considered a function of the average package, although a measure of

protection can be attained by highly specialized packages employing insulating materials. It would seem that cautionary label statements are the only practical means of providing protection against temperature extremes. The *United States Pharmacopoeia* definitions of various temperature conditions are accepted as standard. A *cold place* has been defined as one which has a temperature not exceeding 15° C. (59° F.). When *refrigeration storage* is specified on the label, a temperature between 2° and 15° C. (36° and 59° F.) is indicated. *Excessive heat* or *excessive temperature* refers to a temperature which exceeds 49° C. (102° F.).

Earlier it was shown that possible chemical reaction between the product and packaging materials with which it is in contact should lead to careful selection of the latter. This section will discuss briefly the most common types of packaging materials that present this problem. Here again the purpose will be primarily to bring to the attention of the package designer the general type of problem that can be anticipated as a result of contact of the product with packaging materials.

Glass containers of all types must be considered in the light of this problem. For the great majority of drug products, no special attention need be given the type of glass used, but there are specialized instances where the chemical action of a liquid product on the inside surface of a glass container will, over varying periods of time, break down the glass structure and either cause an undersirable change in the product or lead to contamination with glass particles. This action may be accelerated if the product is sterilized or otherwise processed after being filled into the glass container. Protection of the product against this action is usually possible by the use of borosilicate glass—the so-called hard glass—which has exceptional resistance to chemical attack. A problem of this type applies for the most part to parenteral solutions and an authoritative discussion of the subject may be found on page 630 of *United States Pharmacopoeia XIII*. In this article specifications are set forth for containers for use with injections and other pharmacopoeial preparations for parenteral use. Test procedures are described

and the suggested types of glass containers for various injectable products are listed. A complete knowledge of official compendium container requirements should be acquired as a basis for packaging parenteral solutions.

Closures of all types must be carefully selected on the basis of possible product incompatibilities. There are two varieties of closures, however, which should receive major attention when used in conjunction with liquid products. The first is any screw-cap type where a separate liner that contacts the liquid is adhered to the inside dome of the cap. This liner is usually in two parts, the backing (generally a resilient material such as cork or paper board), and the facing which is in contact with the product. This facing commonly will be either paper, plastic film, or metal foil, or combinations of any two; and all types may be impregnated or coated with paraffin, waxes, or similar materials. The type of facing most suitable to the chemical and physical characteristics of a product must be carefully determined. In a line of products of various sorts, a number of different liners will probably be required. Many attempts have been made to develop a universal liner, but so far as is known these efforts have not been successful.

The formula of rubber closures used for parenteral solutions should receive similar attention since there is a possibility of chemical interaction between the product and the rubber closure itself or the ingredients used in the process of its molding. The usual experience is that several rubber formulas would be required for a line of parenteral solutions. The field of synthetic rubber offers possibilities for future development as closures for solutions which react in contact with natural rubber, and it can be stated definitely that neoprene is the material of choice for closures to be used for oily preparations.

It should be recognized that any packaging material used as a container and which consequently is in contact with the product—collapsible tubes, tin or aluminum cans, plastic containers—represents potential compatibility problems. As has been stated heretofore, plastics in any packaging application should be carefully scrutinized for possible product reaction.

In all problems of this type, there is much compatibility data available, generally from the supplier of the packaging material involved, but there is no substitute for actual contact tests between the product and the intended material, and the thorough job of package development will include this step.

Consideration must also be given to protection against external factors, such as crushing, marring, scuffing, or soilage. At this point it becomes necessary to differentiate between *packaging* and *packing*. For the purpose of this article, packaging is thought of as involving the immediate container for the product, whereas packing is considered to be whatever additional protection is given the immediate container. Although the packing function will be considered from time to time, and must be recognized as an important phase of the complete packaging job, this discussion will be confined primarily to the immediate package unit.

The possibility of a package being tampered with somewhere in the distribution channel cannot be lost sight of and represents a potentially serious problem. Positive protection is difficult and costly to attain, but a fair degree of protection against casual tampering can be attained by a variety of means, such as fittings on the closure, wrapping with transparent paper or plastic films, or sealed cartons or boxes for the individual container.

A second major criterion in package development is utility in developing factors of ease and convenience of use. The package designer must apply his knowledge of how, and by whom, the package will be used. Method of use must be carefully related to packaging material specifications. As an elementary example, the diaphragm of a rubber closure in a vial containing a parenteral solution must permit easy puncturing with a needle. It is important to keep in mind that the average user seldom is an expert in handling the package and the more usable he finds the package the less likely he is to build up resistance to it.

Design and appearance constitute criteria to be considered in package development. Product protection on one hand, and

merchandising appeal in the form of good design and appearance on the other, probably represent the extremes in approaching the development of a package. Yet both are essential to the final objective of marketing the product, and good design can be accomplished without sacrificing product protection or package utility. Such factors as family resemblance of packages or distinctive features to identify a certain concern, are often important contributions to the successful merchandising of a package. It is somewhat outside the scope of this article to discuss the specialized subject of artistic design, but it must be recognized as a criterion in package development.

A close working relationship must be established between the package designer and those responsible for the assembling and production of the package. There are many aspects of this problem. The first centers around the fact that a package is assembled in progressive steps. A closure and a label are placed on a bottle, the bottle in turn goes into a carton, which in turn goes into a corrugated shipping case. This series of simple assembly steps is typical of many in which the specifications of each unit of packaging materials must be related to the next material in the assembly. The package designer must be fully informed with respect to all production methods involving packages.

If automatic equipment is to be employed, the exact requirements must be known in establishing specifications for each part of the package. Although the use of automatic and semi-automatic packaging equipment probably represents an opportunity in many firms, it is believed that the package designer should guard against building a package around either equipment or established methods at the expense of utility or product protection.

Specialized processing of packaging materials, as for example, the sterilization of rubber closures, should be considered in establishing specifications for such materials.

Brief mention will be made of certain legal requirements which pertain to packaging of drug products and which should be considered in any package development project.

The *United States Pharmacopoeia XIII* contains packaging and storage requirements for many individual products and sets forth definitions for various packaging functions.

The *National Formulary VIII* in a like manner specifies storage and packaging requirements of certain products. The specifications in both of these works must be fully complied with in the marketing of official preparations.

The Federal Food, Drug, and Cosmetic Act contains several sections pertaining to packaging. This Act recognizes the *United States Pharmacopoeia* and *National Formulary* as legal compendiums and sets forth that any drug defined in these compendiums would be considered misbranded if not packaged and labeled in the manner set forth therein.

The packaging and labeling regulations of the Act are closely related in many respects and it is believed important to recognize labeling regulations in the development of the package. For example, the Act states that any word, statement, or other information required by the Act should appear on the label prominently and with such conspicuousness as to render it likely to be read and understood by the ordinary individual under ordinary conditions of purchase and use. Failure to achieve sufficient prominence due to small type or lack of label space is cited as cause for deeming a drug to be misbranded and it therefore becomes apparent that the package should be designed in such a manner as to provide maximum space for label information.

One of the most important sections of the Act to the package designer is 502(i) which stipulates that a drug will be deemed misbranded if its container is so made, formed, or filled as to be misleading. This is the so-called "slack-filled" provision that refers to containers not completely filled so as to give the impression that the quantity of the contents is greater than is actually the case. This section poses a problem for there are certain considerations of product protection or cases of physical characteristics where partially filled containers are either desirable or unavoidable. Some liquid products in suspension form may require a substantial amount of void

space in the bottle in order that a fresh bottle may be shaken properly following long shelf storage. Other products may sift down to less than their original volume during handling. Manufacturing tolerances in the compression of a tablet, for example, may be such that a package designed for the maximum tolerance will appear only partially filled when minimum tablets are produced. So far as is known, no exact definition for "slack fill" in terms of proportion of the volume of a container filled have been established, but as Arthur D. Herrick has pointed out, it is evident that this provision is not intended to apply to drug containers which may be filled as full as practicable under manufacturing practices. Herrick has also shown that while the Act has failed to define what the term "container" encompasses under the law, it can be assumed that both the immediate container and outside containers are included.

The amendments to the Federal Food, Drug, and Cosmetic Act covering the certification of insulin and antibiotic drugs contain specific packaging requirements for these products.

Many individual countries have regulations affecting the packaging and labeling of drug products, and these should be reviewed before attempting a package design project for items destined for shipment to export areas.

There exist specific Interstate Commerce Commission regulations pertaining to packaging. These deal in the main with the degree of protection that must be afforded the immediate container, both by the secondary container and the shipping case. A thorough understanding of the technical specifications set forth in these regulations is essential.

The Post Office Department also regulates the packaging which must be followed for certain types of products.

In summarizing this section, it may be noted that package expense has not been listed as a development criterion. Obviously a package designer must concern himself with all phases of cost, but it is believed that in the packaging of drug products he is justified in first satisfying the needs of product protection and package utility.

It may also be well to stress the scope of the package develop-

ment job. The creation of a package for a drug product is a technical problem, and it has been the experience of many firms that thorough experimental work and laboratory control should be a part of the selection of proper packaging materials. Yet the factors of utility and design are a vital part of the final package. It seems safe to conclude that a versatile individual or group should hold the responsibility of package development.

CONTROL OF PACKAGING

In dealing with a complete package it is necessary to think in terms of the individual components of that package, which are referred to throughout this article as packaging materials. Thus, in a simple example, we have a bottle, a closure, and a carton for the bottle, each representing a packaging material which, when assembled together, make up the complete package.

The final objective of package development is to establish for each packaging material component a complete set of specifications which satisfy the development criteria described heretofore. These can become the purchasing specifications provided to sources of supply. Since the control of these specifications is an important corollary in maintaining the quality of the finished package, it seems desirable to describe the procedures and technic associated with this control. Most firms whose line of products involve a variety of packaging materials have found it necessary to establish a system of inspecting incoming shipments of these materials in which the important specification points are checked, either by dimensional measurements or by chemical or physical tests. In the following, a review will be made of some of the more important packaging materials and the specification points that may be established and inspected. This is by no means a complete list of either materials or specification factors, but it is presented merely as a guide to the individual interested in establishing or improving a packaging material control system. An attempt is made to show the reason for controlling certain specification points, and the relation-

ship of the latter to production methods or other packaging factors.

PACKAGING MATERIAL SPECIFICATION CONTROL

A necessary preliminary step is to determine the sample to be checked from each incoming shipment. This sample must be adequate to give a representative picture of the entire shipment and in many instances adequacy will depend on the incidence of defective goods which may be expected from a particular method of producing the material. Knowledge of production methods, and recognition of quality limitations imposed by such, are necessary prerequisites to development of an inspection system. There is an opportunity for the application of statistical control procedures, and attention is directed to text books which describe statistical sampling and inspection methods.

In establishing specifications for bottles and similar types of machine-produced glass containers, the following points might be considered:

1. Use of bottle. (Product use may determine quality of glass and importance of various specification points.)
2. Style (round–rectangular–special shape).
3. Color (flint–amber–special color).
4. Weight. (Bottle weight represents the amount of glass used in its production and variation from specified weight may indicate poor glass distribution which in turn may cause breakage.)
5. Height. (Bottle height must be controlled because of relation to dimensions of filling and labeling equipment, as well as related packaging containers.)
6. Diameter or width and thickness. (Here also the dimensional relationship to equipment and other packaging materials must be maintained.)
7. Volume to a certain point on the bottle. (Several types of vacuum filling equipment depend on volume being controlled to a certain dimensional point. The accuracy

SPECIFICATION SHEET

Item *No. 200 Bottle* Issued *Oct. 15, 1947*

For *Liquids, 1 pint*

Style *Round, special finish* Closure *Special 30 mm. pour out* Cork Metal Cap

Color *Amber* In Diameter of Neck *9/16" absolute* Minimum

Approx. Weight *12.25 oz.* Wide

Height *7 13/16" ± 1/32"* Thick

Diameter *2 29/32" ± 1/32"* In Row= Minimum Maximum

Volume* *17 ozs. ± 4 cc.* Bottling Equipment *24 Spout, Kiefer Rotary*

Filling Line° for *16 ozs.* is *5 5/8" ± 1/32"* Outside Diameter of Filling Tube ½"

*Base of Neck °Bottom of Meniscus

Special *Label panel height—straight up from base 5 ¼"–5 5/16"*

Related Packaging Material

31 series screw caps

of the fill as well as the provision of adequate headspace will depend on this specification.)

8. Closure (standard or special finish).
9. Inside diameter of neck. (In case of liquids a definite minimum is necessary to insure fit of filling spout.)

It will usually be found desirable to reduce bottle specifications to a blue print showing all significant dimensions. In the case of practically all materials, including bottles, it may prove convenient to develop a specification record. A typical example is shown below for bottles, and a similar form can be drawn up for other type materials.

In establishing specifications for ampuls (glass sealed), the following points might be considered:

1. Type of glass.
2. Style and size of ampul (intended volume, straight or constricted neck).
3. Body diameter and length. (These dimensions may have a bearing on containers employed for holding ampuls during washing and sterilizing, as well as protective packing materials.)
4. Wall thickness of body. (Important in connection with breakage during production and shipping.)
5. Stem diameter and wall thickness at sealing point. (Must be controlled to insure efficient sealing.)

In establishing specifications for metal collapsible tubes, the following points might be considered:

1. Quality of metal (as for example, tin or aluminum of specified purity, or a composition of metals).
2. Diameter and length. (Must be controlled to insure proper volume and satisfactory crimping action.)
3. Gauge of metal. (Variations will affect crimping action.)
4. Strength of metal. (This specification is usually controlled by a bursting test which discloses weak points produced in drawing the tubes.)
5. Type of closure and liner.

In establishing specifications on materials similar to those shown above, it invariably is advantageous to work closely with the supplier of the material. In many instances it will prove possible to use standard materials, in which cases the specifications set by the supplier will prevail. In other instances, because of merchandising policies or specialized production problems, the drug house will wish, for example, to develop a distinctive bottle and build private molds. Under any circumstances experience has shown that a mutual understanding of problems leading to agreement on specifications and tolerances, will be of benefit to both parties.

SPECIALIZED PACKAGING FOR EXPORT

When a product is to be sold in other countries, and particularly in tropical areas, the package designer is faced with problems of a distinctive nature. From the standpoint of product protection, his problem is accentuated in practically all respects. Prolonged exposure to heat and humidity will produce a degree of deterioration in both product and package that is seldom encountered in the United States. The efficiency of the closure for dry products assumes considerably greater importance and many firms find it necessary to employ a secondary closure in shipping products of this type to tropical areas. Mold is a factor and certain types of paper deteriorate rapidly. When plastics are used it is possible that the heat distortion point of the material will be surpassed, and warpage will occur. There has been experience indicating that some liquid products require additional headspace on long heat exposure. In view of these unusual factors, test shipments to new marketing areas constitute a worthwhile precaution.

Different design and appearance characteristics may be required for export packages, and this should be a subject of review with export marketing personnel.

Tampering is more prevalent in export shipments, and special attention should be given both the construction and marking of shipping cases. Recent packaging literature has contained

several excellent reviews of this subject. Of particular interest is an article "Export Pack" by Gordon E. Bouton, appearing in the December, 1947, issue of *Modern Packaging* relative to the unusual conditions encountered in many overseas areas.

As a matter of general interest, there has been considerable expression of thought regarding the need for a policy of maintaining high quality packages for export, thereby avoiding any sentiment associated with inferior merchandise.

ORGANIZATION OF A PACKAGING DEPARTMENT

The organization charts of many concerns will follow a fairly standard pattern with respect to the functions most frequently encountered. The packaging function, however, seems to be an exception. A survey of concerns both in the drug and other fields will show the packaging job to be a responsibility of many branches of these organizations. In many companies the packaging responsibility may be split among several departments, and this is believed to be a situation detrimental to the best interests of a good packaging job. In some organizations the package control unit serves as a staff department, developing the package and issuing instructions for its assembly to production departments.

It is difficult to offer generalized recommendations as to the organization of the packaging department. Influencing factors will be the size of the business, the number and type of products, and the emphasis which must be placed on such factors as package design and utility as a result of marketing policies. If a fairly large packaging unit can be justified, it may prove advantageous to maintain laboratory facilities to carry out experimental work necessary in the selection of proper packaging materials. The internal organization of a packaging department might logically be split into the functional responsibilities of development and control along the lines presented in earlier sections of this article. Above all, it appears extremely desirable to place under the direction of one individual a unit whose responsibilities will embrace the selection of the proper

package to fit the product, the development of specifications for each packaging material component, and the subsequent maintenance of those specifications.

A survey of packaging department organization conducted in 1944, however, revealed that with the complex nature of the over-all packaging job many firms have concluded that the responsibility for determining the most effective packaging medium for a product cannot be done by a jack-of-all-trades when advertising and merchandising factors must be included. It was concluded that at least one person should have a sound knowledge of package and material functions, knowledge of the product, and a scientific background. Other considerations should be obtained from existing personnel in other departments.

SOURCES OF INFORMATION ON PACKAGING

There is voluminous literature on the general subject of packaging and a substantial amount of reference material exists that can be applied to the packaging of drug products. Several periodicals devoted to the packaging field represent an excellent source of new developments in the field.

Certain of these are listed below, and it should be made clear that this is by no means a complete listing, but only those sources which happen to be known to the writer of this article:

Glass Packer, 55 West 42d Street, New York, N. Y.
Modern Packaging, 122 East 42d Street, New York, N. Y.
Modern Packaging Encyclopedia, 122 East 42d Street, New York, N. Y. The 1948 edition of this encyclopedia is a 1205 page compendium covering very completely every phase of packaging.
Modern Plastics, 122 East 42d Street, New York, N. Y.
Packaging Parade, 360 North Michigan Avenue, Chicago, Illinois.
Plastics, 185 North Wabash Street, Chicago, Illinois.
Plastics Catalog, 122 East 42d Street, New York, N. Y.

There are several national organizations which conduct expositions and meetings of both general and specialized packaging interests. Most of these organizations publish original source material on packaging subjects. Included are:

American Management Association–Packaging Division, 330 West 42d Street, New York, N. Y.
Industrial Packaging Engineers Association of America, 20 West Jackson Blvd., Chicago, Illinois.
Packaging Institute, 342 Madison Avenue, New York, N. Y.

One of the most valuable, and in many cases indispensable, sources of information is the packaging material supplier. Most of the latter firms have established packaging research units and in problems involving product protection, package production and utility, are in a position to give valuable assistance to the package designer.

PACKAGING MATERIALS HANDLING AND STORAGE

While this function is usually not the responsibility of the individual primarily concerned with the development of the package, it should be recognized that certain types of packaging materials will deteriorate on aging or when stored under improper conditions. This is particularly true of rubber, plastics, paper, and metal materials. The package designer who has established specifications which apply to product protection should make certain that these specifications are maintained throughout the storage period.

SUMMARY

There is every justification to regard the packaging of drug products as a science, and if the scientific approach is followed in the selection of proper materials on the basis of experimental work, as well as the maintenance of package specifications through careful inspection procedures, the result is almost certain to make a substantial contribution to the successful marketing of the product.

10

The Product and the Patent Law

EDWARD THOMAS

ALMOST every manufacturer developing and marketing new drugs today must keep in mind two aspects of patent law. He may, on the one hand, seek to determine whether his new product may be patented. Equally important is the question that sometimes presents itself as to whether the drug infringes on an existing patent.

Before these questions can be answered, there must be a clear conception of just what a patent is. Strictly speaking, this may be described as the limited monopoly right granted by a "letters patent" over the signature of the Commissioner of Patents for a period of seventeen years. Letters patent contain a full description of the invention and "how it is made and used in such full, clear, concise and exact terms as to enable any person skilled in the art or science . . . with which it is most nearly connected to make, construct and use the same." In it the inventor makes "claim" to the improvement or combination which he regards as his invention or discovery.

A "claim" is really a definition of the invention, most patents containing more than one; thus, one of the adrenalin patents enumerated seventeen. The patent is "infringed" when one, other than the holder, makes, uses, or sells the invention as it is defined in any claim.

In a basic economic sense, the patent law, by thus granting a limited monopoly to a new product for seventeen years, offers a sort of partial insurance that the money preliminarily invested in developing it will not have been wasted. Actually, it insures the manufacturer against competition, and enables him to recoup his investment which frequently involves an expendi-

ture of thousands of dollars for preliminary investigation and tests.

This quasi-insurance afforded by the patent law tends to warrant the expense of those tests and preliminary expenses; usually it serves as a guaranty against cut-throat competition by rival manufacturers. The rewards of a valid patent are often very great if the patented product is widely sold. For example, it has been remarked that $10,000,000 of phenacetine, then protected by patent, had been sold before 1900.

The patent law also offers other forms of similar protection. Thus, if a product patent cannot be obtained, at times a *process* patent, that is, a patent for an "art," may be secured covering the method of manufacture. In many cases, moreover, competition is discouraged by merely marking the product with the words "PATENT APPLIED FOR" or "PATENT PENDING." The psychological import of these legends, if nothing more, affords considerable protection against competition for a time, enabling good trade mark protection to be built up over a period of two or three years, even though no patent is eventually issued.

Of course, it should be borne in mind that the mere existence of a patent is not absolute insurance against infringement. Enforcement of patents, moreover, may be expensive and time-consuming, especially in the case of process patents. Frequently, indeed, serious consideration should be given to whether there is not more to gain by keeping the process secret rather than by patenting it. Unfortunately, there are always those who will infringe patents as long as they feel they can avoid being brought to account. Thus, a process patent, owned by a small manufacturer, may be very difficult to police; this is particularly true if it is impossible to tell from the nature of the product alone by what method it has been manufactured.

INVENTOR'S RIGHTS

It should be borne in mind, despite this last comment, that ordinarily the inventor has no rights which he can use against another until his patent actually issues. But, once granted, the

foundation of his rights dates back at least to the day when he filed his patent application.

It is also interesting to observe that a patent application is kept secret, nor is the inventor applicant under any obligation to reveal his secret while the application is pending. Indeed, the secret may only be broken by the Patent Office if another inventor, claiming the same invention, is found to have filed an application in the Patent Office at the same time; and then only to the extent of revealing the two pending applications privately to the two inventors under certain carefully prescribed rules when an "interference" is declared. Interferences —contests between rival inventors—are discussed elsewhere in this chapter.

If the Patent Office Examiner thinks that more than one invention is claimed in a single patent application he requires division into two or more patent applications. Each divisional patent application under the United States patent law is considered as an amendment of the original application, but it is effective for only seventeen years, irrespective of the time any other of the divisional applications may issue. A patent can be extended only by special act of the Congress.

Printed copies of United States patents, which are sold at 25 cents each, may be obtained from the office of the Commissioner of Patents. United States patents issue on Tuesday of each week, and are indexed and summarized in the weekly *Official Gazette* which is published by the Superintendent of Documents, Washington, D. C., and sells for $16.00 a year plus cost of Annual Indices. Prints of most foreign patents can be obtained from the Commissioner of Patents at 20 cents per sheet.

Of course, United States patent applications and their resulting patents protect only within the boundaries of this country. However, corresponding patent applications may be filed in many other countries of the world. Some countries, however, forbid patents on medicinal products although allowing patents on the processes of making the products, so that the restriction is not absolute. In such instances, it is of considerable importance to include process claims in the United States patent

application. Indeed, it is well to have the United States application set forth more than one process claim, and these of different scope. For example, the presence of such process claims in a United States application helps greatly in prosecuting the corresponding British application.

It is usually advisable to file copies of the United States patent applications in foreign countries before twelve months have elapsed from the time of the United States filing. Most countries have adhered to a Convention which authorizes an inventor, filing in one country, to file within that period in any other Convention country and obtain any advantages he would have had if he had filed in that other country first. However, it might be pointed out that, while the International Convention provides for excusing acts of use or publication during the "convention year," it does not excuse such acts if they are performed before the United States application was filed. Incidentally, foreign competitors seem to have very thorough methods of finding publications and acts of public use.

It is also an interesting observation that an invention may be tried out in public before the application is filed in the Patent Office; and, indeed, may have been publicly sold or described in a printed publication, provided the complete patent application is filed in the Patent Office before one year has elapsed since the first public use and first public sale or first publication. It should be noted that if "public use" is confined to necessary scientific experiments the year does not begin to run until the experimental period is ended.

The patent statute provides that incorrect patents may be modified by "reissues" and by "disclaimers." A reissue provides for the patentee offering to the Commissioner of Patents to surrender his patent for a corrected patent for the remaining unexpired part of the term of seventeen years.

Reissues and disclaimers are often insufficient to provide the desired relief from error. They are hazardous at best, but sometimes they do prove necessary and even successful.

BUYING AND SELLING INVENTIONS

The inventor may sell his invention at any time provided it is properly identified. Similarly, he may sell his patent application, or patent, or grant licenses under the patent application or the patent. However, the inventions of an employee, hired to perform research, within the scope of his employment belong to his employer. An employee employed at laborer's wages, for example, is, on the other hand, under no obligation to assign his inventions to the employer. In some instances, the employer may hold the implied license known as a "shop right" to utilize his employee's invention in his own plant.

Between those limits of implied license and right to assignment, numerous highly specialized situations have arisen, with results so widely diverse as to discourage hypothetical discussion. It may be said, however, that the patent statute does not empower any employee to appropriate his employer's secrets.

Another source of troublesome consequences arises when a firm is asked to consider an "invention" from one outside the organization, particularly when it is offered "in confidence." It has not infrequently developed that the idea thus disclosed is already under consideration; the conflict of rights which may arise is often costly and burdensome. Perhaps the safest procedure is to consider only inventions that have been reduced to a patent application. Similarly, it is rarely advisable to buy or, for that matter, to sell a *part* interest in a patent or invention. The owner of any part interest may in turn sell or license anyone without consulting any other part owner. Moreover, in case of infringement of patent, suit can be brought only by all owners of the patent.

Years ago it was said that "within his domain the patentee is czar"; the situation has changed considerably today in this respect. Recent rulings of the courts make it essential that an inventor granting license must be very careful to avoid running afoul of the antitrust laws. Thus, he should not attempt to control the selling price of a product after it is once sold, nor to

control where a licensee buys his raw material, nor to control the price of a product if his patent covers only the process of making it; nor can he control several other rather ill-defined acts. Indeed, no license agreement that includes price or volume limitations should be drafted without consulting a lawyer familiar with the latest court decisions on licenses.

INFRINGEMENT OF A PATENT

Suits for patent infringement are peculiar only in their subject matter. A case of this nature falls within the broad category of the law known as torts; it differs from an ordinary law suit, however, in two rather important ways. First of all, a patent is infringed by producing the equivalent of the article or process claimed as well as by the article or process itself. Again, an expert in a patent case rarely expresses an opinion or answers a hypothetical question. His task is limited to an explanation of the science involved and the meaning of the description of the invention; ordinarily, however, he is not allowed to express an opinion on a question of infringement.

The mere issuance of "letters patent," it must be borne in mind, does not in every instance afford complete protection. Indeed, not all patents are effective ones in the sense that they are strong and broad and enforcible. In fact, one court has divided patents into three categories: (1) *white patents,* so obviously good that no one is willing to risk infringement, (2) *black patents,* so obviously defective on their face that the owner is unwilling to risk the cost of enforcing them, and (3) *grey patents,* encompassing patents of debatable validity. It goes without saying that almost all patent litigation arises over these last "borderline" patents.

To assure the validity of any patent that may be issued the manufacturer should keep in mind a number of fundamental principles of the law. First, he should remember that a United States patent must be signed by the inventor, ordinarily the one who first reduces the invention to practice. In the case of a drug, "reduction to practice" is generally demonstrated by tests

tending to show its use or, at least, that it is possessed of some utility.

It is frequently difficult to decide between two or more workers as to who is to be considered the actual inventor. In general, a director of research who gives definite suggestions is regarded as an inventor as against the employee, merely carrying out these instructions. However, where generalized instructions only are given, an employee who is an expert in the art is regarded as the inventor.

Secondly, the manufacturer should remember, and impress upon his subordinates, that to prove himself the inventor one's testimony must be corroborated in every essential detail by others. In short, one's own testimony is insufficient to establish the fact of invention.

The manufacturer can be assured of protecting himself in both these situations by insisting that the daily complete notes of each chemist working in the laboratory be read and initialed the same day by a fellow-worker, who should also write the date in his own handwriting after his initials; this enables him at some later time to identify the date as correct.

One more important point can be set forth, exemplified by a contest involving a dye patent. The infringer's defense was based on the fact that the patent stated that the dye was made in the usual autoclave, which, it was shown, is enamel-lined. It was proved, however, that the dye could be made only in an *iron-lined* autoclave, the iron being needed to react with the acid in the color. The patent was held void on the ground that its description was misleading in failing to specify the need for an iron autoclave.

Similarly, a patent on a chewing gum which contained phenolphthalein was held invalid for lack of description. There, too, it was found almost impossible to mix the ingredients properly due to inadequate directions.

SEARCHES BEFORE FILING

Not every new product or combination is, of course, patentable, not merely because of the possibility of an infringement on an existing patent, but rather for the reason that it is not acceptable as a "real invention." It is customary, therefore, for the manufacturer to have a "search" undertaken either by a patent attorney or one of his own experts to determine whether the invention is probably patentable or is technically unpatentable.

In general, an old organic chemical anticipates its homologues, except in cases where unexpected uses develop. Thus, crystalline calcium carbide when first produced was held patentable but a much later decision held crystalline calcium pantothenate unpatentable.

An illustration will further clarify this point. A would-be inventor proposes to add a new drug in chewing gum. A search would show that phenolphthalein has been incorporated in chewing gum, and that other drugs have also utilized the same base. The Patent Office Examiner would probably rule that there was no invention in incorporating the new drug in chewing gum, and would, therefore, deny the applicant a patent. As a matter of fact, such an invention can seldom be patented, because the chewing gum base seldom plays such an unexpected part in connection with the added drug as would warrant its issuance.

On the other hand, the converse situation arose in a patent application relating to a potassium nitrate solution in which the composition including ammonia was held patentable because the proportion of contained ammonia unexpectedly increased the solubility of potassium nitrate. The phenacetine patent, mentioned further below, was also held valid on substantially the same grounds. The prior material was poisonous. The patented substance, however, avoided this toxicity; it was held to be patentable, although actually only a purified form of the article on the market.

PREPARING THE PATENT APPLICATION

Ordinarily the manufacturer who has had experience in patent matters turns over to the patent attorney all data, not only regarding the invention as originally presented to him, but also all material dealing with analogous products or methods to demonstrate the position of the invention in its "art." Indeed, the attorney usually suggests a line of tests or experiments to learn, for example, the results should someone attempt a modification of the product with the thought of attaining its advantages without actually infringing on the prospective patent. Coming from outside of the rut in which the research men may have been working, this suggestion sometimes sets the research men on the track of something better than they had hitherto produced.

Thus, one inventor asked the attorney to prepare a patent application dealing with an amyl ester, demanding a broad patent in the field. It was pointed out that a broad patent could not be obtained on an example of a single ester; and the suggestion was made to try the dodecyl ester. The inventor came back a month later to report that although he had not been able to obtain material to make the dodecyl ester, he had produced the octyl and found it far superior to the amyl ester. Another inventor wanted a patent on a composition including a complicated substituted ammonia ester. He was finally persuaded to try out some of the simpler substituted ammonia esters. He returned later with the announcement that a certain simpler ester was found to be so superior as to be almost revolutionary.

THE SPECIFICATIONS

After a preliminary search has been made and the field found clear, the patent attorney drafts a patent specification which may be summarized as a detailed description of the invention and "how it is made and used in such full, clear, concise and exact terms as to enable any person skilled in the art or science

. . . with which it is most nearly connected to make, construct, compound, and use the same."

The writer of the specification for a chemical patent application faces a far more exacting task than one preparing the specification of a mechanical patent application, partly for the reason that the chemical patent application ordinarily includes no drawing. Thus, there is nothing in the patent application to enable the specification to be checked for accuracy by comparison.

It follows that accuracy is of paramount importance in preparing the specification. Thus, one inventor reacted phosphorus penta sulfide with cresol and patented the product, a mixture of sulfides, disulfides, and mercaptans. Later, however, a rival discovered in the inventor's corresponding Southern Rhodesian patent an affidavit by a chemist of the inventor to the effect that the statements about sulfides, disulfides and mercaptans were incorrect, that the product was a nearly pure complex phospho sulfo cresylic acid. This contradiction defeated the validity of the patent.

Another inventor patented a process of drying milk depending on the temperature of certain rotating rolls. He computed the temperatures from steam pressures used to heat them, forgetting that the surface temperature would be lowered by radiation. His patent was held to be void because the true temperatures of working were far below the computed ones set forth.

The foregoing paragraphs contain only a few of the many illustrations available which indicate that a chemical patent is most vulnerable in its formulation of the specification or disclosure. This must be free from errors and, in addition, must contain every necessary factor to enable proper patent claims to be drawn. The principle is not only applicable to the first presentation to the Patent Office, but also affects modified claims drawn to meet the requirements of the Examiner in the Patent Office.

It is often advisable in preparing a patent application to write a brief exposition on the difficulties, failures, and unsuccessful attempts of the prior "art," and then to proceed with the state-

ment that the invention to be described overcomes those difficulties and failures. In this way, the patent application tends to carry the badge of an improvement on its face. This should be followed by a detailed account of several, preferably three or more, well distributed examples of practicing the invention, and, where appropriate, a summary of the advantages thus obtained. After a statement that the foregoing has described certain embodiments in some detail, the claims should be set forth.

To enable those unfamiliar with drug patents to obtain a better understanding of what is meant by a "claim" in a medicinal patent, a few specimen claims are set forth below. These have been drawn from litigated cases in which the claims were held to be valid. It should be borne in mind, however, that these involve so-called "border-line" claims because they are taken from patents subjected to litigation, and were, therefore, deemed worth fighting over. In considering the subject of claims, moreover, the following very important sixty-year old ruling regarding medicinal patents should be remembered:

A remedial compound which is nothing more than such a compound of medicinal agents as could be made by the exercise of the skill of a physician is not patentable.

The test does not work out as altogether too arbitrary in practice. For example, in one case a patent was allowed on a disinfectant ordinarily of unstable shelf-life when the preparation was stabilized by the addition of three one-thousandths of one per cent of alkali.

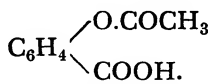
It should also be pointed out that, although "use" claims are no longer granted by the Patent Office where they merely involve a new use for an old composition, nevertheless it is occasionally possible to obtain about equal protection by claiming the active ingredient plus a diluent if that composition is new. For example, the active ingredient in insecticides of the DDT type is an old composition but the patent covering such preparations contains claims to compositions comprising the active ingredient together with a diluent. Indeed, there are a large

number of patents on insecticides containing this type of claims wherein the active ingredient is old but mixtures of it with a diluent appear to be new. Similarly, in the pharmaceutical field it might occur that a new use has been found for an old chemical compound. If it is to be administered in tablet form, for illustration, one might claim the active ingredient plus a special group of diluents broadly, and then more specifically, the active ingredient plus some binder for tablets having an unexpected utility with the active ingredient.

The following are examples of claims that have been held valid in litigated medicinal patents:

Phenacetin: The product herein described, which has the following characteristics: It crystallizes in white leaves, melting at 135° centigrade; not coloring on addition of acids or alkalies; is little soluble in cold water, more so in hot water; easy soluble in alcohol, ether, chloroform, or benzole; is without taste; and has the general composition $C_{10}H_{13}O_2N$.

Aspirin: As a new article of manufacture the acetyl salicylic acid having the formula:



being when crystallized from dry chloroform in the shape of white glittering needles, easily soluble in benzene, alcohol and glacial acetic acid, difficultly soluble in cold water, being split by hot water into acetic acid and salicylic acid, melting at about 135° centigrade, substantially as hereinbefore described.

Adrenalin: A substance possessing the herein-described physiological characteristics and reactions of the suprarenal glands in a stable and concentrated form, and practically free from inert and associated gland tissue.

Hog Cholera Antitoxin: As a new substance hog cholera globulin, consisting only of the hog cholera immune bodies and the globulins obtained from hog cholera defibrinated blood antitoxin, having the active substance in concentrated and sterile form.

Antitoxin for Scarlet Fever: An antitoxin specific to scarlet fever obtained from the blood of an animal which has been injected with sterile toxin specific to scarlet fever.

A sterile toxin specific to scarlet fever.

Benzedrine: [These claims went through a series of complicated steps before the patent issued. Two of the final claims were:]

As a physiologically active therapeutic agent capable of producing effects in animals and man similar to the effect of salts of ephedrine, a salt of 1-phenyl-2-amino-propane.

As a physiologically active therapeutic agent capable of producing effects in animals and man similar to the effect of salts of ephedrine, the hydrochloride of 1-phenyl-2-amino-propane.

With those claims in mind as "border-line" claims a few words of caution are advisable. A Patent Office Examiner often rejects claims as "functional." This means that they define what a substance will *do* instead of defining the substance itself. Sometimes this objection is very difficult to deal with. In general, however, claims along the lines of those quoted above may be won, although only after long effort in some instances.

It may be here pointed out that the word "functional," when used in describing a patent claim relating to a machine, means that the function of the machine is covered rather than the machine itself. In chemical patents, however, the function set forth in the claim may really constitute a chemical test for the identity of the material. Where this tends to prove the identity of the patented substance, the objection implied by using the word "functional" is without foundation.

One other favorite term used by Patent Office Examiners in rejecting claims is that the claim covers an *aggregation*. Although a physician's prescription ordinarily may be regarded as an aggregation in which each ingredient plays a well-known part, the term is not properly applied to a mixture in which one substance, contrary to expectation, alters the efficacy of another.

It will be noted that the claims to drugs, quoted above, include no mention of alternative materials. As a matter of fact, the Patent Office ordinarily refuses to allow claims to alternatives. To escape that difficulty, the practice has developed to frame claims to materials "selected from the group consisting of . . . and . . ." These are called "Markush type" claims. Reliance upon this type of claim, however, is subject to several qualifications. In the first instance, the grouped substances must

constitute a real group, not merely a haphazard collection. Secondly, a Markush group is permissible only if it accomplishes a unitary concept. Finally, a Markush group must be founded on examples set forth in the specification and the enumerated substances of the claim must be named in the examples.

Where it is impossible to define a novel product in ordinary chemical terms, the Patent Office Examiners often allow reaction product claims. Such claims have seldom been before the courts; indeed, it is not clear how the courts will regard them. Reaction product claims are mentioned here only to be sure the possibility of falling back on them is not overlooked when no other form of claim seems available, and also to emphasize that their use is a hazardous form to adopt.

THE APPLICATION

After the patent attorney has secured all apparently needed data and writes out his proposed patent specification, he then formulates claims, as required by law, which define the invention. The wording of the latter is not necessarily final. In other words, if a proper patent specification has been prepared and filed, it can be altered at any time while it is in the Patent Office, provided the alterations keep entirely within the statements of the filed specification and do not amount to "new matter."

However, the patent attorney gives considerable attention to the claims before filing. Not only are they carefully formulated, but they are also compared with the draft specification to be sure that there is an adequate basis in the specification for every element named or implied in the claims.

In drafting the claims, it frequently happens that attention is drawn to further data needed in the specification. The specification should therefore be revised in view of the imperfections which appear from a study of the draft claims; often further experimenting may be essential to fill in the gaps thus discovered.

When the claims are prepared to the satisfaction of the inventor and his attorney, the application is usually filed promptly.

But before filing the patent attorney makes it a practice of determining whether the inventor is withholding any important data which should be revealed, since deliberately withheld essential "secrets" will result in a void patent if the patent ever comes into court and the missing secret step is discovered.

THE PATENT APPLICATION IN THE PATENT OFFICE

The Commissioner of Patents, through his staff, acknowledges the receipt of the patent application and sends it to an appropriate Examining Division. To give an idea of the hurdles a patent application faces, it may be pointed out that there are upward of ten chemical divisions in the Patent Office, each headed by a Chief with ten to twenty Assistant Examiners working on the filed patent applications in the classes of invention allotted to his division.

Between one to two-and-a-half per cent of all patent applications filed are found to claim the same invention contained in another application. For this, and other reasons, the Patent Office insists on certain standard nomenclatures. Ordinarily, the patent attorney is familiar enough with most general chemistry to be able to conform to those rules of nomenclature. The fact remains, however, that nomenclature is exceedingly important and possible mistakes should not be overlooked. The confusion arising from errors may be illustrated by the patent which claimed as one ingredient trichlorethane of a stated specific gravity, boiling and freezing point temperatures. Investigation showed that the particular specific gravity and temperatures really defined dichlorethane.

In the course of time, usually some months, the Patent Office Examiner may sometimes reject the patent application saying that a specified claim, or all the claims, are anticipated by certain prior patents or other publications. It may be noted that the Examiner does not specify whether the rejection is based on the phraseology or on the merits of the invention.

CLINICAL TESTS NEEDED TO MEET PATENT OFFICE REJECTIONS

If the patent application obviously covers a drug or other medical invention, the Patent Office Examiner, in addition, may reject the claims on the ground that the invention has not been proved useful and harmless beyond a reasonable doubt, and therefore is rejected on the ground of lack of utility.

To meet the Examiner's rejection on this ground, it is advisable to obtain or have ready affidavits from at least three physicians regarding clinical tests of the material. Sufficient details to provide proper study and evaluation of the patent may be helpful, in fact, may be necessary.

The number of clinical tests required will vary with the field to which the patent application relates, as well as the personal reaction of the Examiner. In dealing, for example, with an alleged relief for cancer, one Examiner went so far as to hold that several hundred clinical tests were insufficient; his holding, however, was reversed on appeal to the Court of Customs and Patent Appeals. In other cases, twenty clinical tests have been held adequate.

It has been held that when a drug is intended to be used in man, at least a few clinical tests on humans should be included. If possible, tests of the drug on animals, other than human, should also be set forth in the patent application, or be inserted later in the record.

However, one large manufacturer of pure chemical compounds to be used as drugs has reported that while early clinical tests may be desirable in order to establish reduction to practice if the application ever gets into an interference, it has never found it necessary to supply them as proof of utility. The Patent Office, in its experience, has usually been satisfied with results obtained upon experimental animals, such as rats or guinea pigs. In interference cases, of course, it is necessary that such tests have been conducted upon the particular species of animal on whom it would ordinarily be used, usually human beings.

Clinical tests of this nature, properly set forth to the Patent Office, are of value in connection with any new drug, although where the drug is definable as a wholly new substance, not closely analogous to any other pharmaceutical or chemical product, the Patent Office can occasionally be persuaded to allow claims despite the absence of such tests.

HOMOLOGOUS AND ANALOGOUS DRUGS AS ANTICIPATIONS

The widening scope of experimental chemistry and the growing development of biological substances have resulted in many tentatively used drugs apt to be more or less analogous to some drug found highly useful. It frequently becomes necessary to persuade the Patent Office that there is a patentable distinction between existing substances which were only tentatively or experimentally used and the new drug claimed to hold great promise. Clinical tests have been found of high probative value in establishing differences of this nature.

In the *Benzedrine* case, for example, the patented product was found to be similar to other prior substances. The patent was nevertheless held good because the new and unexpected properties disclosed by the patent and verified by clinical tests proved an effect on the central nervous system as well as on the sympathetic nervous system.

The importance of presenting such evidence properly is emphasized by a comparison of the *Benzedrine* case with the *Zinc-globin-insulin* case. There less persuasive evidence was presented on behalf of the invention and the patent was held invalid over the prior "art." It is impossible to give general directions for prosecuting a hypothetical patent application of a drug; indeed, only a careful study of the decided cases or experience in dealing with the chemical divisions in the Patent Office can furnish adequate guidance.

Every point raised by the Examiner in his letter of rejection must be either acquiesced in by amendment or squarely controverted if a holding that the answer is incomplete is to be escaped and to avoid resulting in an abandonment of the

application by operation of law. One of the problems facing the patent attorney is to present amended claims tending to demonstrate that the rejection was due merely to terminology rather than substance. This answer must be filed in Washington within six months of the date of the Examiner's letter.

The Examiner may reply to that answering letter of the attorney with further rejections, or may "allow" the claims, as circumstances dictate. If the claims are allowed and all specification errors are corrected, the patent application may then issue as a patent by paying the final fee, usually $30.00, within six months of the date of the allowance.

FURTHER PROBLEMS PECULIAR TO CHEMICAL PATENTS

Patent attorneys, unfamiliar with chemical patents, are likely to fall into several errors. Thus, they may fail to appreciate that a chemical invention may turn on the *absence* of some substance and be patentable in the form of a claim defining that absence. Again, they tend to lack a realization that a broad claim in a chemical patent application is almost invariably rejected unless the specification lends it support by three or more examples well distributed over a wide field.

In other words, in drawing claims, care must be used to make them cover not more than the real invention as set forth in the specification. Thus, claims to a method of killing insects by exposing them to a toxic amount of a given material were held invalid, because the process as disclosed concerned only the vapor of that material.

The patent attorney, furthermore, may fail to utilize the right to make what are called "Markush type" claims, mentioned above. This privilege enables the application to claim alternatives by defining a material as "selected from the group consisting of . . . and . . ."

INTERFERENCE BETWEEN RIVAL INVENTORS

Mention has been made of two inventors claiming the same invention at the same time in the Patent Office. In order to discover who is the first inventor, the Examiner is directed to put into "interference" any two rival patent applications he finds which attempt to claim the same invention, provided the invention is probably new. The first step of the Examiner, generally, is to suggest claims so that each patent application includes at least one claim identical with one in the other application or applications. This serves to place the conflict squarely at issue.

When an interference has been declared by the adoption of an identical claim or claims by two or more parties, each party is required to file a preliminary statement setting forth the dates when the invention was conceived, when it was disclosed to others, when the first written description was made, and when it was reduced to practice. These preliminary statements are sealed up until officially opened by the Patent Office.

Either of the patent applications involved in an interference may be made the basis of a motion to add claims, or to dissolve the interference on the ground that a claim is anticipated, or to dissolve the interference on the ground that an opposing party has no right to make a proposed claim. After preliminary motions, if any, have been made and decided, the sealed statements are opened and the parties are authorized to take testimony at times set by the Patent Office to prove any dates of conception, reduction to practice, or others properly set up in the statements.

Interference proceedings have been described as the most highly technical proceedings known to any kind of law; ordinarily they should be conducted only by an attorney who has had considerable experience in chemical interferences. For example, although one applicant may find that a rival was the first inventor of the invention as he broadly conceived it, some improved form may also be described in his patent application which he is certain that he first reduced to practice in that

form. He should, therefore, move to add a claim (here called a "count") to include the improved form. The result may be that, although the rival may hold a broad patent, the applicant may be entitled to the patent on the commercially useful form.

Many a partly defeated patent application has been turned into a valuable patent by this procedure. On the other hand, the failure to resort to this maneuver has cost many inventors a valuable invention.

INFRINGEMENT SEARCHES

If the drug manufacturer asks whether the new product infringes an existing patent he is, perhaps unwittingly, putting a question which usually calls for an extremely expensive answer, an answer, indeed, which can only be made after a prolonged search of all classes in the Patent Office likely to contain patents that might be infringed.

The difficulties inherent in such a search may be illustrated by the fact that the class of Chemistry, Carbon Compounds, 260, in the United States Patent Office contains upwards of 800 subclasses. Many chemicals might be classified in any one of several of those subclasses.

In addition, the report on an infringement search usually includes an opinion by the searcher regarding the probable validity or invalidity of any claims which are considered to be infringed. Thus, it happens that a patent on a composition of matter, appearing on its face perfectly valid, may be anticipated by a prior patent which only incidentally used the same composition of matter as part of a structure or of a more complicated composition. Locating such structures and complicated compositions often requires a prolonged search.

Questions arise in such a search which can only be answered by a chemist familiar with the particular field in which the patent falls, and at times only after experiments designed to verify the suspicion of concealed imperfections in the patent, for example, that a substance not mentioned in the patent will be produced on performance of the process stated. Thus, an

inventor claiming a new use for diastase was held to be anticipated by material which, although it was not described as containing diastase, actually did so.

INHERENCY

One of the problems facing patent lawyers is one which arises almost exclusively in connection with chemical patents although, theoretically at least, it may be present elsewhere in patent law. That problem stems from the fact that an inventor is entitled to claim in his patent application not only what he describes in it, but also anything inherent in his description.

The task of determining whether a given step or product is inherent in a specification arises mostly within the Patent Office, usually in interferences between inventors who have solved a given problem from different points of view. We have noted above that no "new matter" can be added by amendment to a patent application once it is filed in the Patent Office. To set forth in the specification factors or steps which were necessarily inherent in the original disclosure is not, however, considered such "new matter." This doctrine entitles an inventor to support an amendment to his patent application by affidavits of himself or of others skilled in the art to explain the inherency of the proposed addition. Affidavits of this character must be filed in the Patent Office as part of an amendment; often they become extremely important. They must be drawn with great care to avoid the implication that the specification is defective, and equal skill must be exercised to exclude misleading statements from affidavits.

INFRINGEMENT SUITS

It is usually sound advice, when a manufacturer is threatened by a rival with an infringement suit on a drug patent, not to be unduly alarmed. A large proportion of threatened suits on such patents are, it has been shown, founded on seriously defective patents.

In one instance the manufacturer of a compound including an ester of benzoic acid was threatened with suit founded on a patent broadly claiming the ester although it was based on a specification which only named the acetic acid ester. Study of the patent showed limitations in it that were necessarily read into its claim and thus effectively prevented the successful prosecution of the suit. Letters to the owner of that patent pointed out that the specification of the patent described only a single ester based on the simplest aliphatic acid, whereas the accused material contained no aliphatic chain at all, but was built up from the utterly different benzoic acid. The threatened suit was dropped before any papers were filed in court.

In another instance a manufacturer was making a metallic suspension in a wet way, so that it contained a little moisture. Another company owning a patent on parallel material made so as to be anhydrous and claimed as anhydrous, threatened suit. It was possible to persuade the company making the threat of suit that it was wasting both time and money in a hopeless proceeding if it attempted to bring a suit based on its anhydrous patent against one who was admittedly using a wet process.

When a patent is used by a competitor as a basis of a threatened infringement suit, it is also often possible to attack it for failure of description in that the patent may use such terms as "short," "long," "much," "little," "great," "small." Where numerical values would have been a real guide these terms depend wholly for their meaning on an unexpressed relationship. The same objection applies to "concentrated" and "dilute" and sometimes to the use of the word "powdered" without describing the fineness of the powder.

WHAT CAN BE PATENTED BESIDES DRUGS

It should be pointed out here at the risk of seeming repetitious that a patent must be either for a machine, a manufacture, a composition of matter, or a process. A few patents to the "use" of a material have been granted and held valid, although the courts found it necessary to construe them either as covering a

composition of matter or a process. As a matter of fact, nothing is gained by attempting to obtain a patent on the "use" of a material. Indeed, the effort may well be so confusing as to cause the patent to be held void for lack of ability to classify it as either a composition or a process.

The above remarks regarding drugs and patents have been based on the supposition that the invention brought to the manufacturer's attention is a *composition of matter.*

The manufacturer should, however, bear in mind and impress upon his research department that a patent on a "manufacture" may be equally valuable and may sometimes be obtainable where no patent on a composition of matter could lawfully issue.

A *manufacture,* as the term is used in patent law, refers to any article made by the hand of man which is something more than a mere printing upon a piece of paper, or some similar product. Thus, it may be cotton combined with a solution of boracic acid and glycerin. It may be cod liver oil in tablet form. It may be a tape having a special coating. It may be a special package of adrenalin solution. It may, indeed, be any one of a large variety of other useful products.

For example, a new vaccine for immunizing horses was held to be patentable because the vaccine, contrary to accepted belief, was not obtained from the diseased tissue of the same type of animal. One manufacture defined as "fish livers preserved in certain ammoniacal solution" was held patentable.

Occasionally the drug manufacturer is offered an invention which is more in the nature of a machine than a composition of matter, such as a device for measuring blood pressure, or a cardiograph. Such inventions seldom present any of the problems inherent in medicinal compositions of matter and for that reason need not be discussed in this chapter.

It was stated earlier in this chapter that it may be possible to secure a patent on the process of making a drug even though the drug itself may be unpatentable. Process patents can be obtained because they come under the word "art" in the patent statute; they are discussed separately since they involve many peculiar problems, although they have one advantage in that

they are not forbidden by the laws of any nation. It will be remembered that some countries forbid patents on drugs. Since it is possible to obtain patents on the process of making the drug, it is well to include at least one process claim in every United States patent application so, if nothing else, that copies can legally be filed in any country in the world.

One of the peculiar problems arising out of a process patent is that it depends on and relates to an act, which, of course, cannot ordinarily be illustrated by a blue print or by a sample, nor being transitory—motion or heat or electrical or magnetic—can it be stored away and examined or studied at leisure.

Moreover, a process patent is infringed only where the process is carried out, while a product patent is infringed wherever the product is made or sold or used. The owner of a *product* patent can, for example, sue a retail druggist and obtain an adjudication of the patent wherever it is sold. This enables him, if he wishes, to choose a favorable jurisdiction for a patent infringement suit. It is interesting to observe that the courts in the Northern and Eastern industrialized States tend to uphold patents, whereas judges in the Southern agricultural States are inclined to overthrow them.

In the case of a process patent, however, it is often difficult to obtain evidence of an infringement and to prove it in court. As we have observed, the *act* is transitory, so a judge cannot examine it at leisure as he would the blue print of a machine, or a sample of a product. The infringing act, again, is hard to appraise as a basis for computing damages, except in terms of the product; this limitation further redounds to the advantage of the defendant.

One handicap confronting the patentee who sues on a patent for the treatment of living material is to show that the patent defines steps enough to constitute a process. As a matter of fact, it is impossible to lay down broad principles for determining whether a process is patentable or not. Some instructive distinctions may, however, be drawn. For example, a patent was allowed for removing odors from vitamin-containing oils by a process of distilling the mixture at very low pressure. In con-

trast to this, it may be noted, another inventor was denied a patent for refining crotonic nitrile by azeotropic distillation.

Sometimes patentability turns on the discovery of a difficulty and correcting it, even though the method of correction seemed obvious once the difficulty is discovered. A process of emulsifying a vitamin D concentrate was accepted as patentable, whereas the production of a vitamin by activation was held to be unpatentable.

As stated above in this chapter, a method of treating a disease is ordinarily regarded as not patentable. But a method of diagnosing a disease electrically was once held patentable, as was a method of testing hearing.

Many patents on inventions involving enzymes have been issued. Thus, one dealt with a process for tenderizing animal tissue with an enzyme. Again, a process of making ice cream, depending on using various salts to control *p*H, was held patentable. Nor was any objection found to a process for preparing a vitamin concentrate. On the other hand, a process for manufacturing sugar was held invalid because the steps were all old as applied to liquids generally. A process involving homogenization to produce in America a foreign type of cheese was held patentable, and also a method of imparting flavor by adding a functional derivative was held patentable.

A few other stumbling blocks must be kept in mind if valid patents are to be obtained. One of these is loosely called "double patenting." That term is used to apply to the situation which arises when an inventor obtains one patent which, of course, remains valid for seventeen years from the day it issues, and then obtains a second patent claiming essentially the same invention, so that practicing the first invention necessarily involves infringing the second patent. The result is that the inventor obtains one seventeen year term on his second patent over and above the monopoly received from his first and, in effect, procures a monopoly of more than the seventeen years to which he is entitled. In this situation the second patent is usually held void, although in many complicated situations the result has turned out otherwise.

11

Drug Trade-Marks and Labels

WALTER J. DERENBERG *

THE selection of an effective trade-mark is always accompanied and influenced by many questions of a technical legal nature. No matter how attractive a new name may appear from the manufacturer's point of view, it will have to meet the numerous tests required by the common law and by Federal and State legislation as a prerequisite for statutory protection. In the great majority of industries, moreover, manufacturers are not required to go outside the scope of Federal trade-mark legislation in the process of selecting a valid trade-mark, the standards and provisions of the Federal trade-mark Acts ordinarily furnishing sufficient guidance to business in this regard. This is not true, however, with respect to the drug trade. In fact, as this chapter will demonstrate, the selection of a valid trade-mark for new drug products is fraught with a number of additional complications which are quite unique to this industry.

It would seem indispensable, therefore, for the purposes of this chapter to discuss not only the more important provisions of the new Federal legislation regarding trade-marks, but to embrace in the discussion a number of collateral legal and practical limitations which cannot be ignored in adopting a trade-mark or new name for drug products. Thus, some mention of the Official Rules of the Council on Pharmacy and Chemistry of the American Medical Association is essential. Similarly, no treatment of drug trade-marks would be complete or even adequate without some reference to the present attitude of the

* The views herein expressed are the author's personal views and do not necessarily reflect the official position of the Patent Office.

Food and Drug Administration in connection with its requirement to refer to "the common or usual name" of the drug on its label.

With such collateral problems clearly in mind, this chapter will be divided into seven separate parts as follows:

I. The protection of drug marks and names at common law in the absence of registration.
II. The registration of drug trade-marks on the principal register of the new Trade-Mark Act of July 5, 1946 which became effective on July 5, 1947.
III. The registration of drug trade-marks on the supplemental register of the same Act.
IV. The conversion of registrations previously recorded under the old Trade-Mark Acts of 1905 and 1920.
V. State registration of drug trade-marks.
VI. Copyrighting of drug labels and advertisements.
VII. The preservation of drug trade-marks and protection against becoming "a common or usual name" or "a common descriptive term."

PROTECTION OF DRUG MARKS AND NAMES AT COMMON LAW

Manufacturers and trade-mark owners in all branches of the drug trade sometimes erroneously assume that the law will not afford them protection against unfair competition unless they avail themselves of the various means of statutory protection which govern the registration of such marks or names. Fear is sometimes expressed that it would be hazardous even to commence business under a certain trade-mark or name unless some form of public recording is first secured. These fears and misapprehensions are, of course, unwarranted. Today, all statutes providing for special protection of trade-marks and trade names are considered but a part of the more general branch of the law which insures effective legal protection against any form of unfair competition, including not only imitation of a competitor's mark or name but such practices as betraying trade secrets,

disparaging a competitor's merchandise, and numerous others as well.

In other words, the goodwill created by a manufacturer or dealer is protected by law against any form of misappropriation or theft by others. No Federal or State legislation is or ever was required in order to enjoin a competitor from passing off his merchandise as that of another, and our courts always have and will continue to grant relief against any palpable and deliberate business fraud, including particularly the adoption of the same or a deceptively similar trade-mark, name, package or other devices. Unfair competition—according to a recent pronouncement by a New York court—"is a species of commercial hitchhiking which the law finds offensive and therefore prohibits."

There are many practices in the drug industry which may thus be enjoined as unfair competition without the invoking of special Federal or State legislation. For example, the repackaging or rebottling of trade-marked merchandise has long been considered an unfair method of competition unless the original manufacturer's consent is obtained or his trade-mark removed or used only with an explanatory statement informing the public of the repackaging or rebottling. Even the benefits and privileges conferred by the various State fair trade laws which are of such paramount interest in the drug field, and which are considered in some detail elsewhere in this book, may be invoked by any drug manufacturer or distributor regardless of whether the particular brand name involved is registered in the United States Patent Office or in one or more of the individual States as a trade-mark. As long as the drug which is sought to be protected by resale price maintenance agreement retains the characteristics of an "identified" product, it automatically comes within the scope of all State fair trade legislation except in Kansas which makes the applicability of its fair trade act contingent upon previous registration of the particular mark involved in the U. S. Patent Office.

In considering the various methods through which additional statutory protection may be gained for trade-marks, trade names

and other forms of "get up," a trade-mark owner should, therefore, be constantly aware of the fact that trade-mark registration and other statutory methods of protection are, in effect, ancillary tools which implement and strengthen the broad legal protection available to all under the established rules against any form of unfair trade practices or unfair competition.

THE NEW FEDERAL TRADE-MARK ACT OF 1946

REGISTRATION OF DRUG TRADE-MARKS ON THE PRINCIPAL REGISTER. While it has thus been shown that drug trade-marks and names partake in the general protection of the law against unfair competition and trade-mark infringement, practically all countries in the world, including the United States, have recognized for at least the past fifty years that it would be to the great interest of trade-mark owners, and the public as well, to have a public record established for the recognition of exclusive rights in trade-marks. The purpose of such register is a two-fold one: On the one hand, it should furnish a guide to the trade and to the public as to what marks or names have been appropriated as trade-marks and are therefore no longer available. On the other, it should give the owner of a registered mark definite legal title thereto which may be proved, if challenged, by reliance on the certificate of registration alone.

These two objectives could not be as fully recognized in the United States as in most other countries because of the fact that the Congress was not granted exclusive legislative authority over the subject of trade-marks; the Constitution of the United States confers such exclusive jurisdiction upon the Federal Government only with regard to patents and copyrights. Federal trade-mark legislation had to be based on that clause of the Constitution which grants power to the Congress to regulate interstate commerce. Consequently, the recently repealed Trade-Mark Act of 1905, as well as the new Trade-Mark Act of 1946, provide for registration of those marks only which are used "in commerce," *i.e.,* in any commerce which is subject to regulation by the Federal Government. In view of the fact that

our courts have given an extremely broad interpretation to the word "commerce," it is entirely safe to state that today by far the greatest part of trade and industry in which trade-marks are used occurs in "commerce" which is within the Federal control. At the same time it must not be forgotten that trade-marks which are purely locally used within one State are outside the control and scope of Federal trade-mark law.

Ever since the Trade-Mark Act of 1905 was enacted there was a growing realization that it failed to provide sufficient incentives to trade-mark owners to register their marks at the United States Patent Office and that in order to create a really reliable record of existing registrations a new act should be enacted which would provide such an incentive and confer substantive rights of considerable importance to those trade-mark owners who secure Federal registration of their marks. The new Trade-Mark Act of 1946 is the culmination of these efforts. It not only affords vastly greater protection to registered trade-marks but also considerably enlarges the scope of registrable marks and improves the methods and procedures for registration.

INCENTIVES TO REGISTER AND BENEFITS OF REGISTRATION. Under the Act of 1905, the following major benefits accrued to the owner of a registered trade-mark, all of which are continued and much enlarged by the new Act:

1. Under the Act of 1905, registration was only "prima facie" evidence of ownership. The certificate never became conclusive evidence of ownership under the old Act. The new law, however, provides that a mark registered on the principal register, which has been in continuous use for five consecutive years subsequent to the date of registration, shall be "incontestable" if an affidavit claiming such incontestability is filed within one year of the expiration of the five-year period. And Section 33(b) provides that if the right to use the registered mark has become incontestable under Section 15, "the certificate shall be conclusive evidence of the registrant's exclusive right to use the registered mark in commerce on or in connection with the goods or services specified in the certificate . . ." It is true that

these sections proceed to state a number of exceptions to the principle of incontestability which need not be discussed in the framework of this chapter. These exceptions do not detract from the great importance of the basic principle of incontestability now for the first time established in the law of the United States. The sponsors of the new legislation confidently expected that this promise of incontestability alone would provide a great incentive to trade-mark owners now to apply for Federal registration even of those marks or names which have not been registered before.

2. Both under the old Act of 1905 and the Act of 1946 a certificate of registration may be deposited with the customs authorities in order to prevent importation of merchandise bearing the same or an infringing trade-mark. These provisions are supplemented by Section 526 of the Tariff Act and are of particular importance to drug manufacturers in their effort to stop counterfeits and infringements of their marks or names at the point of import into the United States rather than at a later time when such infringing articles may already be offered for sale to the consuming public in different parts of the United States. It may be mentioned in passing that under these provisions the owner of the registered trade-mark may also give detailed instructions to the customs authorities as to exactly how many items of each trade-marked article may be imported into this country. In the cosmetic trade, and to some extent in the drug trade, it has become an established practice to issue such minute instructions to the various customs authorities. For instance, the American owner of the trade-mark "Bourjois" for perfume would issue instructions to the various port authorities not to permit importers or returning United States citizens to bring into this country more than, let us say, 20 bottles of a certain designated perfume, even though such person or passenger may be willing to pay duty therefor.

3. Under both the old and the new Acts the owner of a registered trade-mark may bring infringement actions in the Federal courts on the basis of his registration certificate alone and regardless of any other jurisdictional requirements, such as

diversity of citizenship or the involvement of a minimum amount of $3,000.

4. Under both laws, the registrant is entitled to collect "treble damages" and to obtain a court order requiring the destruction of any bottles, labels, etc., bearing the infringing trademark.

5. Under Section 32 of the new Act, infringement actions may be brought not only against a direct infringer but also against a person who is engaged solely in the business of printing the mark for others. The new law contemplates the issuance of injunctions even against newspapers or magazines but limits such injunctions to enjoining the publication of infringing advertising matter in future issues, if the infringement occurred innocently. It is also provided in the new Act that no such injunction shall issue where its effect would be to delay the delivery of the periodical after the regular time.

6. Certificates under both the old and the new Acts will serve as evidence of protection in the United States in case of applications for registration in foreign countries which make registration in the country of origin a prerequisite to registration abroad. A great many foreign countries still have such provisions. Any drug manufacturer engaged in foreign trade would, therefore, be almost compelled to obtain a registration in the United States in order adequately to protect his mark in foreign countries. It should be observed in passing that in numerous foreign countries title to a trade-mark is not acquired by priority of use (as is the case in the United States), but by registration alone, so that it becomes of vital importance to American trademark owners to register their marks in such countries immediately in order to prevent piracy by a resident of the country who may have learned about the American trade-mark before it has been registered abroad.

7. The new law for the first time expressly provides that Federal registration shall be "constructive notice." The effect of this important provision will be to make it impossible for any newcomer to acquire rights in good faith in any part or territory of the United States after the mark or one similar has

been registered for the same or a confusingly like class of products. This benefit of constructive notice is extended even to marks now registered under the Act of 1905 or 1881 so that, at least from the effective date of the new Act, no new rights, however territorially limited, may be acquired in the same mark by newcomers. The practical effect of this provision will be that a drug manufacturer, once he obtains a registration on the principal register, may rest assured that no one else may acquire rights to the same mark in the drug field at a subsequent time even in an area of the United States where the manufacturer may not yet have used the mark himself. It may be noted here that the new Act for the first time provides for so-called "concurrent registrations" in situations where a second user may have used the registered mark in good faith in some part of the United States in which the registered owner had not done business; but concurrent registration will be granted only, according to the express language of section 2(d) of the Act, if such bona fide use antedated the filing date of the registrant's application.

REGISTRABILITY. The Act of 1946 is characterized by a set of much more liberal provisions concerning registrability than was the old Act of 1905. In discussing the types of marks which still do not qualify for registration under either Act, it may be well to distinguish between absolute and relative unregistrability. The following types of marks are absolutely unregistrable under both Acts:

(a) Immoral, deceptive or scandalous marks; the new law adds to this marks "which may disparage or falsely suggest a connection with persons living or dead, institutions, beliefs, or national symbols, or bring them into contempt, or disrepute."

(b) Marks consisting of or comprising the flag or coat of arms or insignia of the United States, or of any State or municipality, or of any foreign nation. The Red Cross symbol is protected by special legislation with an exception only for those users who may have used the Red Cross symbol prior to the year 1905. The White Cross symbol is also protected by a special Act of Congress.

(c) Marks which consist of or comprise "a name, portrait, or signature identifying a particular living individual, except by his written consent, or the name, signature, or portrait of a deceased President of the United States during the life of his widow, if any, except by the written consent of the widow." The old Act of 1905 required written consent only in case of use of a portrait of a living person while the new Act extends the prohibition to the *name* of a particular living individual.

(d) Both the old and the new laws prohibit registration of marks which so resemble a previously used or previously registered mark "as to be likely when applied to the goods of the applicant . . . to deceive purchasers." Under the previous Act, however, this prohibition applied only where the respective goods involved were merchandise "of the same descriptive properties." This test has been abolished by the new law and likelihood of confusion has been made the only applicable yardstick.

All the above-mentioned grounds for rejection are absolute in the sense that no extent of use or popularity can ever transform such marks into valid registrable trade-marks. Under the Act of 1905, there were to be added to this list also marks which consisted merely in words or devices which were descriptive of the goods or the character or quality of such goods, or were merely a geographical name or term or were merely the name of an individual, firm, corporation, or association not distinctively displayed. Such marks were forever barred from registration under the Act of 1905 no matter how famous they may have become after the effective date of that Act. Only where it could be shown that such names or designations had been in exclusive use prior to 1905 were they registrable under the so-called 10-year proviso of the Act. As more fully explained hereafter, such names will be registrable under the new Act as soon as they have acquired "distinctiveness."

(e) To the statutory grounds of absolute unregistrability should be added one other ground which is not expressly mentioned in either the old or the new Act but is of extreme importance to the drug industry: No designation which is the proper or generic name of an article may ever be registered as

a valid trade-mark. This would seem to exclude from registration not only the proper chemical formula of drug trade-marks, such as acetylsalicylic acid, but also those abbreviated generic names which are prescribed by the Council on Pharmacy and Chemistry of the American Medical Association. It cannot be stressed too much that under the Official Rules of the Council, as last revised in 1947, the generic name selected by the Council for the particular drug product is not and never can be a trade-mark. An additional name, such as "LUMINAL, brand of PHENOBARBITAL," should be selected which would then serve as a trade-mark. According to the present Council's rules, the latter no longer objects to the use of such trade-mark in addition to the common or generic name of the article if the use of such "protected name" is not deemed harmful to health and "if the common or generic names are not unduly subordinated to such trade-marks in the labeling and advertising of the products." The present policy of the Council with regard to "protected names," *i.e.*, valid registered trade-marks, is discussed in another chapter of this book. It seems mandatory, therefore, for drug manufacturers to select a trade-mark in addition to the chemical formula and to supplement the common or generic name approved by the Council for the particular product.

The Act of 1946 does not change this situation. On the contrary, it contains an express and absolute prohibition against registration of all generic names. It does, however, reduce some of the other formerly absolute grounds for rejection, such as, particularly, descriptiveness, geographical significance and surname significance, to "relative" rejection grounds in the following important respects: Under the new Act, any mark whose registration is not absolutely prohibited as previously explained may be registered on the principal register if it "has become distinctive of the applicant's goods in commerce." It then provides that proof of substantially exclusive and continuous use of the mark for a five-year period immediately preceding the date of the filing of the application may be considered as prima facie evidence of "distinctiveness."

The effect of this new provision will be that a mark which

originally may have been a surname, or a descriptive term, such as "NU-ENAMEL," or a geographical term, may yet become registrable on the principal register on the ground that over the course of years it may have acquired a "secondary meaning" or, as the new law calls it, "distinctiveness." Under this provision thousands of trade-marks which were held unregistrable under the Act of 1905 may now become registrable on the principal register.

The new Act does not, however, limit itself to reducing the above-mentioned grounds of unregistrability to the status of "relative" rather than "absolute" rejection grounds. It changes in some important respects the applicable test itself in the following ways:

(a) Under the new law, geographical names are objectionable only if they are *primarily merely geographical* as applied to the goods of the applicant.

(b) Surnames likewise are unregistrable only if the mark is *primarily* merely a surname.

(c) In order to be rejected as merely descriptive or deceptively misdescriptive, the mark has to be found to be so "when applied to the goods of the applicant." It should be noted that the new law is somewhat less liberal in connection with descriptive terms than it is in connection with geographical terms or surnames, since a descriptive term is unacceptable even if it is not *primarily* so. The Patent Office and the courts have always recognized a distinction between suggestive terms—which are valid—and descriptive terms—which are not; and that distinction still remains the law. The following marks have, for example, been held invalid as being *descriptive:* "ANTISEPTION" for soaps and other cleansing preparations; "ASEPTIKONS" for vaginal suppositories; "DRY-ICE" for solid carbon dioxide; "MICROBE KILLER" for a medicine; "NERVINE," alone or in combination with "SAMARITAN," for a nerve tonic. The following have been held valid *suggestive* marks: "NO-TO-BAC" for a medicine designed to cure the tobacco habit; "RUSTICIDE" for a chemical preparation to remove rust; "WORMIX" to describe a remedy for hogs and other livestock. In selecting new trade-mark for drugs, abbre-

viations or other names which are merely suggestive may, therefore, be valid trade-marks. But in case of doubt, a manufacturer would be better advised to coin an entirely new name with no descriptive significance at all. In this connection, it may be mentioned that in the United States words which are descriptive in a foreign language have always been held unregistrable and will in all probability remain so under the new law.

(d) Under the absolute prohibition against registration of somebody else's corporate name which was found in the old Act, it was possible for a corporation by merely filing its certification of incorporation, to prevent others from registering the identical name even for entirely different merchandise. This anomaly has been eliminated in the new Act and corporate names enjoy no greater privileges than ordinary trade names or trade-marks.

(e) The new law expressly provides that unregistrable matter which is part of a composite mark may be "disclaimed" but permits re-registration at a subsequent time on the ground that the disclaimed part of the mark may have acquired distinctiveness. As previously indicated, a truly generic name may never acquire such distinctiveness although a descriptive term or a geographical term or a surname may. The old Act of 1905 did not specifically provide for disclaimers, but the practice grew up in the Patent Office and was approved by the United States Supreme Court; however, it was established practice under the old law, contrary to the express provision of the new Act, not to permit registration of a formerly disclaimed part of a mark on the ground that it subsequently acquired trade-mark significance. In permitting such conversion, the new Act marks an important step forward in this connection.

(f) An entirely new concept is found in the new Act in its provision in Section 3 for the registration of so-called "service marks." Under the old Act, a mark adopted by an insurance company or a transportation concern or a cleaning institution was not registrable when it indicated or identified services rather than merchandise. Under the new Act, such marks may be registered as service marks. The definition of service mark

is extremely broad. The term means: "a mark used in the sale or advertising of services to identify the services of one person and distinguish them from the services of others and includes without limitation the marks, names, symbols, titles, designations, slogans, character names, and distinctive features of radio or other advertising used in commerce." When applied to the drug industry, these new provisions would make it possible for a drug manufacturer to select a mark or a symbol for a particular service which he is regularly rendering his customers even if it is not associated with the sale of merchandise. But it should be noted that advertising slogans and the like cannot be registered as service marks for goods and that titles of radio programs, such as, for instance, "INFORMATION PLEASE," are registrable only as service marks in the name of the person or concern who actually owns such program. It is believed that under the new Act hospitals, universities or other educational or non-profit making organizations may register their symbols or emblems as service marks.

(g) Finally, the new law recognizes and defines so-called "collective" marks and "certification" marks. A certification mark is ordinarily a mark used, for instance, by a testing laboratory as applied to certain merchandise tested by it. The Good Housekeeping emblem is usually referred to as a good illustration of such mark. It should be emphasized that the new law does not permit registration of a certification mark in any case where its owner will, in effect, certify his own goods. It also provides for cancellation of certification marks in cases where the owner displays favoritism in the use of the symbol and does not make it available to all those who "maintain the standards or conditions" which the mark certifies. The term "collective mark" as employed in the new Act means "a trade-mark or service mark used by the members of a cooperative, an association or other collective group or organization and includes marks used to indicate membership in a union, an association or other organization."

It is thus clear from the foregoing discussion that the new law opens up a wide variety of new avenues of statutory protec-

tion which were either undeveloped or entirely unknown under the previous law.

OTHER SIGNIFICANT FEATURES OF THE ACT OF 1946. In addition to providing new incentives for registration and liberalizing the provisions regarding registrability, the new Trade-Mark Act of 1946 has modernized our trade-mark law and practice in numerous other respects. Outstanding among such new principles are these:

1. *"Related companies."* For the first time, the statute expressly recognizes legitimate use of trade-marks by subsidiary companies or ordinary licensees provided only the parent company or licensor retains adequate supervision or control over the quality and ingredients of the product. It will now be possible for a drug manufacturer who does not himself use the mark but permits its use by subsidiaries or licensees to register the mark in his own name on the ground that such use will inure to his benefit.

2. *Partial assignment.* For the first time, the new law permits the assignment of a trade-mark with that particular part of the goodwill of the business which is symbolized by the mark. In other words, a drug manufacturer who has been using ten different trade-marks for ten different products may now separately assign each one of these while under the former law, such mark could only be assigned together with the entire business and goodwill. This new provision follows a recent trend all over the world and recognizes modern business exigencies.

3. *Trade-mark "affixation."* Under the old law, the Patent Office and many courts were extremely strict in requiring physical affixation of the trade-mark to the merchandise as a prerequisite for trade-mark protection. The new law recognizes that use of a mark in "displays associated with" the goods may constitute trade-mark use. It should be stressed, however, that use in advertising alone is not considered adequate for this purpose, but use of the mark in window displays in close association with the merchandise will now be considered as a sufficient basis for registration and protection.

4. *False descriptions and designations of origin.* The new Act

also aims at broadening all available statutory protection against unfair competition. In one of its most important sections, it gives a private right of action to any competitor who may deem himself injured by someone else's use of a false designation of origin or description. In other words, a competitor may bring a civil action on its own behalf in such cases instead of bringing it to the attention of the Federal Trade Commission. He may bring such an action regardless of whether he himself has any registered trade-mark.

REGISTRATION OF DRUG TRADE-MARKS ON THE SUPPLEMENTAL REGISTER

American trade-mark owners discovered some thirty or forty years ago that the trade-mark laws of certain foreign countries had much more liberal provisions with regard to the registrability of trade-marks than were found in our own Trade-Mark Act of 1905. Some countries permitted, for instance, the registration of packages or labels as trade-marks but would not be in a position to register these for American trade-mark owners in the absence of the submission of a registration certificate in the United States. In other words, even these more liberal foreign laws did require registration in the country of origin as a prerequisite for registration there. As already indicated, there was no provision in the Act of 1905 for the registration of trade-marks which were originally defective but which had acquired distinctiveness, or as it was called in legal terminology, a "secondary meaning," over the course of years (unless such significance had been acquired through exclusive use 10 years prior to the year 1905). In order to assist American manufacturers in getting foreign protection for such unregistrable marks, a new register was created in 1920 and is continued under the name "supplemental register" by the Act of 1946 which permits registration of the vast majority of marks ineligible for registration on the principal register. Section 23 of the Act of 1946 contains the following definition:

For the purposes of registration on the supplemental register, a mark may consist of any trade-mark, symbol, label, package, configuration of goods, name, word, slogan, phrase, surname, geographical name, numeral, or device or any combination of any of the foregoing, but such mark must be capable of distinguishing the applicant's goods or services.

It should be noted that even under this extremely broad definition the mark must still be "capable of distinguishing the applicant's goods" in order to be registrable. Therefore, the generic name of an article or an ordinary wrapper or bottle would, of course, not qualify for registration even on this hybrid register. Certainly no drug designation which is considered the common or usual name by the Food and Drug Administration or which has been selected as the generic name by the American Medical Association Council on Pharmacy and Chemistry could ever qualify for registration even on this supplemental register.

In the light of the extremely broad coverage of this register and particularly in view of the fact that the primary purpose of its existence is to serve as a basis for foreign rather than domestic protection, it will not be surprising to realize that such registrations do not partake in any of the more important benefits which the new Act of 1946 confers upon trade-marks registered on the principal register. To be specific, registrations on the supplemental register are especially excluded from the following major advantages under the new Act:

1. Such marks will never become "incontestable."

2. They do not have the effect of "constructive notice."

3. Of particular importance to drug manufacturers is that they may not be used to stop importation of drugs bearing an infringing trade-mark through deposit with the various customs authorities.

4. A certificate on the supplemental register is not even prima facie evidence of ownership of the mark.

On the other hand, there are some benefits which even owners of marks registered on the supplemental register may enjoy:

1. They may use the registration notice on their articles (the new Act of 1946 provides that a registrant may either use the full notice, "REGISTERED U. S. PATENT OFFICE," or the new abbreviated form, ®.)

2. If the owner of such registration can satisfy the court that the registered word has actually acquired distinctiveness and secondary meaning in the United States, he may not only enjoin an infringing use but he may also be able to collect "treble damages." Thus, the United States Supreme Court held a few years ago that the word "NU-ENAMEL," by the defendant's own admission, had acquired so wide a secondary meaning that its owner was entitled to all statutory protection which is normally not available to the owner of a mark registered under the Act of 1920 or the supplemental register. Following the reasoning of the Court in that case, the new Act of 1946 provides that registration on the supplemental register shall not preclude subsequent registration on the principal register. This was not true before the new law became effective. It is rather doubtful, however, whether the principle of this provision will be extended to situations involving registrations of configurations of goods, labels, etc., on the supplemental register, since such devices, in order to become registrable on the principal register, must satisfy the definition of a "trademark" in Section 45 of the new Act which includes "any word, name, symbol, or device or any combination thereof." It is unlikely that the word "device" can be stretched so as to include configuration of goods and similar material whose registration is permitted expressly "for the purpose of registration on the supplemental register."

3. The great majority of foreign countries in the past were accepting certificates issued under the Act of 1920 and in all probability will continue to accept certificates on the supplemental register as proof of registration in the country of origin. Under the terms of the International Convention for the Protection of Industrial Property and the Inter-American Convention, both of which have been ratified by the United States, the submission of such a certificate in the country of origin will be

sufficient basis in other Convention countries for the granting of a registration regardless of whether the mark has actually been used by the registrant in the foreign country before the date of the filing of the application. In other words, American drug manufacturers will be able to secure registration of their marks in most foreign countries in the absence of use in such countries and based solely on registration in the United States on the supplemental register. To assist American manufacturers and exporters further in expediting foreign protection, the Act of 1946 provides, contrary to the Act of 1920, that the applicant may obtain a registration even in the absence of the normal prerequisite of one-year's lawful use in commerce prior to the filing of the application, if he can show that he requires the domestic registration only as a basis for foreign registration. The last paragraph of section 23 reads as follows:

> Upon a proper showing by the applicant that he has begun the lawful use of his mark in foreign commerce and that he requires domestic registration as a basis for foreign protection of his mark, the Commissioner may waive the requirement of a full year's use and may grant registration forthwith.

An American drug manufacturer would thus be enabled to obtain speedy registration in this country of a mark which he intends to use only for export purposes or as a basis for foreign protection. The new rules and regulations of the Patent Office embody the same principles in Rule 8.7 and require a separate showing for the waiver of the one-year use requirement. The new rules have also been adapted to the registrability provisions of the Act of 1946 with regard to configuration of goods, wrappers, etc. Thus, it is expressly provided in Rule 9.1 that, for purposes of registration on the supplemental register, the drawing of the mark which must accompany the application "may be the drawing of a package or configuration of goods." With regard to the five specimens of the mark, which must also accompany the application, Rule 10.2 provides that in appropriate cases five copies of a suitable photograph or other suitable reproduction may be submitted in place of actually used specimens.

One more word about renewal of marks on the supplemental register. Under the Act of 1920 registrations were perpetual. The Act of 1946 provides that registrations on the supplemental register shall expire—like marks on the principal register—at the end of twenty years unless properly renewed at that time. It also provides that marks now registered under the Act of 1920 shall expire twenty years from their date of registration, or six months from the effective date of the Act, whichever date is later, and that they may be renewed on the supplemental register only if such renewal is required for the purpose of supporting foreign registrations.

CONVERSIONS OF REGISTRATIONS PREVIOUSLY RECORDED UNDER THE ACTS OF 1905 AND 1920

Special consideration should, of course, be given at the present time by drug trade-mark owners to the problem of what action to take under the recently enacted new Trade-Mark Act with regard to marks which they may have already registered under one of the predecessor statutes. Generally speaking, such trade-mark owners now have a threefold option:

1. Old marks may be republished to obtain the benefits of the new law. This may be done by the mere filing of an affidavit setting forth those goods stated in the original registration on which the mark is in use at the time of the conversion and claiming the benefits of the new Act. Republication does not change the renewal date for the original registration or mark the beginning of a new twenty-year period of protection. But five years after the date of republication, a republished mark may be claimed incontestable by the owner's filing another affidavit asking this benefit. Upon incontestability the mark can no longer be attacked on the ground of a defective title on the registrant's part or on the ground of an original technical defect.

2. By reregistering an existing mark under the Lanham Act, an owner may still retain his registration under the 1905 Act, and there may thus exist side by side two valid registrations.

"Reregistration" differs from "republication" in that the former is based on an entirely new application, treated as an original application, subject to opposition and all formalities and conditions observed for new applications.

Some owners may wish to take advantage of the double protection offered by reregistering marks under the new law and also keeping the old mark alive by timely renewal.

3. A third alternative for owners is to do nothing with marks registered under the 1905 Act until the time for their renewal arrives. While such action deprives the owner of certain benefits under the Lanham Act, it would also protect against certain disadvantages. Thus, under Section 14 of the Act the Federal Trade Commission is given jurisdiction to institute cancellation proceedings at any time for a variety of reasons against an owner of a mark registered on the principal register. Similar jurisdiction was not conferred upon the Commission with regard to any mark registered under the Acts of 1905 and 1881 and not republished or reregistered.

STATE REGISTRATION OF DRUG TRADE-MARKS

In addition to the Federal Trade-Mark Act which now covers all commerce within the control of Congress, such as, for instance, interstate commerce, foreign commerce, commerce with the territories, or within the District of Columbia, there may still be some local uses of drug trade-marks which do not qualify for Federal registration because of strictly local use. While the number of such trade-marks is probably decreasing today with the ever-growing use of nationwide advertising and merchandising, it should still be remembered that practically all the individual States have registration statutes which offer a public record for intrastate trade-mark rights. It should be noted, however, that in none of these States is registration compulsory and a registrant within a State will not prevail over another party who can prove prior use of the same or a similar mark in the same territory. Many years ago, the courts cancelled State registrations of such well-known trade-marks as, for instance,

"COCA-COLA," on the ground that the comman law rights of the trade-mark owner could not be defeated or impaired by a surreptitous registration in the name of another party in one or more of the individual States. To illustrate: Many years ago, a small concern which did business in the State of Illinois succeeded in obtaining state registration for the words "A COCA AND COLA DRINK." The Coca-Cola Company, although it never obtained state registration in Illinois, had little difficulty in obtaining a cancellation of this mark on the ground of its nationwide use of the word "COCA-COLA."

On the other hand, it must be considered that, contrary to our Federal statutes, most of these State registration laws provide for criminal sanctions, although in actual practice these sanctions are rarely invoked. It is true also that in a number of States a mark may be registered on the basis of a statement that the applicant *intends* to use the mark in that State; such a declaration of intention is insufficient as a basis for Federal registration. For these reasons the manufacturer of a new drug product may consider registering the name in a few key States for the purpose of establishing a public record there, but there would appear to be little, if any, reason for the trade-mark owner to obtain forty-eight different State registrations. The new Federal Trade-Mark Act will, it is strongly suggested, reduce to a bare minimum the necessity for State registrations, for which much misleading propaganda is still being made by so-called "state registration specialists." It is significant to note in this regard that one of the avowed purposes of the Act of 1946 is stated to be "to protect registered marks . . . from interference by State or Territorial legislation."

COPYRIGHTING OF DRUG LABELS AND ADVERTISEMENTS

As previously mentioned, the Trade-Mark Act of 1946 expressly provides that a label, package or configuration of goods may be registered on the supplemental register if such label is "capable of distinguishing the applicant's goods or services." It is thus clear that for the first time the law expressly provides

for registration of wrappers, bottles and similar devices even though they may be suspectible of protection under the design patent laws.

Similarly, an entire label used on a drug product or in connection with it, containing a great deal of pictorial material or directions for use, may conceivably qualify for registration on the supplemental register although it would primarily come within the scope of the so-called "Print and Label Law" which expressly provides for copyright protection of commercial labels and advertisements. It would seem rather important for drug manufacturers to keep this last possibility distinctly in mind, since a copyright for an entire label would insure a wider scope of protection than would a mark on the supplemental register. As previously indicated, such registration has very little legal significance for purposes of domestic trade and is primarily intended to secure a foundation for registration abroad.

On the other hand, the copyright protection afforded to a commercial print or label, while seldom tested in court, goes considerably beyond this. What is protected by the copyright is the entire appearance of the advertisement or label. Any simulation of the entire label or a part thereof may constitute plagiarism and therefore infringement of the copyright. Moreover, it is not necessary, in order to prove copyrighted infringement, to prove likelihood of confusion among purchasers; once it is proved that the advertisement or label has been actually simulated or imitated, a cause of action for copyright infringement is established and minimum statutory damage of $250 for each infringement is guaranteed.

Drug manufacturers would do well, therefore, to obtain copyright protection for their labels and advertisements even though they may be able under the new Trade-Mark Act to register separately some of the elements of their advertising as marks on the supplemental register. The Copyright Office furnishes upon request its Form KK for applications covering registration of prints or labels. The statutory fee for such registration is $6, and the certificate remains in effect for 28 years and may then be renewed for another 28-year period. It should be particu-

larly emphasized that, contrary to trade-mark registration, the copyrighted print or label must contain the copyright notice (the word "COPYRIGHT" or the letter "C" enclosed in a circle, ©) at the very time when the print or label is originally published, *i.e.,* put into circulation. If the label should be published without such notice, no valid copyright can be acquired.

PRESERVATION OF DRUG TRADE-MARKS

It is, of course, axiomatic that the task of a trade-mark owner is not completed with the selection and registration of a legally valid and effective trade-mark. At least equally important, particularly in the drug field, is constant vigilance on the owner's part to keep the mark before the public eye without impairing its integrity or validity. It has already been pointed out that the [new] Trade-Mark Act of 1946 is intended to insure a greater degree of security to the owner of registered marks after an initial period of five years' use. The new law provides that after such five year period the owner, by filing an appropriate affidavit as specified in Section 15 of the Act, may acquire an "incontestable" title to his registered mark. Such incontestability, while subject to numerous exceptions not relevant for purposes of the present discussion, guarantees the owner of a registered mark immunity against two major attacks which have been customarily launched against registered trade-marks in the past:

(a) The technical validity of the mark can no longer be challenged by cancellation proceedings on the ground that the mark was originally defective because of descriptiveness, being a surname or similar reasons;

(b) Most important, no third party may attack an incontestable registered mark on the ground that he had used the mark prior to the first date of use by the registrant.

Until July, 1947, a registered trade-mark remained at all times subject to this attack which, if proven, led to invalidation of a registered mark even if such first use may have occurred not on the part of the person raising this defense but on the part

of another party who was a complete stranger to the proceeding. The incontestability provisions of the new law completely change this situation by providing that such prior use will at most be considered as a personal defense available to such prior local user without otherwise impairing the validity of the registrant's mark. It cannot be gainsaid, therefore, that for this reason alone registration on the principal register of the new Act will greatly strengthen the position of the trade-mark owner and that every drug manufacturer, in surveying all available avenues of legal protection for his trade-mark, should bear this privilege of incontestability distinctly in mind at all times.

On the other hand, it cannot be emphasized too much that even under the Act of 1946 drug trade-marks will be found in a uniquely precarious situation in the following extremely important respects: The new Trade-Mark Act provides that no incontestable right shall ever be acquired in a mark or name "which is the common descriptive name of any article or substance, patented or otherwise." Moreover, Section 14 of the Act provides that a registered mark is subject to cancellation at any time—upon application by a third party or, indeed, by the Federal Trade Commission—if it becomes the common descriptive name of an article or substance "on which the patent has expired."

Consequently, the incontestability otherwise available to the owner of a drug trade-mark after five years provides no protection whatsoever against a frontal attack of the mark on the ground that it has been over-popularized and has therefore become generic, or—as the new Act calls it—"a common descriptive term." It has already been mentioned previously in this chapter that under no circumstances should the generic name selected by the Council on Pharmacy and Chemistry be used as a trade-mark but that the drug manufacturer should select an additional arbitrary name and then label the drug "x brand of y." In this way, the public is informed from the very outset that the word "x" is claimed as one particular manufacturer's means of identification and is not used in a generic way. It will then be necessary for the manufacturer carefully to scrutinize

trade papers, magazines, newspapers, dictionaries, and other publications in order to make sure that the trade-mark significance of his registered mark is duly emphasized. The Patent Office has always fully cooperated with the trade-mark owner in this respect. A notice reissued by the Commissioner of Patents on November 18, 1947 with regard to the use of trade-marks in patent applications includes the following significant paragraphs:

> The attention of the Office has been repeatedly called to the use of trade-marks in specifications as common descriptive nouns. Such use is often cause for embarrassment to the party owning the trade-mark.
>
> The relationship between a trade-mark and the product it identifies is sometimes indefinite, uncertain and arbitrary. The formula or characteristics of the product may change from time to time yet continue to be sold under the same trade-mark. In patent specifications, every element or ingredient of the product should be set forth in positive, exact, intelligible language, so that there will be no uncertainty as to what is meant. Arbitrary trade-marks which are liable to mean different things at the pleasure of manufacturers do not constitute such language.
>
> However, if the product to which the trade-mark refers is otherwise set forth in such language that its identity is clear the examiners are authorized to permit the use of the trade-mark if it is distinguished from common nouns, as by capitalization and/or quotation marks.
>
> If the trade-mark has a fixed and definite meaning it constitutes sufficient identification unless some physical or chemical characteristic of the article or material be involved in the invention. In that event as also in those cases where the trade-mark has no fixed and definite meaning, identification by scientific or other explanatory language is necessary.
>
> Where the identification of a trade-mark is introduced by amendment it must be restricted to the characteristics of the product at the time the application was filed to avoid any question of new matter.

On the other hand, the present rules and regulations of the Food and Drug Administration and its established policy appear to reflect a certain attitude of indifference toward the preservation of validly acquired trade-mark rights. No provision of incontestability in the new Trade-Mark Act or careful vigilance

on the part of the trade-mark owner can at present overcome the inherent threat to the continued validity of trade-marks which has resulted from the present official position of the Food and Drug Administration. Briefly speaking, the Administration is inclined to treat registered trade-marks as "common or usual names" for the purposes of the labeling provisions of the Federal Food, Drug, and Cosmetic Act.

Until 1941, the Administration had taken a contrary position and held that a valid registered trade-mark should not be considered the common or usual name of a drug. This attitude was unequivocally expressed in the so-called "Mercurochrome" and "Ichthyol" trade correspondence. The latter letter signed by Mr. W. G. Campbell of the Food and Drug Administration read as follows:

> We have your letter of April 29 in regard to the use of the titles "Ichthyol" and "Ichthammol" for the chemical ammonium ichthosulfonate which is listed in the Sixth Edition of the *National Formulary*. You ask which of these titles is to be regarded as the common or usual name of the drug.
>
> It is our understanding that "Ichthyol" is a trade name which is owned by one manufacturer. While this drug may be more widely known under the name "Ichthyol" we cannot regard a name which is the private property of a single manufacturer and cannot be freely used by all manufacturers as constituting a common name.
>
> The question as to whether the official name "Ichthammol" or the proprietary name "Ichthyol" is to be used for declaring this ingredient will depend entirely upon whether or not the owner of the second of these names will permit its general use in connection with all ammonium ichthosulfonates meeting the *National Formulary* requirements.

Subsequently, however, there was a reversal from this position which is, perhaps, best explained by the author of the Mercurochrome trade correspondence letter himself during the hearings on regulations to implement Sections 502(d) and (e) of the Federal Food, Drug, and Cosmetic Act.

> . . . The proposed regulations [published in the Federal Register of January 30, 1941] declared that the names of certain derivatives which were found to be habit-forming should be listed in the final

regulations by their "common or usual names" and about twenty well-known trade-marks were thus referred to in the proposed regulations as "common or usual names."

* * * *

At the time that I wrote the mercurochrome letter, I based it on the theory that the common name is the name that may be commonly used by any manufacturer of that article. The attitude of the Administration now is that the common name means the name by which people commonly know these articles, and that regardless of the effect they may have on any trade-mark, this law is not intended to adjust trade-mark matters. That belongs to other laws and other divisions or agencies of the government. When under this law, what constitutes the common name has been determined, the question of what the effect may be on the trade-mark is none of this Administration's affair.

In view of this situation, the question of whether the meaning of the term "common or usual name" under the Federal Food, Drug, and Cosmetic Act and the meaning of the language "common descriptive term" under the new Trade-Mark Act are synonymous will become an issue of extreme importance for the drug industry. As a matter of self preservation, it would appear necessary for the industry to take the position, first, that even a reference by the Food and Drug Administration to registered marks as common or usual names does not result in such marks becoming a common descriptive term under the new Trade-Mark Act, and, secondly, that such a finding should not be made unless through some fault on the trade-mark owner's part the registered mark has actually lost all trade-mark significance, examples of which would be "MILK OF MAGNESIA" or to a large extent "ASPIRIN" in this country.

In some instances, drug names of formerly patented articles will probably be dedicated to the public upon expiration of the patent. This was, for instance, true in the case of insulin which may now be manufactured under that name by any manufacturer who meets specific government standards and specifications for the production of that product. But in the normal case of a registered drug trade-mark which has become popular the proper test should still be found in the observation made some

years ago by a New York court in connection with the "PYRAMIDON" trade-mark:

> . . . The fact that a large part of the public may associate a trade-name with a generic name for a product is a tribute to the skill with which the firm has popularized the name. To put a penalty upon such skill and to say that the generalization of the trade-name by the public as a result of the originator's publicity must deprive him of his monopoly in the name would, in the absence of special circumstances, be the height of injustice.

Let it therefore be stressed in conclusion: The best policy for drug manufacturers in selecting a trade-mark would appear to be to choose an arbitrary name to be used in addition to both the established chemical formula and any abbreviated generic name designated by the Council on Pharmacy and Chemistry for the product. If the product is thus marked "X brand of Y" ("Y" being the suggested generic name of the Council), then there would be reasonable assurance that "X" name will be regarded by the public and by the Food and Drug Administration as the manufacturer's individual means of identification and will consequently enjoy all the benefits of a registered trade-mark under the Act of 1946.

12

Drug Regulation

ARTHUR D. HERRICK

FEW will find any exaggeration in the observation that drug products are hedged about with more governmental regulation than perhaps any other types of commodities on the market. This ubiquitous control, in many instances, extends from the very character and nature of the article to its processing, packaging, labeling, advertising, and promotion generally. In few other industries, moreover, is the responsibility of the drug manufacturer or distributor so extensive and exacting. Under several statutes, for example, he is held criminally accountable for acts performed without intent to violate the law or indeed knowledge of wrongdoing and for unauthorized errors in judgment or performance committed by his employees or subordinates.

Despite the trenchant and frequently burdensome character of the regulation imposed on these products, however, one finds it difficult to quarrel with its objectives. The very health of the nation is involved in the production and marketing of honest and safe drugs. Much of the legislation, moreover, is designed to prevent the recurrence of needless tragedies that have marked the industry's history. And the discipline imposed by these statutes, it must be admitted, has had a salutary effect in that it has brought about considerable reform and progress, not only to the ultimate benefit of the American people but to manufacturers and distributors as well.

This comment, however, must be tempered by the observation that drug regulation is, by and large, difficult to grasp and equally formidable to apply in practice. One of the lesser reasons for what may appear unnecessary complexity is that much

of the legislation is a patch-quilt of older statutes, to which, as events required, new provisions have been added. Thus, the habit forming labeling requirement of the Federal Food, Drug, and Cosmetic Act still retains two substances, alpha eucaine and bromal, which have not been employed clinically for over a generation. They were continued in the new enactment, however, because of the possibility that, were they deleted, manufacturers would return to their use to avoid the habit forming legend.

Moreover, the schema of drug regulation as a whole constitutes a complex and intricate lattice, differing widely not only in its subject matter but also in its applicability. Even if we ignore the complications that sometimes flow from overlapping Federal, State, and even municipal statutes, regulations, and ordinances, we are confronted with the fact the laws are not uniform in their objective or operation, a situation apt to contribute a measure of confusion. Some, for example, are primarily concerned with economic fraud and deception, others with hygiene and sanitation, still others with commercial and individual morality. Part of the legislation is directed at what one does or fails to do; part at the product itself, without regard to acts of commission or omission.

Further difficulties are created by the varying construction accorded to the legislation. For instance, those viewed as criminal statutes generally are subject to a strict interpretation; possible violations must be weighed in relation to the "letter of the law." On the other hand, an important segment of the regulation is addressed to the eradication of certain wrongs against the people as a whole. In view of this remedial character—and despite the fact that the statutes may provide for criminal penalties—the courts are inclined to apply their provisions broadly in order to accomplish more readily their general purpose. In such cases, the "spirit" of the law takes precedence over the "letter." The Federal Food, Drug, and Cosmetic Act, for illustration, is generally considered to come within this category, although the courts are not in full agreement on this score. Again, some of the legislation is enforced

at the fact-finding level by administrative tribunals or personnel, necessitating yet another approach to the subject.

But perhaps the main cause of obscurity and confusion in interpreting this legislation is inherent in its nature. As the law of the land, it must, of course, be cast in legal terminology and construed in accordance with accepted legal principles. Yet, in point of fact, it can only be understood and applied on a highly technical plane. For example, the injunction against false and misleading labeling found in the Food, Drug, and Cosmetic Act must necessarily be read, in any particular instance, with a full knowledge of the principles of pharmacology and therapeutics, to name merely two of the sciences that may be appropriate. The same is true as to what constitutes "adequate" directions for use. To the legal mind, consequently, the statutory inhibition or requirement is scarcely intelligible without the medical background. On the other hand, the chemist, pharmacist, or physician who attempts to cope with the subject sooner or later finds himself enmeshed in legal ramifications wholly foreign to his approach and mental processes.

It is interesting to observe that several judges have appreciated the limitations implicit in the situation. One court, for example, admitted:

> It may be regrettable that such issues of fact as these . . . must be submitted to a judicial tribunal, but however regrettable that is, the law does that. In some countries I have been informed in a case of this kind the judge of the court would call to his assistance a lay judge, so-called, learned in the field of science, to aid him in his determining such an issue. That is not our system. A judge trained only in the law, necessarily must have some difficulty in deciding such an issue of fact as . . . this case presents.

As a matter of fact, the Congress, in recognition of the same plight, has not only refrained from fixing enforceable standards in the case of official drugs, instead adopting by reference those formulated by the pharmacopoeial conventions, but has also authorized the Federal Security Administrator to promulgate technical regulations in some instances after administrative hearings on the subject.

Confronted by a problem of this magnitude, we cannot expect, of course, within the scope of this chapter to extend to scientific personnel a full and workable comprehension of legal tenets, nor, on the other hand, implement the lawyer with an understanding of the medical and pharmacologic principles that may be involved in construing any particular provision. If we are able to orient the reader to the extent and applicability of the pertinent legislation, our task will have been accomplished.

THE PATTERN OF DRUG REGULATION

Some of the difficulties of the average manufacturer and distributor, in his attempts to comply with legal requisites, may be attributed to the fact that all too frequently he tries to proceed with but a vague and incomplete knowledge of the statutory origin of these requirements. Although we are apt to think of it in such terms, there is, of course, no such thing as "the law of drugs," except in an abstract collective sense. One who seeks to legitimize a particular product or a particular activity can only do so with full appreciation that all drug regulation stems from one or more acts on the statute books. There can be no expectation of compliance, consequently, unless the manufacturer or distributor has at least a working familiarity with the entire pattern of drug legislation, and knows what portion of it is applicable to the situation.

To assist in understanding the general scope of legislation affecting drugs and their production and marketing, we have divided it into two main categories. In the first group will be found those laws which are relevant in the case of all drugs generally. These, in a sense, may be viewed as the basic regulatory statutes. The second group, on the other hand, may be considered as encompassing laws that are specifically directed either at a particular type of product or merely one phase of their production or their promotion. The details of the latter legislation need have attention only in appropriate instances,

although, of course, they must be borne in mind to prevent their being disregarded inadvertently.

Considered in this light, the first category of drug legislation comprises the following two Federal statutes:

Federal Food, Drug, and Cosmetic Act. This law is undoubtedly the most comprehensive statute dealing with drug regulation; it is, in addition, more intimately concerned with the product itself—its composition, methods of preparation and manufacture, packaging, and labeling—than perhaps any other Federal enactment. Briefly, it deals with:

(*a*) The sanitation of the article.
(*b*) The quality, purity, and strength of the article.
(*c*) The economic cheapening of the article.
(*d*) The claims made on behalf of, and in direct connection with, the article.
(*e*) The information that is required to accompany the article to assure its safe and proper use.
(*f*) The packaging of the article.

This enumeration does not, however, complete an outline of the scope of the statute; this must await our more detailed discussion. We might, however, mention at this time several administrative aspects of this legislation, such as the certification of batches of coal-tar dyes employed to color drugs and the regulation of imports and exports.

Federal Trade Commission Act. Although originally designed to regulate unfair trade practices affecting competition, this legislation has been extended, by a series of broadening amendments, to the marketing generally of drug products, among other articles of commerce. In one sense it is complementary to, and supplements, the Food, Drug, and Cosmetic Act; it should not, however, be considered subordinate to the latter, either in compass or in applicability. It will also be found that the authority of these two statutes frequently overlaps and that both therefore have concurrent jurisdiction over the same acts. A truce to the occasional resulting conflict, formalized in a rule of the Commission, seems to have been

breached by the Food and Drug Administration in recent enforcement action based on advertising material. Lest we be drawn too far afield at this point, we need only summarize the broad objects of the Federal Trade Commission Act as being addressed to:

(*a*) Unfair acts, affecting the general trade in products of a similar character.
(*b*) Fraudulent practices committed in connection with the merchandising of the article.
(*c*) Published and radio advertisements relating to drugs, among other products, that are false or misleading.

As we have observed, the statutes found in the second category of drug legislation are of a more specific nature. Generally speaking, they are concerned with either a particular type of product, such as a disinfectant or a serum, or at a comparatively restricted phase of activity, for example, using the United States mails for a fraudulent purpose. These limitations, however, do not in any way reduce their importance or materiality to the drug manufacturer or distributor; on the contrary, their specialized character often imposes more exacting supervision. To summarize them:

Insulin Amendment. Although enacted as an amendment to the Federal Food, Drug, and Cosmetic Act and enforced within its framework by the Food and Drug Administration, this legislation bears little resemblance to the other provisions of the Act. It deals rather with a system of certification set up to assure the potency of insulin.

Penicillin and Streptomycin Amendments. In these two relatively recent amendments to the Federal Food, Drug, and Cosmetic Act, certification procedures were further extended to these antibiotics. Their parallelism to the Insulin Amendment is, of course, evident; however, they mark a greater advance in this type of regulation than the previous enactment.

Virus, Serum, and Toxin Act of 1944. This legislation—Part F of Title III of Public Law 410 (Public Health Service Act)—superseded, with minor additions, an earlier Virus, Serum,

Toxin, and Antitoxin Act. It provides, as did its predecessor, for a system of licensing establishments producing viruses, serums, toxins, antitoxins, and analogous biologics, or arsphenamine (or its derivatives), or any other trivalent organic arsenic compound, and specifies information required upon the law. It should be noted that it concerns only those products utilized in the treatment of human beings.

Virus, Serum, Toxin, and Analogous Products Act of 1913. Not to be confused with the previous statute described, this law forbids commerce in worthless, contaminated, dangerous or harmful viruses, serums, toxins, and veterinary biologics intended for use in the treatment of domestic animals. It also provides for the licensing of establishments.

Federal Insecticide, Fungicide, and Rodenticide Act. This is a new statute, enacted in 1947, which supplants the Insecticide Act of 1910. Broadly speaking, it may be viewed as an economic poisons law dealing with the adulteration and misbranding of products described in its title. It becomes of considerable importance to the drug industry primarily because it also embraces "fungi . . . and other forms of plant or animal life," including bacteria, except those on or in living man or animal. In a number of instances, therefore, it imposes additional requirements upon the labeling of products also used for drug purposes.

Federal Caustic Poison Act. This Act is designed to safeguard the distribution and sale of stated caustic or corrosive acids, alkalies, and similar products by requiring precautionary labeling. It has, in some cases, been applied to drug products containing the specified chemicals.

Narcotic Laws. A number of opium and narcotic laws are of varying interest to drug manufacturers and distributors. Among these may be listed the Narcotic Act of Congress (1914), the Narcotic Drugs Import and Export Act (1922), the Marihuana Tax Act of 1937, and the Uniform Narcotic Drug Act (1938), regulating the manufacturing, dispensing, selling, and possession of narcotic drugs in the District of Columbia.

Postal Laws. The United States Criminal Code §215 is di-

rected at the use of the mails to execute a scheme or artifice designed to defraud, or for obtaining money or property by means of false or fraudulent representations, pretenses or promises. Authority is also given to the Postmaster General under the postal statute to issue orders forbidding delivery of registered and other mail and payment of money orders to persons or concerns found, upon evidence satisfactory to him, to be using the mails in the conduct of a lottery or to obtain money or property by means of false pretenses, representations, or promises. The Criminal Code §217 also makes it an offense to mail poisons, explosives, inflammable materials, and intoxicating liquors.

This completes our brief summary of the Federal legislation directly affecting the labeling, packaging, adulteration, and marketing generally of drug products and similar articles. Obviously, it is impossible to make it wholly complete. For example, the patent laws at times assume considerable importance in drug development; it has been deemed advisable to treat these subjects (patents and trade-marks) in separate chapters. Similarly, no reference has been made to the law governing the use of alcohol in drugs; here, too, the specialized practice makes any attempt at general discussion unprofitable. The law of imports and exports, moreover, calls for more space than can be readily allotted. Nor have we considered antitrust and pricing legislation. State legislation, however, is described at a later point in this chapter.

In the following sections attention is extended to the provisions of the statutes above described with the object of familiarizing the reader generally with the scope and applicability of each law. But it must be borne in mind that tomes can—and, indeed, have—been written about the different statutes without exhausting the subject entirely. Our review, unfortunately, can only follow the statutory frame of each law, permitting only a superficial understanding of the regulation involved to be grasped in most instances. Indeed, it is not too much to compare the outline of the statute to the skeleton, the flesh being filled in not only by the rules or regulations issued in explana-

tion or supplementation but also by the practices and procedures which have been developed within the regulatory agency in the administration of its provisions. Nor should we lose sight of the fact that the courts, in construing the different provisions of these statutes, have not infrequently extended their application in some cases, and in others, limited it.

THE FEDERAL FOOD, DRUG, AND COSMETIC ACT

In 1938 the Federal Food, Drug, and Cosmetic Act supplanted the Food and Drugs Act which for almost thirty-two years had represented the fundamental regulatory statute of its kind in the United States. The new Act marked almost a revolutionary advance in the control of drugs moving in interstate commerce. Although it retained many of the tested features of the prior legislation, it so broadened governmental regulation over the production, labeling, and marketing generally of articles subject to its terms as virtually to transform industry's conception of its obligations. This becomes apparent by merely comparing the labeling requirements imposed on drugs by both statutes. The Food and Drugs Act, for example, characterized as misbranded only drugs whose labels bore false or misleading statements of identity, quality, and origin, false and fraudulent representations of therapeutic value, and those that were imitations, or were offered for sale under the distinctive name of another article, or contained substituted contents. The sole affirmative label requirement necessitated was a declaration of the quantity of specified narcotic ingredients, and their derivatives. Today's labeling covers several pages of small type.

It is not surprising that a statute carrying so many innovations and calling for such comprehensive revisal of existing practices has raised a host of questions as to its provisions. Some of these, indeed, still remain unanswered with complete finality. Fortunately, the Food and Drug Administration, entrusted with the enforcement of the law, has repeatedly demonstrated not only that it has a clear and farsighted grasp of the

statute's objectives but also its generosity in rendering interpretative assistance to the industry.

Any approach to a concise and elementary analysis of the Act as it affects drugs is made difficult by the very nature of the legislation. For it must be appreciated that the law, in a literal sense, is truly an omnibus statute, or, to be more precise, a series of statutes combined in one, each differing from the other in subject matter and applicability. In one phase it is, for example, a criminal statute, penalizing the individual or firm trafficking interstate in misbranded or adulterated drug products or committing other acts prohibited by its terms. In another sense, it is a policing statute, designed to remove from the channels of interstate commerce by summary means drugs capable of being injurious or causing economic loss. Under somewhat similar circumstances, the Government is authorized to sue to enjoin continued violations of the law. Again, we find in the statute a glossary or lexicon of what acts of commission or omission constitute "adulteration" and "misbranding." The law also enforces the integrity of pharmacopoeial standards and specifications. It provides for various types of certification services and implements their effectiveness. It guards the safety of new drugs. Another section is devoted to the regulation of drug imports and exports. And its provisions set up a comprehensive procedure of administrative law-making where the exigencies of scientific development make such steps advisable.

Of course it may be acknowledged that these various phases of regulation are not disjointed or distinct from one another; on the contrary, there exists a neat and precise interrelation between all which contributes cleverly to the effectiveness of the statute as a whole. Nevertheless, many violators have been disconcerted at the swift change in pace from a seizure proceeding—which may be accepted with a certain degree of complacency—to a criminal information filed against them for the same transgression of the statute. Others have discovered that, while they can rely upon the courteous and helpful assistance of the Food and Drug Administration in their efforts to comply

with the law, violations bring stern and uncompromising police action from the same officials.

Perhaps the best point to begin our discussion of the provisions of the Act is the character of the articles subject to its terms. For it is rather important to bear in mind that the statute is concerned primarily with physical products that fall within its definitions of foods, drugs, devices, and cosmetics. Indeed, all regulatory action revolves about one or more of such tangible objects; thus, a circular, an advertisement, a radio announcement, a formula, cannot bestow jurisdiction upon the Food and Drug Administration unless it is directly concerned with an extant drug, for example. Despite this elementary principle, however, it must be admitted parenthetically that several recent court decisions have tended to overlook the necessity of this nexus; it will take us too far afield to go into the subject of "textual relationship" at this point.

Definitions assume additional materiality, moreover, because of another situation. It will be found that the requirements imposed on foods, drugs, devices, and cosmetics differ considerably. This frequently calls for keen analysis to determine precisely within which group a particular article falls. The question is further complicated by the fact that the definitions are not mutually exclusive; in other words, a product may be both a drug and a food, or a drug and cosmetic. An illustration of the former is a vitamin preparation, of the latter, a sunburn cream claimed to prevent burning. As a general rule, the labeling of such "combination" articles is resolved by treating the preparation as a drug for all practical purposes.

Four types of preparations and substances are viewed as "drugs" under the Federal Food, Drug, and Cosmetic Act. First, all articles recognized in the currently official *United States Pharmacopoeia, National Formulary,* and *Homeopathic Pharmacopoeia* are included in the statutory definition. While the law does not place any restrictions upon this class, note should be made that the compendiums themselves generally limit the substances listed therein to those intended for medicinal use. Thus the mere accident of bearing a name also appearing in

one of the pharmacopoeias does not characterize an article as a "drug" unless it is intended for therapeutic purposes. Whisky and water are examples of such a circumstance. Again, it may be accepted that a preparation designated by an arbitrary title will not be considered an "official" article, even though it is prepared from the identical specifications described in the formulary; its name must be identical or synonymous with the official title if it is to be so designated.

Also deemed to be "drugs" within the purview of the Act are articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals. Here the test is the nature of the claims made for the preparation; the character of the article is of no import. Thus, plain water is considered a drug if its label recommends it for the treatment of any disease. Incidentally, the term "disease" as employed in this definition, appears to have a wider significance than its customary dictionary meaning; it includes injuries resulting from accidents, conditions due to age, and the like. The distinction between "disease" and such functional disturbances as menstrual disorders, for example, is so vague and wavering that it would be difficult to draw a line of demarcation. Any effort to do so, moreover, would probably be wasted since the particular preparation would undoubtedly fall within the next division of the definition of "drug."

What constitutes a representation that a product is "intended for use" for therapeutic purposes is difficult to answer beyond remarking that the Administration considers almost every implication or intimation of this nature as a claim of medicinal value. Thus, the words "healthful" in a tooth powder's labeling and "health" on the label of a jar of honey have been deemed equivalent to such a representation and have classified the articles as drugs. Certainly, the mention of a disease condition by name has this effect, even though it does not appear in the labeling of the article but in an advertisement.

The third type of product coming within the statutory definition are articles intended to affect the structure or any function of the body. It will be noted that this characterizes as a

"drug" a preparation designed to bear on any physiological function—as distinguished from a pathological condition. It brings within the scope of the law such products as obesity treatments and perspiration suppressants. Food, however, is expressly excluded from the purview of the definition.

Finally, all substances intended for use as components of any of the other products defined as drugs are also included in the definition of that term and, in consequence, are subject to the provisions of the statute. This embraces not only bulk pharmaceuticals and crude drugs but also the raw materials that are used to make either the finished drug or such drug components.

Even after almost a decade, there are many in the drug industry who have no clear idea of how the Act is violated or how it is enforced. In broad outline, violations center about a section which sets forth "Prohibited Acts." These proscriptions are twelve in number, ranging from the introduction into interstate commerce of an adulterated or misbranded drug to the representation that a "new drug" application is effective, the breach of which may evoke enforcement measures. For the most part, these prohibitions deal with the interstate traffic in violative products, rather than with the products themselves. This is because the authority of the Congress to regulate this subject-matter is constitutionally restricted to interstate commerce; it could not, save by indirection, control the local or intrastate aspects of the drug business.

Once a breach occurs, the authority of the Government to institute enforcement action may well be compared to a trident. The largest and sharpest prong is, of course, criminal prosecution. The commission of any one of the stated "prohibited acts" constitutes a misdemeanor, penalized on conviction (as a first offender) by imprisonment for not more than one year, or a fine not to exceed $1,000, or both. A subsequent conviction may bring a jail term up to three years, or a fine of not more than $10,000, or both. However, should the first offense be committed with intent to defraud or mislead, the heavier penalties are imposable.

Another barb is known as "seizure." As the remedy indicates, it consists of attaching the violative merchandise and condemning it after civil trial. Condemnation need not, however, be followed by destruction; frequently, the court permits the goods to be brought into compliance with the law. The final enforcement procedure available is another civil action directed at enjoining or restraining violations of the Act. Should the injunction thus obtained in turn be violated, punishment as for contempt of court may ensue.

Of course, these various procedures are surrounded by general provisos—appropriate in all criminal or civil proceedings in the Federal courts—and also by special conditions, peculiar to enforcement practices under this Act. In the latter category, for example, may be mentioned the unusual requirement that a prospective defendant to a criminal prosecution be given an opportunity in advance to justify or otherwise explain his actions and to show why he should not, in this instance, be prosecuted.

It will have been noted that the acts prohibited deal to a considerable extent with "adulterated" and "misbranded" drugs and other products. These states, however, are not left to the whim of a judge or jury for delineation. On the contrary, the law supplies its own glossary of what constitutes adulteration and misbranding. In fact, a large part of the Act is devoted to specifying under what conditions and circumstances the article "shall be deemed to be" adulterated or misbranded. This careful treatment has not infrequently confused and confounded violators who have placed their reliance upon the generally understood significance of the expressions "adulterated" and "misbranded," rather than the sometimes arbitrary statutory "definitions." For example, several have argued that a product cannot be *mis*labeled if it bears *no* label; the contention has met with short shrift.

One who endeavors to simplify discussion of the labeling provisions of the Federal Food, Drug, and Cosmetic Act is confronted with an enormous task. The statute, it must be acknowledged, does not readily lend itself to easy dissection

and explanation; indeed, any attempt to do so may be compared with trying to pick up a handful of water. If we are to be too elementary or laconic in our analysis, moreover, we cannot expect to present any sort of complete or helpful understanding of its terms.

Under the circumstances it will probably best contribute to our task to divide our discussion of these provisions into three broad categories for the purposes of exposition. For example, we can examine the statute from the viewpoint of negative and affirmative labeling requirements. Again a distinction may be drawn between regulations applicable, on the one hand, to official preparations, and, on the other, to so-called nonofficial drugs. Finally, we can compare the different treatment accorded drugs that are safe for lay use and those considered too dangerous for use without medical supervision or advice.

Quite naturally the labeling sections fall into acts that are forbidden and steps that must be taken if compliance is to be had with the terms of the Act. In the former group are broad injunctions against:

(*a*) Labeling that is false or misleading in any particular.
(*b*) Labeling that fails to display information required by the statute in a conspicuous manner and in understandable phraseology.
(*c*) Packaging and labeling, in the case of an official drug, which does not comply with pharmacopoeial specifications.
(*d*) Packaging containers so made, formed, or filled as to be misleading.
(*e*) Drugs that are imitations of other drugs or offered under the name of another drug.
(*f*) Drugs that are dangerous to health when used as recommended.

With the exception of the last prohibition, which will be discussed later, these provisions are broadly directed against various forms of economic fraud in the marketing of drugs and should be interpreted in the light of this objective. Of course,

the most comprehensive interdiction is that relating to false or misleading labeling. That it pervades every aspect of the material employed, directly or indirectly, in promoting the sale of the drug is clear when one remembers that the "labeling" of a drug includes not only its label and package and inserts but also all printed matter that accompanies the product, physically or otherwise, in its journey from the manufacturer to the consumer, and even extends, according to some courts, to advertisements and other forms of communications, such as lectures, whose context relates in some way to the use of the drug.

By employing the expression "false or misleading," the statute submits every particular of the labeling to two tests. Falsity, of course, is determined upon an objective basis; it necessitates truthfulness in every labeling statement. Misleading, on the other hand, is a form of subjective deception, depending upon the mental receptivity of the buyer. It is interesting to observe that a representation may be literally true, yet have the effect of deceiving the one to whom it is addressed. Incidentally, the *intent* to cheat need not be present, nor, indeed, must it be shown that the labeler knew that the statement was false.

A regulation gives lip-service to the proposition that since medical knowledge is constantly in a state of flux the manufacturer should not be penalized for expressions of opinion of therapeutic value, provided he discloses that scientific opinion differs. Thus §2.3 of the general regulations characterizes as misbranding the failure to reveal the existence of a difference of opinion among qualified experts as to the truth of any representation if there is a material weight of opinion contrary to such statement. This would seem to mean that any therapeutic claim can be made in labeling, no matter how slightly supported, when it is accompanied by a declaration that a difference of opinion prevails. In practice, however, the Food and Drug Administration has tended to proceed on the premise that if a particular representation is not itself substantially sustained by scientific evidence, *no* difference of opinion exists, and the qualification accordingly does not preclude a charge of misbranding.

It is evident that the entire purpose of the Act is defeated where the information required by the law is not displayed with sufficient prominence and in such terms as readily to be understood by the customary purchaser of the drug. The mere presence of the essential statement, of course, is no assurance that it will come to the attention of the user. Similarly, obscure phraseology conveys no intelligence to the user; labeling is not intended "to be carefully dissected with dictionary in hand." This is particularly true in the case of labeling written for the public, "who," one court recognized, "are not, as a whole, experts in grammatical construction. Their education in parsing a sentence has either been neglected or forgotten."

The statute therefore insists that mandatory statements be displayed prominently and be so phrased as to convey the requisite information clearly and without ambiguity. It should be observed that falsity or deception are not elements of this type of violation. The general regulations offer detailed constructive comment regarding adequate label display and prominence; in several instances, moreover, they provide for exemptions.

The packaging of the drug, as distinguished from its labeling and composition, may also support a charge of misbranding. The injunction deals with containers that are made in a form that may be misleading, such as glass bottles with overthick sides and bottoms, containers that are shaped in a deceptive fashion, such as indented panels or bottoms, and, finally, slack-filled containers. This provision is not concerned with short-weight; rather it rests on the fact that the purchaser may be misled into assuming from the shape and appearance of the package that it holds more of the product than it actually does. The inhibition, it must be admitted, has more applicability in the case of foods and cosmetics than drugs but should nevertheless be borne in mind in designing the package.

In many instances the official compendia stipulate the manner of packaging and required label statements in their monographs. Failure to follow the directions thus prescribed constitutes misbranding under the Act. It should be noted, however, that

the method of packing may be modified with the consent of the Federal Security Administrator.

The final negative provision discussed under this group relates to imitations and drugs offered under the name of other drugs. For all practical purposes, the prohibition is the same. It should be observed that drug imitations are wholly forbidden, unlike similar foods which may be sold if the imitative nature of their composition is properly disclosed. The "offering" referred to in the statute need not, incidentally, be made in the labeling; indeed, a salesman's representations, an invoice, a letter, an advertisement may all serve as the vehicle. These provisions have also been invoked where material variations were made in the composition of a drug without changing the title.

On the other side of the coin of negative-positive labeling requisites are, of course, affirmative requirements—information that must appear on the labels or in the labeling of specified types of drugs. It should be noted that many of these are essential only in special instances. This group includes the statement of:

(*a*) The name and address of the manufacturer, packer, or distributor of a drug in package form.
(*b*) The quantity of contents in terms of weight, measure, or numerical count for drugs in package form.
(*c*) "WARNING—MAY BE HABIT FORMING" where the drug contains any quantity of specified narcotic or hypnotic substances, and the quantity of such ingredients.
(*d*) Adequate directions for use.
(*e*) Adequate warnings against use under specified conditions which are necessary for the protection of the user.

Other affirmative labeling requirements will be treated in our discussion of official and nonofficial drug preparations.

To determine the precise applicability of the provision calling for the name and address of the manufacturer, packer, or distributor of a drug in package form generally only two questions necessitate study; one, whether the product is in "package form," and, two, what acts characterize a firm as the

manufacturer. This last inquiry gains importance primarily because the manufacturer is allowed to set forth its name without qualification while a packer or distributor must describe its precise relation to the product by a statement such as "PACKED BY," or "DISTRIBUTOR."

As a general rule it may be assumed that drugs packed in any form of container that is capable of being labeled will be considered "in package form." As a matter of fact, almost every item falls within this category with the exception of bulk shipments, such as chemicals transported loose in a freight car or tank cars of liquids. In the case of smaller units in larger containers, for example, 1 cc. ampuls packed 100 to the package or pills in a bottle, whether or not the individual pieces must be labeled with the requisite information depends upon the form in which the product is offered for sale and actually delivered to the ultimate user. If the large package is delivered as one unit, only it need be so labeled; on the other hand, if the package is broken and separate sales made, each unit should bear the required statements.

The firm that completes the manufacturing process may designate itself as the manufacturer. However, a concern that encapsules, compresses tablets, bottles, or otherwise packages the drug can only declare itself as packer. It should be borne in mind that ampuling and subsequent sterilization are viewed as manufacturing. In listing the distributor of the preparation, only one firm need be so designated, even though the drug passes through various distributing channels before it reaches the consumer.

To do justice to the statutory requirement that drugs in package form bear a statement of the quantity of contents would require more space than we have available. Extensive general regulations elaborate upon the subject; they discuss whether the net or gross quantity of the product must be declared; the various measures that may be used; in which instances units of weight and units of volume may be employed and where numerical count may be the mode of expression; and the variations and exemptions that are permitted. After

these formalities are settled, of course, it is equally necessary to see to it that the declaration expresses an accurate statement of the contents. The maintenance of correct weight, volume, or count is a constant problem in drug production and packaging.

Although the Act does not prohibit the marketing of habit forming drugs, it does impose the requirement that the consumer be advised of the possibility of habit formation and of the presence and quantity of such narcotic or hypnotic ingredients in the preparation. This label statement is necessitated in cases where the drug contains alpha eucaine, barbituric acid, beta eucaine, bromal, cannabis, carbromal, chloral, coca, cocaine, codeine, heroin, marihuana, morphine, opium, paraldehyde, peyote, or sulphonmethane, or any derivative of these substances which, by special regulation, have been found to be habit forming. In addition, the quantity or proportion of the ingredient must be declared, and, in the case of a derivative, the name of the substance from which it has been derived.

With the objective of making medication safer and more effective, the statute requires that all drugs be labeled with (*a*) adequate directions for use, and (*b*) adequate warnings against misuse under specified circumstances. These requirements, perhaps more than any others, have proved a source of difficulties for the drug manufacturer. The Food and Drug Administration, moreover, has employed them as weapons against objectionable advertisements and against inert parenteral solutions and to impose a uniform system of "caution statements" upon drug products, some of which, unfortunately, may seem incongruous.

Directions for use are considered adequate only where they set forth correct and appropriate dosage, time and method of administration, frequency of administration, and other pertinent information about the preparation. And except in the case of relatively commonplace drugs the instructions are required to mention the disease condition or conditions for which the article is offered or intended. On this premise, "adequate" directions for use cannot, the Administration believes, be writ-

ten for inert parenteral preparations. Moreover, should a disease be referred to in the drug's advertisements—even though it does not appear in the labeling—the directions may be considered inadequate because they do not encompass all conditions. At a later point, we will discuss under what circumstances directions for use may be omitted from the labeling.

Although adequate warnings are technically limited to cautions against misuse in pathological conditions, by children, and against unsafe dosage or methods of administration, actually another section of the Act considerably expands the necessity of such statements. This provision characterizes as misbranding the failure to reveal any fact that may become material in the light of any representation made regarding the consequences which may result from the use of the article. In the appropriate case, this requires that label claims or directions be qualified by a caution as to any untoward effects.

The responsibility for adequate warnings against misuse rests primarily with the manufacturer or distributor, who is assumed to have canvassed these aspects. However, the Food and Drug Administration has, from time to time, suggested acceptable cautions for different types of drug ingredients or preparations; these have generally been adopted verbatim by the drug industry, at times with wholly unrealistic application. A revision of recommended warnings is now under consideration.

As we have indicated, a further division is made by the Act between the treatment accorded official and nonofficial drug preparations. "Official preparations" are, of course, those substances and drugs recognized in the currently official *United States Pharmacopoeia, National Formulary,* and *Homeopathic Pharmacopoeia of the United States.* The integrity of articles of this character is preserved under the "adulteration" provisions of the statute, and need not have our attention at this time. It is material to note, however, that official drugs are tacitly exempted from compliance with several important labeling requirements; this privilege rests on the assumption that since the official monographs provide all essential specifications and identity, such data are generally available and familiar to

the persons using these drugs. Similar information is, of course, not known about other preparations offered for medicinal purposes. The labels of these products, therefore, are required to disclose:

(*a*) The common or usual name of the preparation, if it has one.
(*b*) Of preparations fabricated from two or more ingredients:
  (1) the common or usual name of each active ingredient;
  (2) the quantity, kind, and proportion of any alcohol contained in the preparation;
  (3) the name and quantity of specified stimulants, depressants, sedatives, and cumulative substances, regardless of activity;
  (4) the quantity or proportion of each active ingredient where the drug is potentially toxic and the directions for use exemption is invoked.

The requirement that the label bear the common or usual name of the drug has the purpose, of course, of identifying it. But it is also directed at the prevention of fraud in that a fanciful or elaborate name cannot be substituted as a facade for a common preparation. The law imposes an alternate direction: that either the *common* or *usual* name be supplied. The former is usually the nontechnical title, the designation in common usage. On the other hand, the usual name may well be a chemical term if that is the way the particular article is ordinarily known to the consumer or the generic title bestowed by the Council on Pharmacy and Chemistry.

There are several notable aspects to this labeling mandate. First, if no such name exists, it need not, of course, be declared. This is true, for example, of novel or unusual compositions. However, most drugs have some identification, if not in identity of components, then in use or purpose, such as "LAXATIVE," or in condition for which offered, as "COUGH DROPS," or in therapeutic action, like "ANTHELMINTIC." Again, a private brand or

trade name cannot be considered either common or usual; it may, indeed, only supplement the regular title.

There is no need, in a brief discussion of this nature, to review what is meant by the statutory language "fabricated from two or more ingredients." It is appropriate, however, to consider under what circumstances an ingredient is "active." Broadly speaking, such an ingredient may be defined as any substance which effects, or assists in effecting, the purpose for which the preparation is offered or intended. The Food and Drug Administration, in this connection, has commented that "any particular ingredient which a manufacturer introduces into his preparation is obviously introduced for some purpose." If that purpose is its therapeutic or physiological activity—as against its use as a vehicle, flavoring, coloring, emulsifier, excipient, lubricant, preservative, solvent, or the like—it must be declared.

Care must be taken to state the active ingredient by its common or usual name and also to so list the ingredients as to avoid misleading implications. It may also be observed that the declaration of the complete formula does not serve as compliance with this provision, unless inert and active ingredients are separately designated.

In declaring the alcohol content of the drug, several important aspects must have attention. The statement "ALCOHOL" may only be used to describe ethyl alcohol; all others must be expressed by their common or usual name. In expressing percentage, moreover, the manufacturer is required to do so in terms of absolute alcohol at 60°F., and with substantial correctness.

Should the nonofficial preparation contain any quantity of bromides, ether, chloroform, acetanilid, acetophenetidin, amidopyrine, antipyrine, atropine, hyoscine, hyoscyamine, arsenic, digitalis, digitalis glycosides, mercury, ouabain, strophanthin, strychnine, or thyroid—or any derivative or preparation of these substances—it is necessary to declare not only the name but, in addition, the quantity or proportion of the drug. Fur-

thermore, if a derivative or preparation is utilized, the fact of derivation must be disclosed, unless it is self-evident.

As we have suggested above, the labeling sections of the Act may be distinguished in the manner in which they treat drugs that are safe for use and application and those that are considered too dangerous for use without medical supervision. Two statutory provisions have been utilized to channelize this type of regulation into the present way in which it is handled. One of these is the authority extended to the Federal Security Administrator to exempt drug labeling from bearing adequate directions for use when this "is not necessary for the protection of public health." The other section bans, as mislabeled, drugs that are dangerous to health when used in the dosage, or with the frequency or duration prescribed, recommended, or suggested in their labeling.

The Administration has interpreted this last provision, not as a blanket prohibition of the marketing of all dangerous drugs of this nature, but rather as a means of dividing preparations into two different categories: (*a*) those that are considered proper for use by the public for purposes of self medication, and (*b*) those that are deemed unsafe for indiscriminate or unsupervised use by the laity. However, the last class is, it is to be noted, accepted, with rare exceptions, as not being "dangerous to health" when the label limits the drug to use by or under the supervision of a physician, dentist, or veterinarian.

Of course it was recognized that, if the labeling of such dangerous preparations bore statements indicating the conditions for which they may be employed together with directions for such use, toxic drugs falling into the hands of the public might be self-administered, with the consequence that the "prescription legend" would afford little, if any, substantial protection. On the other hand, a label that is silent as to conditions and directions, it was felt, discourages unauthorized use.

Evidently with this thought in mind, the Administrator has issued comprehensive regulations exempting from the requirement that their labeling carry adequate directions for use all drugs that are potentially harmful by reason of their inherent

toxicity or method of administration. To come within the scope of the exemption, these products are required not only to bear the "prescription legend," limiting their dispensing to medical prescription but they must also be so dispensed in fact, used in prescriptions, or employed for manufacturing purposes. In addition, information adequate for their use by the medical professions must be readily available, and no representation with respect to the conditions of use are to appear in their labeling. Furthermore, as we have remarked, nonofficial drugs of this character must bear a label statement of the quantity or proportion of each active ingredient. Other types of preparations and substances that are entitled to take advantage of the regulatory exemption are:

(*a*) official drugs, in crude or powdered form, sold for exclusive use in compounding prescriptions or for manufacturing purposes;
(*b*) inactive ingredients of other drugs, such as coloring matter, emulsifiers, excipients, flavorings, lubricants, preservatives, and solvents;
(*c*) drugs sold directly to members of the medical professions to be dispensed by them in the course of their professional practice; and
(*d*) drugs sold to a dealer or manufacturer to be used in the production of another drug.

It is to be observed, however, that these last exemptions are not dependent upon the drug being toxic. Moreover, a drug intended for administration by iontophoresis or parenterally, among others, cannot under any circumstances elect to omit adequate directions for use.

The scheme of restrictive labeling thus contemplated raises one important question. May the manufacturer of a dangerous drug limit the preparation to use by or under the direction of a physician and at the same time set forth complete directions for use, addressed to the doctor, in the labeling? Any exemption, particularly one conditioned upon several factors, would seem to be offered for the optional utilization of the labeler;

should he decide *not* to take advantage of the invitation, may he be penalized as violating the statute? The problem still awaits final answer.

The general picture of labeling requirements thus presented does not, however, exhaust this subject. Not only must further reference be made to the explanatory general and special regulations, but it should be observed that the glossary of "adulteration," contained in the Act, also bears materially upon the label statements made. Indeed, it has been suggested that the adulteration provisions relating to standards might well have been included within the labeling sections. The truth of this remark will become evident as we discuss the adulteration of a drug under the Food, Drug, and Cosmetic Act.

Broadly speaking, adulteration falls within two categories: one concerned with the safe and sanitary production and packaging of the drug, the other with the maintenance of standards of purity, quality, and strength. The first group need have our attention merely in outline; it defines as adulterated a drug that:

(*a*) consists in whole or part of any filthy, putrid, or decomposed substance;
(*b*) has been prepared, packed, or held under insanitary conditions with the result that it may have become contaminated with filth or rendered injurious to health;
(*c*) is packed in a container composed, in whole or in part, of any poisonous or deleterious substance which may render the contents injurious to health;
(*d*) bears or contains, for purposes of coloring only, a color other than one from a batch that has been certified in accordance with the coal-tar color regulation.

We have had occasion to describe what the Act views as an "official" drug. The designation "official" is, in a sense, a misnomer. The specifications of the drugs described are established and promulgated, in point of fact, by private organizations, of a non-profit, public character, such as the United States Pharmacopoeial Convention and the American Pharmaceutical

Association. Although it may at first glance appear that the Congress has recognized these standards and provided a means of enforcing them, of course, what the Government actually does is to penalize deviations when the manufacturer has, by assumption of the official name, impliedly represented that his product conforms to the pharmacopoeial monographs.

Thus, the Act provides that a drug is deemed to be adulterated if it purports to be or is represented as being the "official" preparation and its strength differs from, or its quality or purity falls below, the standard set forth in the compendium. However, where the label plainly states how and to what extent it differs from these standards, variations in strength, quality, or purity to the stated extent are permissible. This distinction is usually made by declaring "NOT U.S.P." or "NOT N.F." and the deviation; however, it is not, for example, sufficient to qualify the title merely by the term "SPECIAL."

Nonofficial drugs may also be considered adulterated if they fail to meet the strength, purity, or quality that they purport or are represented to possess. For example, an ampul "purports" by its nature to be sterile; if it lacks such sterility, it is adulterated under this provision. Similarly, when express representations are made of a drug's potency, variations—whether they be more or less than that claimed—constitute adulteration. The representation need not, of course, be made in the labeling; it may, for example, be found in the invoice of the shipment.

Also viewed as adulteration in drugs is the cheapening of the product (*a*) by mixing or packing another substance with it to reduce its quality or strength, such as excessive quantities of foreign material in crude drugs, or (*b*) by substituting another substance in whole or in part of the article. An illustration of this fraud is shipping *Ipecacuanha filbrose,* which lacks the active principle of true ipecac (*Cephaelis ipecacuanha*), in place of the latter.

This relatively short survey must suffice for our review of the pertinent provisions of the Federal Food, Drug, and Cosmetic Act. Obviously, we have only been able to skim over the full

story of its impact on the production, labeling, packaging, and distribution of drug products moving in interstate commerce. Many other important aspects have necessarily been omitted. The reader is referred to other chapters in this volume which discuss labels and labeling, "new drugs," and the certification of coal-tar colors, insulin, and antibiotics, among other phases of the regulation, and to the bibliography, which lists a number of more complete references.

FEDERAL TRADE COMMISSION ACT

The second major piece of legislation dealing with the promotion and marketing of drugs in interstate commerce is the Federal Trade Commission Act. This statute differs in concept and procedurally from the Food, Drug, and Cosmetic Act in that it sets up an independent agency, the Federal Trade Commission, to enforce the laws entrusted to it for administration. The Commission is composed of five Commissioners appointed by the President and confirmed by the Senate. In addition to his general duties, each Commissioner is assigned to supervisory charge of the work of one or more of the several offices, divisions, and internal organizations into which the Commission is divided. A staff of over 600 officials and employees, including attorneys, economists, accountants, and administrative personnel, carry out the functions of the Commission.

The omnipresence of the Commission in all phases of a violation of the Act calls for an explanation. Surprise has occasionally been expressed that the Commission, and its personnel, appear to act in the capacity of investigator, complainant, prosecuting attorney, trial court, and judge in the conduct of "cease and desist" proceedings. Although the practice seems incongruous to those accustomed to the rigid impartiality and separability pervading civil and criminal court cases, nevertheless it is now a more or less familiar feature of administrative law, where it is not unusual for one agency to be entrusted with the investigation, trial, and adjudication of matters within its special jurisdiction. A sharp delineation of duties amongst person-

nel, a keen sense of propriety and fairness, and the availability of an appeal to the courts all serve as assurance that substantial justice will be done.

The Commission was originally organized under the Federal Trade Commission Act, enacted in 1914 to effectuate the intent of the Congress to create an independent agency which would assist in the successful operation and perpetuation of free enterprise and the competitive system of economy by preventing and correcting unfair commercial methods of competition. In 1938, the Wheeler-Lea amendment to the statute broadened the Act by extending the authority of the Commission to the prevention of unfair and deceptive acts in commerce (without regard to their effect on competition), thus extending the same protection to the public at large that the original legislation accorded to competitors in industry.

The same amendment also made specific provision for the prevention of the dissemination of false advertisements of food, drugs, devices, and cosmetics. As one step in this direction, it characterized as an "unfair act or practice in commerce" the circulation of an advertisement about such a product which is misleading in a material respect, thus enabling the Commission to proceed against advertisers by way of complaint and order to cease and desist. In addition, the Commission is authorized to bring suit in the Federal courts to enjoin the publication of false advertisements, whenever it has reason to believe that the proceeding would be in the public interest. A temporary injunction of this nature remains in effect until cease and desist proceedings are finally resolved.

The law further provides that the dissemination of a false advertisement of a food, drug, device, or cosmetic, where the use of the article advertised may be injurious to health or where the advertisement is published with intent to defraud or mislead, constitutes a misdemeanor. Conviction subjects the offender to a fine of not more than $5,000, or imprisonment of not more than six months, or both. Succeeding convictions may result in a fine of as much as $10,000, imprisonment up to one year, or both fine and imprisonment.

Under the circumstances, it is material to examine just what the Act views as a "false advertisement," This is statutorily defined as an advertisement, other than labeling, which is misleading in a material respect. In determining the deceptive aspects of such a publication, there is to be taken into account not only representations made or suggested, but also the extent to which material facts are omitted where these bear upon consequences that may result from the use of the article. An important qualification of the definition for drug manufacturers is the condition that no drug advertisement is to be considered false if it is addressed only to members of the medical profession, contains no false representation of a material fact, and includes, or is accompanied in each instance by truthful disclosure of, the formula quantitatively disclosing each ingredient of the preparation.

A case before the Federal Trade Commission may originate in any one of several ways. For example, a consumer or a competitor may complain of some practice, by letter setting forth the facts in detail accompanied by all evidence in the possession of the complaining party in support of the charges made. Another source of complaints are Federal, State, or municipal agencies. Of course, the Commission itself may initiate an investigation to determine whether the laws administered by it are being violated.

In this last connection, the Commission maintains a Radio and Periodical Division to conduct expeditious investigations of cases involving false or misleading advertising violative of the Act. The survey includes magazines and newspapers, radio commercial continuities, mail-order catalogues, almanacs, and foreign-language publications. Questioned advertisements noted in these studies not only form the basis of prospective cases not previously investigated but also provide a means of verifying whether advertisers are complying with orders and stipulations to discontinue false and misleading representations. About three out of every five advertisements thus reviewed concerns a drug product. Incidentally, in matters involving advertising, the investigations embrace the practices of advertis-

ing agencies who may have participated in preparing the advertisements to determine whether they should be joined as parties in any corrective action by the Commission.

Upon receipt of an application for complaint, the Commission first considers the essential jurisdictional elements before deciding whether it shall be docketed for investigation. The matter may then be assigned to an attorney for the purpose of developing all the material facts. Where the case calls for field investigation, the general procedure is to interview the party complained against, advise him of the charges and request such information as he may care to furnish in defense or in justification. If the facts warrant, competitors of the prospective respondent may in addition be interviewed to determine the effect of the practice from a competitive standpoint. Often, moreover, it is desirable to talk to consumers and members of the general public to obtain their assistance in ascertaining whether the alleged practice constitutes an unfair method of competition or unfair or deceptive act or practice, and also to establish the existence of the requisite public interest.

After developing all relevant facts, the examining attorney summarizes the evidence in a report, reviews the law applicable, and recommends the action he believes the Commission should take. The record is reviewed by the Chief Examiner or the Chief of the Radio and Periodical Division, and is then submitted, with a statement of facts as well as his conclusions and recommendations, to the Commission for its consideration. Thus, the heads of these divisions may recommend that:

(*a*) the case be closed without further action because of lack of evidence or because the practice does not violate any law administered by the Commission;
(*b*) the case be disposed of by having the respondent sign a stipulation as to the facts, and an agreement to cease and desist from practices set forth therein;
(*c*) a formal complaint be issued.

It should be borne in mind that the settlement of a case by stipulation will generally only be recommended in those in-

stances where the law has been violated unintentionally, through misunderstanding or carelessness. The privilege will not be allowed where the violation involves an affirmative intent to defraud or mislead, or where the drug thus advertised is one inherently dangerous or capable of probable injury. Nor will it be considered where the Commission is inclined to feel that the procedure will not be effective in preventing continuation of the objectionable practices. In short, it is the Commission's policy to extend the offer of a stipulation only where the interest of the public will be served and protected by this action.

Where the matter is considered appropriate for settlement by stipulation, the proposed respondent is served with a statement of the allegedly illegal practices. The respondent may reply by correspondence or he may confer with the Director of the Division of Stipulations, or with a designated attorney-conferee, either in person or through a representative. The conference is, in a sense, an informal hearing. After a frank and thorough discussion of the issues involved, amicable settlements are usually reached whereby previous errors are corrected, matters without public interest eliminated, and stipulations disposing of the case are thereupon drafted, signed, and presented to the Commission for its consideration in settlement of charges that are considered to have been substantially proved. The recommendation to the Commission, if the facts warrant, may include a closing of the case in whole or in part.

Where the Commission decides to issue a formal complaint, the procedure follows the provisions of the Rules of Practice governing adversary proceedings. Issued in the name of the Commission acting for the public interest, the complaint names the respondent or respondents, alleges a violation of law, and contains a statement of the charges. A respondent desirous of contesting the proceedings must within twenty days from the service of the complaint file his answer admitting or denying each allegation. He is given the alternative, however, upon request timely made, to ask for an opportunity to submit for consideration offers of settlement or proposals of adjustment

where time, the nature of the proceedings, and the public interest permits.

Evidence is usually taken both in contested cases and in those where the respondent has failed to file an answer. The matter is set down for hearing before a trial examiner. Hearings of this nature may be held anywhere in the United States. Frequently, in contested procedings, the testimony is voluminous, many hearings being held and a host of witnesses heard. The Commission's complaint is supported by one of its trial attorneys, the respondent having the privilege of appearing in his own behalf or by attorney. Although counsel supporting the complaint has the general burden, the proponent of any factual proposition is required to sustain the burden of its proof.

After all evidence in support of the complaint and on behalf of the respondent has been submitted, the trial examiner prepares and files as recommended decision which includes a statement of (*a*) findings and conclusions, as well as the reasons or basis for each, upon all the material issues of fact, law, or discretion presented on the record; and (*b*) an appropriate order. Either counsel may take exceptions to the trial examiner's recommendation.

Briefs may be filed within a stated time after the trial examiner's recommended decision is made. Various questions may be presented to the Commission for consideration and decision on final hearing. In the discretion of the Commission, it may permit oral argument before it on request of either side. The Commission studies the record and briefs; should it decide that the complaint is sustained by the evidence, it makes its findings as to the facts and states its conclusion that the law has been violated. Thereupon an order is issued requiring the respondent to cease and desist from such violation.

An order to cease and desist becomes final sixty days after date of service upon the respondent, unless within that period he petitions an appropriate U. S. Circuit Court of Appeals to review the order. The appellate court has power to affirm, to affirm after modification, or to set aside the order. Either party

may apply to the Supreme Court of the United States for review, by certiorari, of the action of the circuit court.

Violation of an order to cease and desist, after it has become final, subjects the offender to a civil penalty of not more than $5,000 for each violation, recoverable by the United States. These proceedings are brought in the Federal courts by the United States attorney.

We have presented this brief outline of the practice and proceedings under the Federal Trade Commission Act because of the singular and often unfamiliar character of administrative adjudication. As may be observed, it differs radically from ordinary litigation as conducted in courts of law. As an instrument of preventing and correcting unfair and deceptive acts and practices, however, it is perhaps better adapted to its objective than accustomed procedure, although this observation is a debatable one. Thus, the Food, Drug, and Cosmetic Act, which relies for implementation upon recognized civil and criminal enforcement means, has not, it may be remarked, suffered in accomplishments as a result.

The Act enjoins as unlawful "unfair methods of competition in commerce, and unfair or deceptive acts or practices in commerce." This phrase is not defined in the statute. Nor have the courts extended any clearer significance to the terminology. For example, the Supreme Court has classified as "unfair methods of competition" any practices "opposed to good morals because characterized by deception, bad faith, fraud, or oppression, or as against public policy because of their dangerous tendency unduly to hinder competition or create monopoly." Consequently, the only way to judge what commercial methods the Commission views as unlawful is to review typical acts and practices it has condemned from time to time in its orders to cease and desist. The following list, paraphrasing the 1946–47 *Annual Report of the Federal Trade Commission,* illustrates the type of cases in which it has acted:

False or misleading advertising and labeling. These embrace misstatements regarding drug ingredients, quality, purity, origin, source, attributes, or properties, or nature of manufacture;

their sale under deceptive names and circumstances, such as misrepresentations of therapeutic and corrective properties; the false representation, expressly or by failure to disclose their potential harmfulness, that such preparations may be safely used; the description of various symptoms falsely indicative of diseases and abnormal conditions which the product advertised will cure or alleviate.

Commercial practices. These include bribing buyers or other employees of customers and prospective customers to obtain or hold patronage; procuring competitors' business or trade secrets by espionage or bribery; inducing competitors' employees to violate their contracts and enticing them away in such numbers or under such circumstances as to hamper or embarrass the competitors in the conduct of their business; making false and disparaging statements respecting competitors' products and business, for example, through purported scientific, but in fact misleading, demonstrations or tests; making widespread threats in bad faith to the trade of suits for patent infringement, arising from the sale by competitors of alleged infringing products, to intimidate the trade and hinder or stifle competition, and claiming, without justification, exclusive rights in public names of unpatented products; conspiring to maintain uniform selling prices, terms and conditions of sale through the use of a patent-licensing system; passing off goods for products of competitors through appropriation or simulation of trade names, labels, dress of goods, or counter-displays; buying up supplies for the purpose of hampering competitors and stifling or eliminating competition; using concealed subsidiaries, ostensibly independent, to obtain competitive business otherwise unavailable, and selling below cost or giving products without charge, with intent and effect of hindering or suppressing competition.

Unlawful combinations. These may be summarized as the formulation of combinations of, or agreements between, competitors to fix, enhance, or depress prices, maintain prices, bring about substantial uniformity in prices, or divide territory or business, to cut off or interfere with competitors' sources of supply or to close markets to competitors; or use by trade asso-

ciations of so-called standard cost systems, price lists, or guides, or exchange of trade information calculated to bring about these ends or otherwise restrain or hinder free competition; intimidation or coercion to cause producers or distributors to organize, join, or contribute to, or to prevent them from organizing, joining, or contributing to, producers' cooperative associations or other associations; coerced and forced uneconomic and monopolistic reciprocal dealing.

"Special" false offers. This relates to methods employed to create the impression that the customer is being offered an opportunity to make purchases under unusually favorable conditions when such is not the case, such sales plans in which the seller's usual price is falsely represented as a special reduced price for a limited time or to a limited class, or false claims are made of special terms, equipment, or other privileges or advantages; the use of "free goods" or services to create the impression that something is actually being thrown in without charge, when it is fully covered by the amount exacted in the transaction as a whole, or by services to be rendered by the recipient; the use of misleading trade names calculated to create the impression that a dealer is a producer or importer selling directly to the consumer, with resultant savings; the offering of false "bargains" by pretended reduction of a fictitous "regular" price; false representations that goods are not being offered as sales in ordinary course, but are specially priced and offered as a part of a special advertising campaign to obtain customers, or for some purpose other than the customary profit.

Misleading containers. Considered an unfair practice is the use of containers ostensibly of the capacity customarily associated by the purchasing public with standard weights or quantities of the particular product, or using standard containers only partially filled to capacity, so as to make it appear to the purchaser that he is receiving the standard weight or quantity.

Misleading or false statements of standing or status. This relates to misrepresentations in various ways of the necessity or desirability or the advantages to the prospective customer of dealing with the seller, such as the false claim of being an

importer, technician, diagnostician, or manufacturer, or a wholesaler, selling to the consumer at wholesale prices; or, by a manufacturer, of being also the manufacturer of the raw material entering into the product, or, by an assembler, of being a manufacturer; the false representation that the seller owns a laboratory in which the product offered is analyzed and tested; the false or misleading claim of patent, trade-mark, or other special and exclusive rights; and the grant of seals of approval by a magazine to products advertised therein, misrepresenting that they have been adequately tested.

False promises. This embraces obtaining business through undertakings not carried out and not intended to be carried out, and through deceptive, dishonest, and oppressive devices calculated to entrap and coerce the customer or prospective customer, including misrepresenting that the seller fills orders promptly, ships kind of merchandise described, and assigns exclusive territorial rights within definite trade areas to purchasers or prospective purchasers; obtaining orders on the basis of samples displayed for customer's selection and failing or refusing to respect such selection thereafter in filling of orders; promising results impossible of fulfillment; falsely holding out guaranties, or the right of return, results, refunds, or replacements; and failing and refusing to deal justly and fairly with customers in consummating transactions undertaken through such practices as refusing to correct mistakes in filling orders or to make promised adjustments or refunds, and retaining, without refund, goods returned for exchange or adjustment, and enforcing, notwithstanding agents' alterations, printed terms of purchase contracts, and exacting payments in excess of customers' commitments.

Misleading names. This refers to giving products misleading names so as to extend to them a value which they would not otherwise possess, and includes the use of names that imply falsely that the products were made for the Government or in accordance with its specifications and of corresponding quality, or that the advertiser is connected with the Government in some way, or that the products have been passed upon, in-

spected, underwritten, or endorsed by it; that they are composed in whole or in part of ingredients or materials which in fact are present only to negligible extent or not at all; that they were made in, or came from, some locality famous for the quality of such products, or are of national reputation; that they were made by some well and favorably known process; that they have been inspected, passed, or approved after meeting the tests of some official organization charged with the duty of making such tests expertly and disinterestedly, or giving such approval; that they were made under conditions or circumstances considered of importance by a substantial part of the general purchasing public; that they have the usual characteristics or value of a product properly so designated, as through use of a common generic name to designate a product lacking necessary ingredients; that they are of greater value, durability, and desirability than is the fact, or that they are designed, sponsored, produced, or approved by the medical profession, health and welfare associations, hospitals, celebrities, educational institutions and authorities, such as the use of the letters "M.D." and the words "RED CROSS" and its insignia.

Foreign trading. This includes dealing unfairly and dishonestly with foreign purchasers and thereby discrediting American exporters generally; and entering into contracts in restraint of trade whereby foreign corporations agree not to export certain products to the United States in consideration of a domestic company's agreement not to export the same commodity, or to sell to anyone other than those who agree not to so export same.

In concluding our discussion of the activities of the Federal Trade Commission, it may be observed that in addition to its activities described above the Commission administers:

(1) Section 2 of the Clayton Act, as amended by the Robinson-Patman Act, prohibiting price and other discriminations, and Sections 3, 7, and 8 of the same statute, dealing with tying and exclusive-dealing contracts, acquisitions of capital stock, and interlocking directorates, respectively.

(2) The Export Trade Act, also known as the Webb-Pomerene Law, which permits the organization of associations to engage exclusively in export under stated restrictions.
(3) Those sections of the Lanham Trade-Mark Act which delegate to the Commission certain duties with respect to the cancellation of trade-marks registered with the Patent Office.
(4) The Wool Products Labeling Act of 1939.

Furthermore, the Commission undertakes general investigations for public information and use; of interest to the drug industry, for example, is its report to the Congress, *Resale Price Maintenance,* December 13, 1945. Nor should mention be omitted of its formulation and promulgation of trade practice rules. Rules defining and cataloguing unfair trade practices have been established for over 150 industries.

VIRUS, SERUM, AND TOXIN ACT OF 1944

Also known as the Biological Products Law, this Act supplanted the original Virus, Serum, and Toxin Act, enacted in 1902. As a matter of fact, the present law only slightly changes the old. In brief summary: control is expressly extended to arsphenamines and other trivalent organic arsenic compounds; another section furnishes criteria to guide administrative action in the issuance of licenses; an explicit statement confirms that products subject to this law are not exempted from the Federal Food, Drug, and Cosmetic Act, except for the provision relating to "new drugs"; and, to complete this statement of the modifications, the Public Health Service, under certain circumstances, is authorized to prepare biological products.

The statute should not be confused with the Virus, Serum, Toxin, and Analogous Product Act, which concerns itself with veterinary biologicals. It relates to any virus, therapeutic serum, toxin, antitoxin, or analogous product, or arsphenamine or its derivatives (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of diseases or

injuries of *man,* forbidding interstate traffic in these products unless:

(*a*) The biologic has been propagated or manufactured and prepared at an establishment holding a valid license to produce or transport it; and

(*b*) Each package of such a biologic is plainly marked with the proper name of the article it contains, the name, address, and license number of the manufacturer, and the date beyond which the contents cannot unquestionably be expected to yield their specific results.

Licenses for the maintenance of establishments for the propagation or manufacture and preparation of biologicals are issued only upon a showing that the plant and product meet prescribed standards, designed to insure the continued safety, purity, and potency of such preparations. In the case of new products, similar criteria are invoked. These standards have been described in the biologic regulations. In addition, the National Institute of Health has issued minimum requirements for each licensed biologic. Thus, the monograph for Dried Thrombin specifies:

1. *The Product*: The proper name; definition; source; the thrombin unit; reagents and tests on which the unit is based; other characteristics of the unit.
2. *Plasma Collection and Processing*: Procedure to be used.
3. *Control Tests*: Sterility; safety; moisture; solubility; reference standard; potency test using fibrinogen; potency test using plasma.
4. *General Requirements*: Preservative; storage; labeling; dating; requirements for release.

Appendices: Preparation of fibrinogen for the thrombin potency test. Type of protocol to accompany sample for release by the National Institute of Health.

No additional advantage will accrue by extending our discussion of the regulations, and the practice thereunder at this point; the subject is developed in detail in another chapter.

Violations of any provisions of the Act are punishable, on conviction, by a fine of not more than $500 or by imprisonment not exceeding one year, or both fine and imprisonment, in the discretion of the court.

VIRUS, SERUM, TOXIN, AND ANALOGOUS PRODUCTS ACT

In a brisk, laconic single paragraph that extends scarcely one page in length, the Act of March 4, 1913 (together with an earlier authorization to the Secretary of Agriculture, approved February 2, 1903), provides for the regulation of the preparation, sale, barter, exchange, shipment, importation of viruses, serums, toxins, and analogous products intended for use in the treatment of domestic animals, and the importation and interstate shipment of organisms or vectors. The law applies not only to products recognized in its title, but also to antitoxins, vaccines, tuberculins, malleins, live micro-organisms, killed micro-organisms, bacterins, and to cultures or collections of organisms or viruses, or their derivatives, from a foreign country which may introduce or disseminate any contagious or infectious disease of animals. It includes, for example, brucella abortus vaccines, anthrax vaccines, blackleg vaccines, fowl-laryngotracheitis vaccines, fowl-pox vaccines, ovine-ecthyma vaccines, hog-cholera viruses, and canine-distemper viruses.

The interstate commerce in such products is forbidden unless it has been prepared under and in compliance with regulations prescribed by the Secretary of Agriculture at an establishment holding a valid license issued by the Secretary. In addition, the law prohibits traffic in such viruses, serums, toxins, or like articles should they be worthless, contaminated, dangerous, or harmful. Imports require a permit from the Secretary, and are examined and inspected to determine their compliance with law by the Bureau of Animal Industry. Violation of the statute constitutes a misdemeanor, subjecting the offender to a fine of not exceeding $1,000, or imprisonment of not more than one year, or both.

The statute is implemented by comprehensive regulations that encompass every aspect of the preparation, sale, and importation of the products subject to its terms. Their very detail mitigates against an adequate discussion of their various provisions. The reader seeking additional information should communicate with the Bureau of Animal Industry, United States Department of Agriculture, Washington 25, D. C.

FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT

Although a discussion of an economic poisons law would, at first glance, appear to take us rather far afield of the scope of this volume, nevertheless it becomes necessary to review the provisions of the Federal Insecticide, Fungicide, and Rodenticide Act, enacted in 1947, because of its probable impact upon certain categories of drugs products.

Generally speaking, the statute does not concern itself with therapeutic agents. It is, in fact, directed at substances designed, intended, or marketed as "economic poisons" for the eradication of so-called "pests." However, it is interesting to observe that the statutory definition of the term "economic poison" includes:

> . . . any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any insects, . . . fungi, . . . and other forms of plant or animal life or viruses, except viruses on or in living man or other animals . . .

Moreover, the definition of "insecticide" refers to "any insects which may be present in any environment whatsoever," and expressly embraces mites, ticks, and lice. Similarly, the term "fungicide" relates to all fungi—non-chlorophyll-bearing thallophytes, including bacteria—except those on or in living man or other animals. The regulations, moreover, make it clear that this last definition encompasses disinfectants, antiseptics, and sterilizers, exempting only those for use *exclusively* on or in living man or other animals. In consequence of this extended scope it is evident that such preparations as tincture larkspur,

larkspur lotion, hospital creosol compound, and products containing quaternary ammonium salts and benzyl benzoate are subject to the provisions of this Act.

The new statute differs considerably in its regulatory control from not only the earlier Insecticide Act of 1910, which it replaces, but also such laws as the Federal Food, Drug, and Cosmetic Act, principally in granting the enforcing agency advance information about the formula, label, and claims made before an economic poison is offered to the public. Thus the Act requires the registration of any product subject to its terms with the Insecticide Division, Livestock Branch, Production and Marketing Administration, U. S. Department of Agriculture, before its introduction into interstate commerce, on application forms obtainable upon request from the Division. The Secretary may require the submission of the complete formula of the preparation. Proposed claims in the labeling are passed upon, and, if deemed to be warranted by the composition, the economic poison is accepted for registration. If objections are taken to the claims, however, the registrant is afforded an opportunity to make the corrections considered necessary. Should the applicant still insist upon the propriety of the representations, the Secretary will register the article, but under protest. Interstate shipments of the preparation may thereafter be made on the registrant's own responsibility. Registrations may be cancelled, unless requested to be continued in effect, at five-year intervals.

Both the law and regulations impose specific label requirements. Thus, the label of the economic poison must bear the following information:

(*a*) It must show, clearly and prominently (1) the name, brand, or trade-mark under which the article has been registered; (2) the name and address of the manufacturer, registrant, or person for whom manufactured; and (3) the net weight or measure of the content.

(*b*) An ingredient statement setting forth either (1) the name and percentage of each active ingredient, together with

the total percentage of the inert ingredients, in the product; or (2) the name of each active ingredient, together with the name and total percentage of the inert ingredient, if any there be, in the product.

(*c*) A warning or caution statement, when necessary to prevent injury to living man and other vertebrate animals, useful vegetation, and useful invertebrate animals, disclosing clearly and in nontechnical language the particular hazard involved in the use of the product, for example, ingestion, skin absorption, inhalation, inflammability or explosion, and the precautions to be taken to avoid accidents, injury, or damage.

(*d*) In the case of an economic poison which is highly toxic to man, the symbolic " skull and crossbones" is required to appear, together with the word "POISON" in red on a contrasting background. In addition, an antidote statement is required; this must include directions to call a physician immediately. The regulations set up criteria to determine when a poison of this character is viewed as being highly toxic to man.

The statute also enumerates those acts of omission or commission which are designated as "adulteration" and "misbranding." Similarly, it follows the Food, Drug, and Cosmetic Act in providing for seizure of offending preparations. Criminal prosecution is likewise authorized; in this connection, a variety of penalties is provided to fit the crime, so to speak. Thus, the commission of any specified "prohibited act" is characterized as a misdemeanor, subjecting the violator, on conviction, to a fine of not more than $1,000. Violation of any other provision of the Act is penalized by a fine not to exceed $500 for the first offense, subsequent offenses (committed within five years) permitting a fine up to $1,000 and a sentence of imprisonment, or both. Moreover, similar penalties are imposable if the violation stems from a registration "with warning." And finally, in case any person, with intent to defraud, uses or reveals information relating to formulas of products acquired

under the authority of the registration provision of the Act, he may be found guilty of a felony and fined up to $10,000 or imprisoned for not more than three years, or both.

A word is necessary regarding the statute's effective date. Although the law became effective upon its approval on June 25, 1947, rodenticides and herbicides were exempted until December 25, 1947, and the provisions relating to insecticides and fungicides were postponed one year. Moreover, the Secretary has authority to exempt any economic poison from the provisions of the Act, if it had been labeled, shipped, and delivered by the manufacturer before the pertinent section became applicable.

FEDERAL CAUSTIC POISON ACT

This statute became law on March 4, 1927. It is designed to insure the use of the "POISON" label on caustic or corrosive acids, alkalies, and other harmful products of a similar nature, packed in a parcel, package, or container suitable for household use. Its principal objective is to place consumers on guard by calling attention to the dangerous properties of these articles, and to give first-aid directions should they be consumed accidentally. Additional information is required on the label to inform the physician, who may be called to treat the case, as to the identity of the substance swallowed, thus facilitating prompt administration of the most effective antidote.

Although this legislation is directed primarily at the prevention of accidents to small children, many of whom have been seriously and even fatally injured as a result of swallowing lye and similar substances unwittingly, it is nevertheless applicable also to the labeling of drug products should they contain the chemicals described in the specified amounts. Thus a remedy for athlete's foot, containing equal parts of phenol and camphor, has been held to be amenable to this statute. Incidentally, the law is enforced by the Food and Drug Administration.

The Act concerns itself only with the following chemicals and preparations:

1. Hydrochloric acid (muriatic acid; chlorhydric acid) and any preparation containing free or chemically unneutralized hydrochloric acid (HCl) in a concentration of ten per cent or more;

2. Sulfuric acid (oil of vitriol) and any preparation containing free or chemically unneutralized sulfuric acid (H_2SO_4) in a concentration of ten per cent or more;

3. Nitric acid (aqua fortis), and any preparation containing free or chemically unneutralized nitric acid in a concentration of five per cent, or more;

4. Phenol (carbolic acid; phenic acid; phenylic acid; phenyl hydroxide; hydroxybenzene; oxybenzene), and preparation containing phenol in a concentration of five per cent, or more;

5. Oxalic acid, and any preparation containing free or chemically unneutralized oxalic acid in a concentration of ten per cent, or more;

6. Any salt of oxalic acid, and any preparation containing such salt in a concentration of ten per cent, or more;

7. Acetic acid, or any preparation containing free or chemically unneutralized acetic acid in a concentration of twenty per cent, or more;

8. Hypochlorous acid, either free or combined, and any preparation containing the same in a concentration so as to yield ten per cent or more by weight of available chlorine. Excluded from the application of the statute, however, is chlorinated lime (calx chlorinata, calx chlorata; bleaching powder; calcium hypochlorite; chloride of lime);

9. Potassium hydroxide (potassium hydrate; caustic potash; potassa), and any preparation containing free or chemically unneutralized potassium hydroxide, including specifically potassium hydroxide with lime (potassa with lima; Vienna caustic or paste; potassa lime), in a concentration of ten per cent, or more;

10. Sodium hydroxide (caustic soda; sodium hydrate), and any preparation containing free or chemically unneutralized sodium hydroxide, including specifically lye (lixivium; household lye), in a concentration of ten per cent, or more;

11. Silver nitrate (lunar caustic), and any preparation containing silver nitrate in a concentration of five per cent, or more; and

12. Ammonia water (ammonium hydroxide; aqua ammonia; spirit of hartshorn), and any preparation containing free or chemically uncombined ammonia, including specifically hartshorn (ammonium carbonate), in a concentration of five per cent, or more.

Four distinct markings are required to appear conspicuously

upon the label of a product of this nature. In the first instance, the word "POISON" must be printed in uncondensed Gothic capital letters. The type must be at least one-third of an inch high if the trade name or any other word on the label contains a letter of this height. If there is no letter this large, the poison legend must be printed no smaller than the largest letter on the label. Secondly, the common name of the caustic or corrosive substance is required to be stated. This declaration is not only informative for those who use the product in the home, but is of particular value to the physician as he is thus enabled to give immediate and appropriate treatment. Again, the name and place of business of the manufacturer, packer, distributor, or seller must appear on the label.

Finally, directions for treatment of the poisonous substance is required. These should be designed primarily for the relief of the patient until a physician arrives to administer more thorough treatment, if necessary, and are consequently phrased in terms understandable to the layman. Since the Food and Drug Administration has published antidotal treatments for each of the twelve substances dealt with by the law, the appropriate statement should be adopted in any particular instance, copies being obtainable on request from the Administration.

POSTAL LAWS

There is no one statute directed at the use of the mails for illegal purposes; on the contrary, more than eight sections of the United States Code interdict one or more practices of this kind. As a matter of fact, the Wheeler-Lea amendment to the Federal Trade Commission Act may, in a sense, also be considered to encompass postal frauds since its terms make unlawful the dissemination of any false advertisement "by United States mails" or otherwise. However, for the purposes of this discussion, we shall confine ourselves, first, to the section of the Criminal Code making it an offense to use the mails in execution (or attempted execution) of any scheme or artifice to defraud, or obtaining money or property by means of false or

fraudulent representations, pretenses, or promises, and to the authority of the Postmaster General to issue orders forbidding delivery of registered and other mail, and payment of money orders, to persons or firms found, upon evidence satisfactory to him, to be using the mails to obtain money or property by utilizing false pretenses, representations, or promises.

To constitute an offense within the scope of the Criminal Code two elements are essential: (1) the devising of a scheme or artifice to defraud, and (2) the use of the mails to execute the plan. It must be understood that the statute is not concerned exclusively with drugs, their labeling or advertising; although it has been invoked frequently against fraudulent products of this character, it is aimed at every stratagem which is, in fact, designed to defraud and which involves some degree of trickery or deceit.

As may be expected, the reported cases have generally concerned quite obvious frauds. Thus, successful prosecutions have been brought against a head cap sold as a remedy for deafness, an electric belt offered as a cure for human ills, a device claimed to promote absorption of oxygen through the skin, a remedy for sexual weakness represented as a panacea, "vitality pills" advertised as the only known positive cure for lost manhood, a preparation containing morphine presented as curative in itself of the morphine habit, a medicine held out as a certain cure for pulmonary tuberculosis, and similar nostrums. On the other hand, the indictment was dismissed in a case involving a preparation of gold and sodium choride offered as a cure for syphilis on the ground that the evidence was insufficient to show that the representations were fraudulent. Generally speaking, the types of claims that were amenable to the old Food and Drugs Act of 1906 are open to prosecution under this provision; the degree of proof, it should be observed, is analogous.

The crime, upon conviction, is penalized by a fine of not more than $1,000, or imprisonment for not more than five years, or both. Constitutional requirements make it necessary to institute prosecution by indictment; the practice other-

wise follows the customary trial of a criminal charge in the Federal courts. It may be noted that good faith and an honest belief in the truth of the representations made serve as a complete defense to the prosecution.

A more summary remedy is available to the Postmaster General who is authorized to forbid the use of the mails where these are being employed to conduct a scheme for obtaining money or property by false pretenses, representations, or promises. The similarity of the basis for such action to the criminal charge discussed above is notable; the same character of evidence is requisite in both proceedings. In such instances, the Postmaster General is authorized to issue what is commonly called a "fraud order." This order may briefly be described as a direction to the post office to return all mail addressed to the respondent to the sender, or, if he be unknown, to the dead letter office, with the word "FRAUDULENT" stamped on the envelope. In addition, the Postmaster General may forbid the payment of postal money orders drawn in favor of the respondent. It should be observed, moreover, that once a fraud order issues, *all* mail to the respondent is intercepted, even though only a part of the business is illegally conducted.

The drastic nature of the remedy has caused it to be applied—at least against domestic enterprises—in relatively extreme cases only. This should not lead to the conclusion that the Post Office stands by silently and inactively in other instances; rather, by letter to the offending firm, it calls attention that the scheme is improper and that the advertisements, whatever form they take, are unmailable. Usually, this notification results in a discontinuance of the objectionable practice. If it does not, further action is taken. About 350 domestic fraud order cases are handled annually by the Post Office authorities.

Although the statute authorizes the Postmaster General to act "upon evidence satisfactory to him," and calls for no particular procedure, the courts have affirmed that the person or firm accused is entitled to a hearing on the merits. The conduct of hearings of this kind has only recently been formalized in published Rules of Practice.

Action in fraud order cases is usually initiated by informal complaints made by members of the public, competitors, better business bureaus, and trade and professional associations. If it appears well-supported, the complaint is assigned to a post office inspector for further investigation. A very careful and thorough inquiry into the situation is undertaken, frequently extending over a considerable period. In medical cases, for instance, post office employees may pretend to be prospective customers; they describe their "diseases" in correspondence and may request samples under their own names. The services of medical officers from other Federal agencies may also be utilized.

An extensive report is prepared upon completion of the investigation. This serves as the foundation of a "memorandum of charges" and a trial brief outlining the complete evidence which is prepared by the Fraud Section. The attorney in charge of this Section, after studying the documents, decides whether or not the facts warrant further action. Should he consider a citation appropriate, he transmits the specification of charges to the Solicitor's office, where a notice to the accused to show cause upon a specified date why an order should not be issued against him is framed. Service of the notice, together with a copy of the specification of charges and of the postal statutes involved, is then made on the respondent in person or by mail.

The respondent has several alternatives on being served. Should he desire to contest the charges, he may file an answer. However, he may waive a hearing and ask to be heard on the question as to whether the facts, as admitted, constitute a violation of the law as alleged in the complaint. Where he acknowledges the offense and seeks to dispose of the charges without the stigma of a fraud order, he may apply for permission to file an "affidavit of discontinuance," providing for the abandonment of the practice charged and authorizing the local postmaster to return his mail marked "OUT OF BUSINESS" and to refuse to cash money orders drawn in his favor. Whether permission to file the affidavit will be granted rests in the discretion of the Solicitor. Nor will one be accepted generally

after a case has gone to hearing and the Department's counsel has introduced evidence to substantiate the charges set forth in the complaint.

The hearing is held in Washington, D.C., before a Hearing Officer. Its conduct follows the usual administrative procedure although an interesting provision brings admissible testimony into close resemblance to accepted legal rules of evidence:

> . . . Medical or other scientific books or essays will not be admitted in evidence in lieu of oral expert testimony. Where such publications are cited or relied upon by an expert witness on direct examination, they are then admissible on cross-examination for the sole purpose of showing that they contradict the witness as to the matter upon which he cited them as supporting his testimony. Affidavits of physicians or others containing opinions or statements in the nature of expert testimony are not admissible. Testimonials are inadmissible.

A judicial review of a fraud order, once it has been issued, is obtainable only by bringing an action for an injunction seeking to prevent enforcement of the order. However, as a general rule, the courts have been reluctant in these cases to interfere with the judgment of the Postmaster General.

DUPLICATIVE FEDERAL REGULATION

It must be obvious that the scope of the various Federal statutes, concerned either generally or with one or more phases of drug regulation, occasionally results in an overlapping of jurisdiction and possible conflict in enforcement activities. This duplication, moreover, may prove a source of puzzlement to the manufacturer or distributor whose preparation comes within the purview of two or more laws. Where the requirements or interpretations between the statutes differ, difficulties are patently compounded.

It may be generalized, first of all, that the fact that a particular drug product is subject to regulation stemming from different enactments does not relieve it from the necessity of compliance with each. In the majority of instances, it is clear

that the statutes are not mutually exclusive of each other. It follows, therefore, that the same act may bring retribution from a number of enforcement agencies. Thus, a false or misleading advertisement may, under certain circumstances, be proceeded against under the Federal Food, Drug, and Cosmetic Act, the Federal Trade Commission Act, and the Criminal Code relating to postal frauds. So, too, a preparation may be illegal under both the Food, Drug, and Cosmetic Act and the Caustic Poison Act. A biologic may violate the Virus, Serum, and Toxin Act as well as the Food, Drug, and Cosmetic Act.

Recently, however, there has been a tendency to avoid unnecessary duplication in the administration of statutes relating to the same subject-matter. For instance, the Congress obtained a commitment from the Federal Security Administrator that the Agency would avoid repetitious administration of the provisions of the Virus, Serum, and Toxic Act and the Food, Drug, and Cosmetic Act in the case of biologics. This was subsequently formalized in a statement in which the Administrator assigned to the Public Health Service the primary responsibility for the regulation of licensed biological products, except in emergencies involving protection to the public against preparations which might be dangerous to life or health, when the regulatory procedures authorized by the Food, Drug, and Cosmetic Act would be invoked.

The Federal Trade Commission has also recognized the situation in a statement of policies. Thus, it has expressed a willingness to cooperate with other Federal agencies to avoid unnecessary overlapping or possible conflict of effort. Specifically, it announced that it would not institute proceedings in matters, such as the labeling or branding of commodities, where the subject-matter of the questioned portion of the labeling or branding used is, by specific legislation, made a direct responsibility of another agency. And where action is taken against a drug under the false advertisement provisions of the Act, it declared that its policy would be to take into account the labeling requirements of the Food and Drug Administra-

tion. It is yet too early to appraise the practical application of this expressed intention.

The situation between the Federal Trade Commission Act and the Federal Food, Drug, and Cosmetic Act has frequently proved troublesome to the drug industry. As the statutes read, it would seem that the Congress intended to apportion the supervision of drug *advertising* to the Commission and drug *labels* and *labeling* to the Food and Drug Administration. But this division has never been maintained, and, in fact, has been broken down completely by a series of court decisions which emphasized that no substantial distinction exists between labeling and advertising. In the past, the Commission, moreover, has proceeded against firms on the basis of the product's labeling, supported by its broad powers over unfair or deceptive acts or practices in commerce. The Administration, also, has prosecuted drug concerns because of claims made in advertisements. There is little reason to conclude that such enforcement anomalies will be discontinued.

As we have intimated, the courts have generally held that neither the power nor the duty to condemn misbranded drugs under the Food, Drug, and Cosmetic Act is impaired or diminished by a previous proceeding against the owner of such articles by the Federal Trade Commission. However, should the prior proceeding either before the Commission or as a result of Food and Drug Administration action have ended with a finding that the claim was not improper, other courts have considered this as a bar to action on the same representations by the other agency. The mere pendency of such a proceeding does not, of course, have a similar effect, and it is equally obvious that both subject-matter and claim must be identical in the two cases.

STATE LEGISLATION

It would require more space than we have available to discuss with any degree of detail the legislation of the different States relating to the regulation of drugs. This failure to treat

the subject in greater particular should not, however, lead the manufacturer or distributor to conclude that these laws are of little significance. On the contrary, their violation—whether through inadvertency or design—may have serious repercussions.

It must be admitted, of course, that the largest bulk of pharmaceutical business takes place in what is broadly designated as "interstate commerce." Nor has any one State the right or power to place a burden upon such commerce or attempt to displace or interfere with the Federal law relating to the subject. On the other hand, of course, manufacturing processes and marketing undertaken within the boundaries of a State are amenable to regulation by that State. Moreover, local statutes will not be deemed an interference with Federal legislation where they have been enacted in the exercise of the police power with the object of protecting the health and safety of the citizens of the State.

The Federal courts, of course, have no jurisdiction over purely intrastate operations and transactions—although this distinction is rather a hazy one as a result of two recent Supreme Court decisions—and, in principle, at least, Federal enforcement agencies are blocked from taking action in these cases. In actual practice, a considerable degree of cooperation between Federal and State agencies exists.

There is also an ever-expanding tendency for the different States to adopt legislation closely paralleling Federal statutes; these are commonly called "baby acts" and generally follow a uniform model statute. This practice has several advantages, patently, among which may be recognized that inherent in having the same type of regulation applicable to both interstate and intrastate transactions. However, the enactment of uniform laws is not universal and a number of State legislatures have not hesitated in many instances to append additional requirements to those imposed by the pertinent Federal statute. It should not be assumed, therefore, that the statute of any State conforms in every particularity with its Federal counterpart despite the similarity of subject-matter. Consequently, should

any question arise as to their specific provisions or construction, it is advisable to examine the State statute involved.

The following States have drug laws patterned generally on the Federal Food, Drug, and Cosmetic Act:

Arkansas
California
Connecticut
Florida
Indiana
Louisiana
Missouri
Nevada
New Hampshire
New Jersey
New York
North Carolina
North Dakota
Oregon
Tennessee
Virginia
Washington

The following States have drug laws patterned closely on the prior Food and Drugs Act of 1906:

Alabama
Colorado
Delaware
Georgia
Idaho
Illinois
Iowa
Kentucky
Maine
Maryland
Massachusetts
Michigan
Minnesota
Mississippi
Kansas
Montana
Nebraska
New Mexico
Ohio
Oklahoma
Pennsylvania
Rhode Island
South Carolina
South Dakota
Texas
Utah
Vermont
West Virginia
Wisconsin
Wyoming

13

New Drug Applications

WALTON VAN WINKLE, JR.

BEFORE a new product may be marketed, attention must be given to its status as a "new drug" within the meaning of the Federal Food, Drug, and Cosmetic Act. To be considered are two aspects: (1) Is the product a drug? (2) If so, is it a *new* drug? Surprising as it may seem, the answer to the first question is not always as obvious as it might appear. Some articles may, by popular acceptance, be considered as foods or even cosmetics, but by statutory definition are classed as drugs for the purpose of the Food, Drug, and Cosmetic Act. This category, for example, comprises any article recognized in the *United States Pharmacopoeia,* the *Homeopathic Pharmacopoeia,* and the *National Formulary* currently "official," or any supplement to these. Furthermore, diagnostic, prophylactic, curative, and palliative agents are similarly considered "drugs"; so, also, is any article intended to affect the structure or any function of the body of man or other animals, except foods.

THE NEW DRUG STATUTE

Among the provisions relating to the distribution of new drugs, Section 505 of the Federal Food, Drug, and Cosmetic Act is undoubtedly the most important. This provides that:

> No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an application filed pursuant to subsection (b) is effective with respect to such drug.

Section 505(b) requires, among other things, "full reports of all investigations made to show whether or not such drug is safe for use." In other words, the laboratory and clinical informa-

tion relating to the drug, discussed in previous chapters, will, generally speaking, have to be presented to and reviewed by the Food and Drug Administration. If the data convince it of the safety of the drug, permission to distribute it in interstate commerce will not be refused.

The new drug provisions of the Federal law were drafted as a result of the tragic events following the distribution of the infamous "Elixir of Sulfanilamide." This product, introduced in the fall of 1937 without previous testing other than cursory examination, was responsible for the death of more than one hundred persons. The present statute is specifically designed to prevent a recurrence of such a tragedy.

DETERMINATION OF NEW DRUG STATUS

Section 201(p) of the Federal Food, Drug, and Cosmetic Act defines a "new drug." It will be found that the definition is in two parts which must be considered separately. The first part describes a drug as "new" if its composition is such that it "is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety of drugs, as safe for use under the conditions prescribed, recommended, or suggested in the labeling thereof. . . ." On analysis, this portion of the statutory definition involves two factors: the composition of the drug and its labeling. For example, a new synthetic chemical which has previously not been used in medicine obviously falls in the category of a new drug, regardless of its labeling. Under such circumstances, it is clear that qualified experts have not had an opportunity to "generally recognize" it as safe under any circumstances. So, too, if the drug is a recognized substance, known to be toxic, it similarly falls within this definition because its composition renders it unsafe. Finally, a previously known drug might be viewed as new because of a labeling change which casts doubt on its safety under the new conditions of its use. An illustration of this is a preparation formerly used for external application now labeled with directions calling for its use internally.

Here an exception to this first part of the new drug definition should be noted. A drug that was subject to the Food and Drugs Act of 1906, whose present labeling bears the same representations concerning the conditions of its use as were borne under the old law, will not be considered a new drug. This, in effect, prevents a retroactive application of the statute.

The second part of the definition of a new drug is one often overlooked by manufacturers, and a few careless shippers have received citations by the Food and Drug Administration because of failure to appreciate its import. This makes a new drug of a preparation "the composition of which is such that such drug, as a result of investigations to determine its safety for use under such conditions, has become so recognized [as safe], but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions." This is interpreted to mean that even though a manufacturer and qualified experts, by scientific investigation, are convinced that the new product is safe, it still remains a new drug if it has not been distributed for a substantial period except for such investigational use; and they must consequently convince the Food and Drug Administration that it is safe. The question of what constitutes "material extent" and "material time" is a matter for judicial interpretation; it is probable, however, that this depends on the nature of the drug and the possibility of hidden or delayed toxicity.

Since it is not always easy to decide whether a given new product falls within one or the other of these definitions, the Food and Drug Administration will render an advisory opinion, upon request, if complete information on the quantitative composition and the proposed labeling are furnished. To protect himself from inadvertent violation of the law, the manufacturer should avail himself of this service at any time there is the slightest doubt as to the status of a new product.

THE NEW DRUG APPLICATION

Having determined that a new product will be classed as a new drug, it becomes necessary to comply with the provisions of Section 505(b) of the Federal Food, Drug, and Cosmetic Act.

The preparation of a new drug application is not a simple task. The principal objective of the application is to demonstrate the safety of the proposed product under the conditions suggested for its use. The information submitted, therefore, must be convincing, complete, and logical. Theoretical discussions should be avoided and sufficient factual data supplied to enable the Food and Drug Administration reviewer to draw his own conclusions, independently of those reached by others.

There are six principal requirements for a complete new drug application. These are:

(1) Full reports of all investigations which have been made to show whether or not the drug is safe for use;

(2) a full list of articles used as components of the drug;

(3) a full statement of the composition of the drug;

(4) a full description of this method of manufacture and the facilities and controls used in the manufacture of the drug;

(5) copies of the label and other labeling of the drug;

(6) a statement as to whether the labeling is to bear directions for use or is to be exempt under the regulations under Section 502 (f)(1) of the Act.

The most important and undoubtedly the most difficult part of the application to prepare is the section containing the "full reports of investigations which have been made to show whether or not such drug is safe for use." The other requirements relate to composition, manufacturing process and controls, samples, and labeling. In addition, the regulations require the applicant to state whether or not he proposes to distribute the drug for "over-the-counter" sale or to restrict it to dispensing upon the prescription of a physician, dentist, or veterinarian.

Reports of Investigations. The reports of investigations relative to the safety of the new drug usually consist of two sets of

data, laboratory and clinical. The emphasis should be placed upon those investigations which demonstrate the safety of the article under the proposed conditions of use. Thus, laboratory data should furnish information on the acute and chronic toxicity of the drug, provide an explanation of its mode of action, and give information on its fate and excretion. Clinical data should include tests useful in detecting subclinical toxicity. The nature of these investigations has been discussed in other chapters.

Laboratory data, in most instances, can be presented in tabular or graphic form preceded by a concise statement of the purpose of each experiment and a description of the method employed. A brief summary of the results of an experiment or group of experiments should conclude each presentation. Protocols of individual experiments, if significant or typical, may be added as an appendix. Although a statement of the conclusions arrived at as a result of these experiments may be made, this cannot substitute for the basic data.

In the case of clinical data, detail is an important requisite. Thus, cases should be grouped in accord with fixed classifications. Summaries of each group preceding the actual case histories prove of assistance in reviewing the material. Negative as well as positive findings should always be included; in fact, it is well to state just what tests or examinations were performed on the patients and the results. While it is not always necessary to present individual case histories on all patients, the data, if summarized, should contain all of the information derived from examination of these records. Control observations should be set forth in as much detail as observations on treated patients.

Although proof of safety is the principal consideration of the new drug provisions, safety itself cannot be completely separated from the medical efficacy of the proposed preparation. A drug is "safe" only in so far as its therapeutic effects exceed its undesirable or toxic actions by a reasonable margin. The margin acceptable will vary with the severity of the condition being treated and also with the availability and efficacy of other methods of treatment. It is frequently necessary, therefore, to

demonstrate the therapeutic effectiveness of the new drug and to make direct comparisons with other accepted methods of treatment, particularly in the case of a potent drug. This information will enable the reviewer to view the "absolute toxicity" of the drug in the light of the therapeutic possibilities and thus arrive at some measure of its "relative safety." Indeed, this last factor may prove the controlling one in reaching a decision on the application.

Investigational use of the new drug. The Congress recognized that, as it stands, Section 505(a) of the Act would prohibit, or, at any rate, greatly limit, the gathering of the information necessary for the submission of a new drug application. Section 505(i) of the Act, therefore, was drawn to provide the mechanism for obtaining this information without violation of the law. The wording of this section requires careful study:

> The Administrator shall promulgate regulations for exempting from the operation of this section drugs intended solely for investigational use by *experts qualified by scientific training and experience to investigate the safety of drugs.*

It will be observed that it is left to the manufacturer to determine who is and who is not such an "expert." The task is not an easy one at best and has led to some confusion, many manufacturers having considered that the possession of an M.D. or Ph.D. degree in one of the basic medical sciences almost automatically establishes the "expert's" qualifications.

However, an examination of the wording of Section 505(i) clearly indicates that the Congress, in placing limitations on the distribution of new drugs for investigational use, had in mind qualifications in excess of those usually possessed by the ordinary practicing physician. It is to be noted that the Act limits the distribution of such drugs to *experts.* It specifies further *experts* on the *safety of drugs.* These two statutory qualifications clearly call for a preliminary examination in selecting an individual as an expert of his scientific training and experience.

Consequently, consideration shall be given first to the scientific training of the proposed expert on the safety of drugs. In

general, there are two types of such authorities, distinguished usually by their different training. Those concerned with laboratory investigations, such as chemists, bacteriologists, and pharmacologists naturally possess a background of scientific training sharply at variance from experts in the field of clinical investigation. The laboratory investigators, reporting new drug findings, should have a doctorate or its equivalent in the field of study, or a closely related one, in which they are working. This does not mean that students working towards their Ph.D. degree cannot investigate the safety of new drugs; they cannot, however, be classed as "experts" and their work should be performed only under competent direction. On the other hand, a doctor's degree is indicative primarily of past investigative activity; it does not necessarily assure that its holder is an acceptable expert of the type contemplated by the statute. Such an individual must be actively engaged in some phase of investigative work on drugs or drug therapy. A general measure of such activity may be gained by reviewing the scientific publications of the investigator. As a matter of fact, in order to qualify under the statute, he should have published the results of meritorious investigations in his particular specialty with fair regularity. This, indeed, may be considered by the manufacturer as a broad gauge of his acceptability.

The training of a clinical investigator is more difficult to define than that of the laboratory investigator. The mere possession of an M.D. degree does not certify that the individual is competent as an expert on the safety of new drugs. In the course of his career, the expert should have had training in investigational methods and should, moreover, have pursued some scientific investigations to completion under the direction of competent men. Since the additional training required for certification by most specialty boards includes some investigative work, such a certification, while not conclusive, is somewhat indicative of qualifications superior to those of the average medical graduate.

Obviously, experience on the part of a clinical investigator may substitute for a large measure of formal training. But it

is equally important to consider such experience before utilizing the investigator as an expert on the safety of new drugs. This should include the successful completion of investigations on either the laboratory or clinical actions of drugs. In the case of laboratory investigators, most, if not all, of their research experience should be in the particular field concerned if they are to be qualified as experts. Clinical investigators should have devoted at least half of the period spent in research to problems involving clinical pharmacology or some phase of therapeutics. Nor is the length of time this experience has extended as important as the character of the experience. For example, the routine administration of drugs to patients in the course of the practice of medicine cannot be regarded as qualifying background.

As we have pointed out, it is the responsibility of the manufacturer to examine the qualifications of those to whom he proposes to send new drugs for investigational use and to decide whether these qualifications meet the criteria discussed above. In addition, the regulations under Section 505(i) of the Federal Food, Drug, and Cosmetic Act require the manufacturer to obtain a statement from the prospective investigator showing that he has adequate facilities to conduct the investigation and that the drug will be used by him, or under his direction, for the investigation. Facilities of this nature should include adequate laboratories and staff, together with sufficient patients suffering from the condition under study to enable the carrying out of proper testing of the drug within a reasonable time.

The regulations further require that complete records, showing the quantity, date, and to whom the drug was shipped, be kept and made available to authorized persons. Each container of the drug, furthermore, shall bear a label on which appears the statement: "CAUTION: NEW DRUG—LIMITED BY FEDERAL LAW TO INVESTIGATIONAL USE."

Although the evidence of safety of the drug is the important part of the new drug application, the other requirements must be met in full. In preparing the application, each section should be clearly separated from the preceding one; it assists the re-

viewer, moreover, if each section is clearly identified, preferably by a reference to the appropriate paragraph of the law.

Components and composition. The list of articles used as components of the drug includes all substances employed during the course of manufacture whether they appear in the final product or not. The statement of the composition of the drug should list the quantity of each ingredient, both active and inactive, in a stated amount of the finished product. This latter statement should also reveal the percentage of each ingredient in an average dose of the article.

Manufacturing methods. The description of the method of manufacture should be sufficiently detailed to enable the reviewer to obtain a clear picture of each step in the production of the drug from the time the raw materials are received until the finished product is ready for distribution. In complicated processes, it will be of considerable assistance to furnish a "flow sheet" of the entire operation with the application.

Controls. A discussion of the control methods used during the manufacturing process should conform as closely as possible to the outline suggested by the Food and Drug Administration on the new drug application form (Form F.D. 356 Rev.). The control procedures should be of such a character that any manufacturing errors will be detected before the product leaves the plant. Descriptions of laboratory control procedures should include details of the chemical, biological, or other assays made, or references to the literature in which these tests are described.

Samples. Samples of the drug may be sent to the Food and Drug Administration at the time the application is submitted or at a later date, depending upon the availability of the material. A statement should be made in the application concerning the availability of samples.

Labeling. All labeling, including brochures sent apart from the market package, should be included in the application. It is usually inadvisable to print labeling before an application for the product is effective. The Administration may suggest changes withholding decision on the application pending submission of revised labeling. Accordingly, typewritten drafts or

proofs of labeling are satisfactory for inclusion in a new drug application. The position of each label panel on the package should be clearly indicated. In addition, all brochures or other printed matter should be identified as to their method of distribution.

Preparation of application. The Food and Drug Administration furnishes a form (Form F.D. 356 Rev.) which may be used as a guide in the submission of applications. After each heading on the application form there appears explanatory material which can serve as a guide to the type of information which should be included. Use of this form is not mandatory, however, and the form may be copied in whole or in part in submitting applications. All applications must be submitted in duplicate and care should be taken that all of the supporting material is also in duplicate.

In preparing applications for submission to the Food and Drug Administration, the form prescribed on the application blank should be followed closely. Each section should be on separate sheets of paper and clearly identified. It is not necessary to bind the material as the Food and Drug Administration binds all applications in a uniform manner.

It facilitates handling of an application if all material is submitted on letter size paper; legal size sheets are difficult to work with. Photographs, reprints, and charts should also be mounted on standard-size paper and inserted with the rest of the application.

Occasionally, it is not possible to obtain reprints of published articles for use in an application. No objection is offered to the submission of photostats or microfilm copies. Microfilm and Kodachrome slides, if a part of the application, should be mailed under separate cover, properly identified with the name and address of the applicant and the name of the product for which application is being made.

Submission of application. It is not necessary to submit applications in person, and little is gained by such a procedure since a reviewing officer cannot give an opinion as to the completeness or adequacy of the application from a casual inspection. If it

is thought necessary to discuss some phase of an application before formal submission, it is advisable to send the material to the Food and Drug Administration a few days in advance of the interview in order that the scientific personnel have an opportunity to review the data under discussion.

HANDLING OF NEW DRUG APPLICATIONS

Receipt and notification. If the application is complete at the time it is received by the Food and Drug Administration, it will be filed as of the date of receipt. Consideration of applications is made in the order of receipt. The Administration does not usually inform the applicant of the status of his application until it has had time to review it in detail. This may take from one to four weeks. Under the terms of the statute, it is permitted only sixty days from the date of filing to reach a decision as to whether or not the application should be permitted to become effective. As a matter of fact, if negative action is not taken within the sixty-day period, the application becomes automatically effective.

Where the application contains a considerable amount of data, or it becomes necessary for the Food and Drug Administration to secure additional information, the sixty-day period for consideration of the application may be insufficient. In this event, the Administrator may issue a formal notice to the applicant extending his time for consideration to a maximum of one hundred and eighty days from the date of filing.

Delays in handling. One of the principal reasons for a delay in handling of an application is incompleteness of the information contained in it, even though the application be technically complete. For instance, applications frequently have been submitted to the Food and Drug Administration with reports of chronic toxicity studies of eight weeks or three months' duration in rats. Such studies are of too short a time to be of probative value; in most instances, in fact, these should be conducted over a period of one or two years in order to be certain that insidious or delayed toxicity does not develop. Again, since

different species vary in their reactions to drugs, applications containing reports of tests on only one species of animals are often subject to delay while the Food and Drug Administration requests the applicant to make additional studies.

Inadequate clinical data are all too common. Two extremes of insufficiency of this character are seen. On the one hand, the clinical work submitted may have been done by a single man or group of investigators; on the other, although many investigators may have employed the drug, only a few patients were utilized with the result that none is in a position to draw definitive conclusions regarding its safety or efficacy. Usually the new drug application necessitates clinical reports from several investigators, each of whom has independently studied a sufficient number of cases under proper controls. Considerable detail is needed to arrive at a justifiable conclusion regarding the drug. Clearly, if the conclusions, and data on which they are based, agree in the various reports, the Food and Drug Administration will have less difficulty in reaching a decision concerning the application.

Occasionally, an application may be delayed because of incomplete information on manufacturing procedure and controls. Some manufacturers are reluctant to submit such information in detail since it may involve the disclosure of trade secrets. However, they are protected by Section 301(j) of the Act which prohibits the unauthorized disclosure by any person of information acquired under authority of Section 505 of the Act concerning "any method or process which as a trade secret is entitled to protection." It will be observed that the new drug application form lists ten aspects which should be discussed by the applicant in describing his control procedures. These are: (1) Precautions to insure proper identity, strength, and purity of the raw materials; (2) use of serial numbers on lots of raw materials; (3) method of preparation of formula card and manner in which it is used; (4) number of individuals checking weight or volume of each ingredient entering into each batch of the drug; (5) whether or not the total weight or volume of each batch is determined at any stage of the manufacturing process subse-

quent to making up a batch according to the formula card and at what stage and by whom this is done; (6) check made on total number of finished packages; (7) precautions to insure that the proper labels are placed on the drug; (8) complete description of method of sampling and analytical controls including sterility tests; (9) significance of control numbers; (10) additional control procedures. Additional information should be included wherever it is necessary to furnish a complete picture of the practices of the firm.

Unless the complete labeling, together with a precise indication of how it is to be applied to or accompany the final package, is included with the application, delay in handling may result. If revisions are suggested by the Food and Drug Administration, prompt submission of the revised labeling will also expedite the handling of the application.

Incomplete applications. An application is deemed to be incomplete if it fails to contain information on all of the points designated in the statute and the regulations, or if it is not in duplicate. It should be noted that the regulations also require that the application contain a statement of the conditions under which the drug is to be used, if the labeling does not, expressly or by reference to a brochure or other printed matter, set forth the suggested use of the drug.

Where an application is incomplete, the applicant is notified of this fact, the particulars on which more information is necessary being stated. The application is not deemed "filed" until sufficient data have been received to make it technically complete.

Insufficient information; withdrawal of application. In case the application filed is factually vulnerable, for example, in containing convincing data demonstrating the safety for use of the product, or data indicating that the drug is actually unsafe, or if for any other reason it is not possible to decide that the application should be permitted to become effective, the applicant usually will be notified of this fact and given the opportunity to withdraw his application from consideration. This in

no way prejudices the later refiling of the application should additional data become available.

Aside from insufficient evidence of safety to permit a decision to be made regarding the application, there are several technical reasons for not permitting an application to become effective. These are set forth in the regulations under Section 505(d) of the Act and relate to technical aspects of the labeling. Thus, an application will be deemed to have insufficient information if it is a drug whose labeling is to be exempt from bearing adequate directions for use and, (1) if the label does not incorporate by reference a brochure or other printed matter giving full information adequate for its use, (2) the label fails to state that the drug is to be used as shown in the brochure or other printed matter, and that these are available to physicians, dentists, and veterinarians upon request, (3) the application does not contain copies of the brochure, or, (4) the application fails to show that the brochure is readily available, or will be when the application becomes effective. So readily correctable are these deficiencies that they have not been the cause for refusal proceeding under the Act.

Hearings. If an application is not withdrawn upon the suggestion of the Administration, it is likely that a formal hearing, as provided for by Section 505(d) of the Act, will be called. Notice of the time, place, and issues of the hearing are sent to the applicant; he may thereupon elect to file an appearance, withdraw the application, or ignore the notice. In the last-named instance, an *ex-parte* hearing is held and almost invariably results in denying to permit the application to become effective.

These hearings are closed to the public, although a complete record of the proceedings is kept. The proceedings are quasi-judicial; objections may be entered to any part of the testimony, for example, and exceptions are granted to adverse rulings of the presiding officer. At the hearing, testimony concerning information not contained in the application is not admissible, the theory being that *(a)* it should have been included by an appropriate amendment, and *(b)* the Food and Drug Adminis-

tration will not have had time to review it. If the applicant has new data which he wishes to have considered, the proper procedure is to request withdrawal of the application and to resubmit an amplified application. This can be done at any time before the termination of the hearing. A limited time is usually granted for the filing of briefs.

In the event of an adverse decision, the applicant may appeal for a review of the Administrator's decision to the United States District Court in the district in which he has his place of business or to the District Court of the District of Columbia. Section 505(h) of the Act sets forth the conditions under which an appeal may be taken from an adverse ruling by the Administrator.

The court review provisions of Section 505(h) are similar to those in other administrative statutes. The findings of the Administrator as to the facts, if supported by substantial evidence, are deemed conclusive. These findings are based upon the material, or lack of it, in the application and upon the evidence adduced at the hearing. Furthermore, all objections to the testimony or rulings of the hearing officer must be entered at the time of the hearing; otherwise they cannot be urged on appeal.

Effective applications; conditions. An application which is complete in every detail is usually handled within a few weeks. The length of examination period depends on the number of other applications awaiting review and also the size and complexity of the application under consideration.

If the labeling submitted with an application for a new drug is in need of extensive revision, the Food and Drug Administration usually does not permit the application to become effective until the labeling has been adequately revised. Where minor corrections only are necessary, the application may be permitted to become effective on the assumption that these will be made before the drug is marketed. In any event, final printed labeling should always be submitted to the Administration, and when any revisions are contemplated, copies of the revised labels should also be filed with the application.

The applicant is usually notified promptly as soon as the

Administration has reached a decision with regard to the disposition of the application. Since the statute provides for positive action by the Administration only in the event of an adverse ruling, it is not incumbent upon it to advise the applicant when it has decided favorably on the application. No objection being made, the application would become automatically effective sixty days after filing. However, as a courtesy to the applicant, the Food and Drug Administration does notify him of a favorable decision by means of a letter, commonly called the "effective letter." The phraseology employed to tell an applicant that he may proceed with interstate distribution of a new drug may be confusing to the uninitiated because of the negative manner in which the information is stated. The so-called "effective letter" contains five "form" paragraphs (usually paragraphs two to six inclusive), the first of which informs the applicant that "no order will issue refusing to permit the application to become effective." The other paragraphs specify certain conditions precedent to maintaining the effectiveness of the application. Comments on the labeling usually constitute the last portion of the letter.

Occasionally, the Administration permits an application to become effective under labeling which it considers false or misleading. This occurs when the character of the labeling does not adversely affect the safety of the drug, and when the applicant has refused to bring the labeling into compliance with the general provisions of the law. The letter notifying the applicant of the effectiveness of his application will point out in detail the deficiencies of the labeling and warn him that the product may be the subject of further legal action. Such a course is the Administration's only alternative, since Section 505 of the Act does not contemplate refusal of an application except when it can be demonstrated that the drug will be unsafe when distributed under the proposed labeling.

It must be borne in mind that when an application is permitted to become effective, the Administration does not "approve" the product or the claims made for it. Furthermore, Section 301(l) of the Act prohibits the use, in labeling or ad-

vertising, of any suggestion or statement that an application with respect to the drug has been permitted to become effective under the terms of Section 505.

LABELING AND CLAIMS FOR NEW DRUGS

The claims made for new products, both in the labeling and advertising, should be restricted to those therapeutic actions for which there exist adequate laboratory and clinical data. Claims based on preliminary experiments or on incomplete data should obviously not be put forward. Too often these must later be retracted or modified, and the confidence of the user in the product suffers impairment. It is obviously the better practice to expand therapeutic representations for a product as adequate data become available rather than to delete them after subsequent work shows them to have been unfounded.

Usually the Food and Drug Administration will point out, at the time it permits an application to become effective, those claims which it feels are exaggerated, unwarranted, or outright false or misleading. As indicated, their presence in the labeling will not prevent an application from becoming effective unless, of course, they adversely affect the safety for its use. However, the effectiveness of an application does not act as a bar to future legal actions against the product or shipper under other provisions of the law. Thus, it is quite possible for the Food and Drug Administration to permit an application to become effective under Section 505 of the Act and then immediately seize the product, or prosecute the shipper, under Section 502(a) of the Act for false or misleading labeling. This situation may occur under circumstances in which the applicant refuses to alter labeling claims that are misleading in the opinion of the Food and Drug Administration, but since the article is safe the Administration has no alternative except to allow the application to become effective.

The trend in new medications, other than the antibiotics, has been toward the development of new synthetic chemicals whose actions are more or less specific. Many of these, unfortunately,

have great toxic potentialities. Hence, a greater proportion of the applications received by the Food and Drug Administration are for products whose distribution must be restricted to prescription use. There has been a tendency to make claims in the labeling of these drugs based upon very scanty clinical information or upon the basis of unsupported animal investigations. While these representations, of course, are advanced only to the profession, nevertheless, they may be false and misleading within the meaning of the statute. Indeed, the Food and Drug Administration has no hesitancy in taking legal action in such instances on the theory that physicians in general can be misled with regard to the claims for new drugs because their general professional knowledge is not sufficient to permit them to appraise them critically. Such a possibility is usually indicated to the applicant at the time his application is permitted to become effective. If the claims appear to be highly unwarranted, the Food and Drug Administration may actually undertake laboratory and clinical investigations, the results of which may be used in a legal action against the product or shipper. Therefore, the wise distributor of a new drug will restrict his claims to those supported by existing adequate scientific evidence, leaving others to be first sustained by further investigation. His new drug application can always be amended to incorporate labeling changes when the evidence warrants it.

ADVERTISING AND THE NEW DRUG SECTION

Nor should the advertising of the drug—as distinguished from its labeling—contain claims, express or implied, regarding the extent of its usefulness beyond those contained in the labeling. It is well to remember that one of the regulations adopted for the enforcement of Section 502(f)(1) of the Food, Drug, and Cosmetic Act provides:

> No exemption under any provision of this regulation shall apply to any shipment or other delivery of: (1) a drug if its advertising, disseminated or sponsored by or on behalf of its manufacturer, packer, or other person responsible for making such shipment or

delivery, contains any representation not borne by its labeling and which, if so borne, would make it a new drug. . . .

Claims presented in the advertising of an effective new drug which do not appear in the labeling submitted with the application, may misbrand the drug under Section 502(f)(1) of the Act on the ground that it does not bear adequate directions for use for all of the conditions for which it is advertised. Furthermore, the effectiveness of the application may be jeopardized under Section 505(e)(2) of the Act because of the regulation reading:

> Among the reasons why an application may contain an untrue statement of a material fact are changes in: (1) conditions of use prescribed, recommended, or suggested by the applicant for the drug from the conditions of such use stated in the application. . . .

Thus, if the representations made in advertising differ in a material respect from those contained in the effective application for the product, the effectiveness of the application is subject to suspension.

It is important, therefore, to scrutinize all advertising in the light of the representations made in the labeling submitted with the new drug application. As new claims appear justified by the evidence, steps to amend the application already on file with the Food and Drug Administration should be taken.

MODIFICATIONS OF FORMULA AND CLAIMS

As a new drug becomes widely used by the medical profession, it may become desirable to market additional dosage forms. It is not always possible to predict the most convenient form in which a new drug may be administered, and general use by the medical profession may reveal the need for elimination of certain forms and addition of new ones. Similarly, experience may show that the drug is unstable under certain storage conditions or that it is incompatible with other drugs or substances with which it may be compounded. Any of these circumstances may necessitate a revision in the formula for the product.

Whenever any material revision in formula, method of man-

ufacture, method of distribution, or labeling representations becomes necessary, the effective application for the product must be supplemented by the filing of full and detailed information on the proposed change. If the proposed variation does not make the drug unsafe and is otherwise acceptable, notification of the effectiveness of the supplemental application is usually quite prompt. On the other hand, in case of an unacceptable change the applicant will be so advised and must, by means of adequate scientific evidence, convince the Food and Drug Administration of its propriety.

Submission of information as a basis for altering the conditions under which an application becomes effective should be done by a formal amendment. The new drug application form may be used and only the information which differs from that submitted with the original application need be included in the amending application.

SUSPENSION OF AN APPLICATION

Even the most careful investigations may fail to uncover potential serious toxicity in the new drug. This may be due to the inadequacies of the scientific methods available at the time the application was considered. Perhaps only long-continued clinical use of the drug, not practicable in the preliminary investigations, will reveal these toxic potentialities. Under such circumstances, the Federal Security Administrator affords the applicant a hearing at which the facts are developed, permitting a decision to be reached whether or not to suspend the effectiveness of the application.

Another basis for considering suspension of an application is the discovery of adverse effects by methods which, although known at the time the application was filed, at that time were not considered reasonably applicable to the product. This might have been due to the unavailability of some particular apparatus, or the discovery of a new application of an old test. Obviously, the Administrator must find that this test is valid,

and that a significant degree of toxicity is demonstrated through its use, before ordering suspension.

An application may also be suspended because of an untrue statement of a material fact. This applies to statements which were untrue at the time they were made, *i.e.,* inadvertent or deliberate falsification in the application. It also includes statements which, although true at the time the application was filed, are no longer true, due to labeling changes, changes in composition of the drug, changes in manufacturing procedures, facilities or controls, or changes in claims made for the product. Labeling changes may include changes in directions for use or warnings, as well as changes in claims. Changes in claims need not necessarily occur in the labeling, but may be made in the advertising and result in an alteration of the status of the drug under the provisions of Section 505. It seems likely that to be "material" the variation in such "facts" would have to be shown to affect the safety of the product adversely.

Suspension proceedings are similar to those for refusals. A hearing is accorded the applicant and the right of appeal from an adverse decision is reserved to him. Furthermore, the burden of proof rests with the Government in a suspension proceeding in that it must prove the altered circumstances or untrue statements adversely affect the safety of the drug. This rule differs in refusal proceedings; there the applicant is required to offer affirmative proof of the safety of the drug.

CONCLUSION

The new drug provisions of the Federal Food, Drug, and Cosmetic Act affect every distributor or manufacturer of drugs. A knowledge of their provisions is necessary for the proper conduct of a pharmaceutical business. Although the Federal statute applies only to drugs which will move in interstate commerce, eleven States, California, Connecticut, Florida, Indiana, Missouri, Nevada, New York, New Jersey, North Carolina, Tennessee, and Washington, and New York City have statutes dealing with the distribution of new drugs. In general, they are pat-

terned after the Federal law but provide that if an application is effective with respect to a new drug under the Federal statute, it is automatically effective under the State statute. The provisions in such laws regarding distribution of new drugs for investigational use are also similar to those of the Federal enactment.

14

Biologic Control Regulations

WALTER E. WARD

THIS chapter is written for the sole purpose of giving a general picture of biologic control regulations as these apply to materials designed for human use. Only a brief reference will be made to veterinary biologics. From the title of this chapter it might be concluded that all prophylactic or therapeutic products which result from biologic activity and are intended for human use should be included for consideration. Such an interpretation would result in a discussion of very wide scope. The contents will be restricted, therefore, to those products covered by the Federal biologics law. No attempt will be made to deal specifically section by section with this law. With an understanding of its purpose and an understanding of its coverage the reader will be able to refer directly to regulations for fine detail.

ORIGIN OF REGULATIONS

The original biologics law was enacted by the Congress at the request of a group of physicians in the District of Columbia. Their plea was for an improvement in the quality of products offered for sale in that area. The resulting law which became effective July 1, 1902 met this specific request but in addition it was given a broader coverage so as to include these products whenever offered for sale, barter, or exchange in interstate commerce or for export. It is understandable that, since the original request for control regulations came from physicians, the responsibilities for carrying out the enacted requirements was placed under the responsibility of physicians in the United

States Public Health Service. The law of 1902 was re-enacted as of July 1, 1944 as a part of a recodification of all the laws and responsibilities pertaining to the Public Health Service. The re-enactment did not alter the purpose of the law. Much excellent work has been done by the Service in the past few years in clarifying general sections of the regulations and in reviewing and revising certain advisory information allowable under the law.

PRODUCTS INCLUDED UNDER REGULATIONS

The products covered are any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of disease or injuries of man. Arsphenamine or its derivatives (or any other trivalent organic arsenical) were initially included because of an emergency which developed when they first began to be manufactured in this country. These products have remained under biologics control although technically they do not belong. However, practically such an arrangement has been most satisfactory.

PREREQUISITES FOR MANUFACTURER

The law requires that these products may only be offered for sale, barter or exchange in interstate or export commerce provided they have been produced in an establishment holding an unsuspended and unrevoked establishment license. The license and individual product licenses may be issued only upon a showing that the establishment and any product for which a license is desired meet minimum standards designed to insure the continued safety, purity and potency of such products. These standards are issued as advisory regulations prepared jointly by the Surgeons General of the Army, the Navy, and the Public Health Service. These regulations are designed to be scientifically sound and in general removed from complexities of arbitrary bureaucratic interpretation. To further insure soundness during the preparation of any regulations the prob-

lems involved are fully discussed with persons within the licensed laboratories and with any others who are thought to be in a position to offer helpful advice. Such information is not planned to include manufacturing procedures. In certain instances specific procedures are prohibited only because long experience and scientific evidence clearly shows them to be detrimental to the continued safety, purity and potency of a product.

ENFORCEMENT AGENCY

From the beginning the Congress placed the enforcement of the law in the hands of the National Institute of Health, or its predecessor, the Hygienic Laboratory. This institution, a division of the United States Public Health Service, is engaged in scientific research in those diseases for which the products specified by the law are intended to be used. It is natural, therefore, that the wording of the regulations and their enforcement should be on a scientific level rather than a purely legal basis. The Institute has been exceedingly careful of the license and has recommended an establishment for license only after careful consideration. Once this has been done the scientific staff of the licensed establishment is accepted on the same level as members of the Institute; *i.e.,* as scientists whose objective it is to make the best possible product. Any information of a nonconfidential nature is freely exchanged between the manufacturer and the Institute. Problems involving personnel, laboratory management, and production and control are freely discussed with the first consideration being the production of a biologic which will afford the user the greatest therapeutic result and without risk. Honest and well-informed scientists within the industry and the Institute are of the same mind and thus the final decision falls on the Institute staff only when there are differences of procedural opinion. The Institute's greatest function is to act as an impartial check or control laboratory and referee. Perhaps some would feel that the Institute serves an important function as an additional safety check for the public—

in practice this is true but this comes in the natural course of its obligations.

DEFINITIONS

There are two basic definitions or interpretations which the three Surgeons General have placed in the regulations in order to make clear the full scope of the law.

The meaning of the words "virus, therapeutic serum, toxin and antitoxin" are generally well understood and though they are further defined in regulations they scarcely need elaboration in the present discussion. However, the words "or analogous products" do require detailed definition and this the regulations provide in the following language:

A product is analogous

(*a*) to a virus if prepared from or with a virus or agent actually or potentially infectious, without regard to the degree of virulence or toxicogenicity of the specific strain used.

(*b*) to a therapeutic serum, if composed of whole blood or plasma or containing some organic constituent or product other than a hormone or an amino acid, derived from whole blood, plasma, or serum and intended for administration by a route other than ingestion.

(*c*) to a toxin or antitoxin, if intended, irrespective of its source of origin, for the prevention, treatment or cure of diseases or injuries of man through specific immunization.

Finally, the word "applicable" in the phrase "—applicable to the prevention, treatment, or cure of diseases or injuries of man" must be defined. The definition in the regulations states that a product is deemed "applicable" irrespective of the mode of administration or application recommended, including use, when intended, through administration or application to a person, as an aid in diagnosis or in evaluating the degree of susceptibility or immunity possessed by a person; and including also any other use for purposes of diagnosis if the diagnostic substance so used is prepared from or with the aid of a biologic product.

The foregoing definitions give a fairly clear but somewhat

involved interpretation of the products covered by the law. The definitions necessarily become involved in order to throw a line of demarcation around products which lie close to the borderline of biologic origin. For example, allergenic extracts are not biologics on the basis of origin but they are included within the biologics law because they are analogous to a toxin in that they are used to build up a specific immunity. Antibiotics are not included within the law. They are not toxins and are not analogous to a toxin since they act only as direct bactericidal or bacteriostatic substances and not through an immunity stimulated in the host following their injection, such as is required of toxins or products analogous to a toxin.

It is also possible to visualize a single substance in one condition of usage as being subject to regulation while, when labeled specifically for other use, not being subject to regulation. It is known that certain constituents normally found in human plasma may be given parenterally to great advantage in defined instances. Such a product is of course definitely subject to regulation. However, some work now seems to indicate that this same protein may also be of distinct value when fed orally in other instances. In this case the material is excluded from regulation. This possible example is merely cited to further indicate the possible intricacies of the demarcation.

ACTIVITIES OF PRODUCTS

The group of biologic products under discussion are highly specific in their action and beyond this narrow range they have no therapeutic value. An antigen can only train and stimulate the recipient tissues to produce a new compound which in itself is highly specific and of therapeutic value only against the antigen which served as a pattern for specific antibody formation. Subsequent contact with the same antigen raises the level of the defense mechanism by producing more of the same antibody. Against certain antigens, the amount of antibody which can be produced through repeated injections of antigen becomes sufficiently great so that the antibodies may

be used for passive immunization of another animal. This is the procedure followed in the production of antitoxins and immune serums. However, the high degree of specificity of the antibody is retained and it is valueless except as a neutralizer of the antigen which caused its elaboration. Thus tetanus toxoid within a rather wide dose range is capable only of stimulating the formation of tetanus antitoxin. The latter, in turn, is therapeutically active only in combining with tetanus toxin or toxoid. Beyond these narrow limits tetanus toxoid and antitoxin have no value.

This situation can be further illustrated in the case of influenza. Clinically, this disease can be produced by one of several strains of influenza virus. It is definitely known that these strains may be independently different in antigenic composition. Hence immunity is strain type specific. If one could forecast the time of an epidemic and the antigenic type or types to be involved, immunization would be a relatively simple procedure. This type of specificity puts us at an apparent disadvantage, but it will be granted without debate that in the field of allergy one is fortunate that a single sensitizing agent is not capable of producing hypersensitivity to numerous substances. Thus the development of a new biologic product does not offer the wide range of possibilities which are present in the development of a new pharmaceutical mixture or even of chemical compounds having acceptable and useful therapeutic action. There are, for example, many chemical compounds capable of producing a sedative effect and many more will probably be synthesized in the future.

SAFETY, PURITY, AND POTENCY

Having covered in a broad fashion those products which are included under the term "biologics," one must consider the three cardinal principles specified in the law which are necessary in order to adequately protect the public. The law directs that regulations shall be prepared setting up standards designed to insure the *continued safety, purity* and *potency* of such prod-

ucts. Such regulations have been prepared by the three Surgeons General and are available to those concerned. In addition, a supplement to the regulations is issued wherein the storage temperatures are defined and the expiration date for each type of product. The requirements for each individual product necessary to assure continued safety, purity, and potency are not identical. Therefore, interpretations of the meaning of these three requirements as applied to the individual product are issued separately under the general designation of "Minimum Requirements." These are similar in form and scope to the individual product monographs appearing in the *United States Pharmacopoeia.*

The word "continued" as applied by the law to the safety, purity, and potency of the product is interpreted to apply exclusively to the dating period, and only if the product has been stored under the temperature conditions designated in the regulations and the dating decisions. In general, a wide margin is allowed by the expiration date and the storage temperature in order to assure that safety and potency will remain at a proper level throughout the dating period. Naturally, the period varies with the products. Citrated whole human blood can have a dating period of only twenty-one days whereas many products packaged in the dried state are given a five-year dating period, and some probably could continue several times as long.

The word "safety" is interpreted to apply to the relative freedom from harmful effect to the recipient when a product is prudently administered, taking into consideration the character of the product in relation to the conditions of the patient at the time. There are several factors involved in safety. Sterility is perhaps the most frequently thought of in this connection. While everyone will agree that absolute sterility is desirable yet practical experience has shown that this is impossible unless the product can be sterilized after sealing in the final container and adequate heat applied to assure the killing of all contaminants. None of the biologic products can be treated in this way. Neither can all of the final containers be

used for the sterility test. Practical experience has shown that a requirement for sterility which falls short of guaranteed absolute sterility will adequately protect the patient. This is accomplished by making every effort to keep the product free from any pathogenic bacterial contamination during processing and then, in general, requiring a sterility test on at least the volume recommended as the individual injection. This is taken from final containers picked at random from fillings coming from each bulk container. Even this requirement is impossible in some instances as, for example, normal human plasma where the individual human dose may be as much as one and even two liters. In the case of citrated whole blood and resuspended red cells it is believed by all concerned that sole reliance on the selection of the donor, good collection technic, sterile equipment, the processing technic, and the final appearance of the product is a better safeguard than would be the case if reliance were placed chiefly on a sterility sample withdrawn from the final container. The latter procedure would add an additional contamination hazard because of the need to break the seal on an otherwise unopened bottle.

The absence of pyrogenic substances is also related to safety. As is well-known, pyrogens are substances of micro-organism origin and result chiefly from contaminants getting into the product during processing. But this is not always the case. The organism required for the production of the biologic—as, for example, the typhoid bacillus—is very pyrogenic. The result is that typhoid vaccine is exceedingly pyrogenic and, as a matter of fact, is often used solely for the purpose of inducing fever. In general, it is a good rule to require all products intended for intravenous injection to be pyrogen-free within the limits of the pyrogen test. Products intended for subcutaneous or intramuscular injection should at least be free of pyrogens wherever practicable in the dose recommended even though the need is not so urgent as in the case of intravenous preparations. Actual experience has shown that the substantial elimination of pyrogens during production is not a difficult matter provided good production methods are used along with intelligent supervision.

There is another factor of safety in connection with biologic products, but one which is entirely related to the individual patient. This has to do with the sensitivity, or allergic state, of the patient. Practically all biologics contain protein and in some the protein is of a type particularly liable to cause allergic reactions. Some years ago tetanus and diphtheria antitoxin, both horse serum products, were notorious for resulting in hypersensitivity reactions. However, further research demonstrated that these reactions could be reduced by appropriate chemical treatment of the serum. The final removal of allergenic fractions from heterologous serum is yet to be accomplished. Thus far, products propagated in the chicken egg still retain allergenic proteins which, if injected into a person suffering from asthma of chicken egg, meat, or dander etiology, may result in tragic reactions. Nevertheless, it would not be justifiable to prohibit the manufacture and sale of such products. Their wide field of usefulness is greater than the potential hazard.

The toxicity of biologic products is an additional consideration regarding safety of a product. By "toxicity" is meant the appearance of untoward reactions following administration of the biologic. The cause for such reactions is frequently very difficult to discover. As an example it has been known for some time that some pertussis vaccines produce toxic reactions in the form of local soreness and systemic temperature elevation in a fair percentage of children. The entire causes for these phenomena are not fully understood but it is known that the pertussis organism does contain toxic substances and these are responsible to some extent. It is also known that these toxic substances can be rendered less toxic by suitable means. However, there is an apparent relationship between antigenicity and the presence of some toxicity. In other words it is possible to make a completely non-reacting vaccine but its efficacy for immunization may be in doubt. A great deal of work is in progress on this problem at the present time and there is every indication that before long all marketed pertussis vaccines will have a certain minimum toxicity with respect to antigenicity.

The matter of toxicity is also related to the combination of immunizing agents into a common mixture. In the first place it must be remembered that there is only value in preparing a combination which is practical. Such a combination includes only those antigens of disease-producing agents to which the individual is likely to be exposed. Thus, to immunize a child against both diphtheria and pertussis by a mixed diphtheria toxoid and pertussis vaccine is logical since both diseases are common in children. Further, such a combination can be made which will not produce untoward toxic symptoms. Tetanus toxoid can also be added to the above combination so that a child can then be immunized successfully with a maximum of three injections against all three diseases. Without such a combination a minimum of six injections would be necessary. In addition to the convenience and practicability of such combinations, there is evidence that per given amount of each antigen in the mixture the presence of others increases the immunizing capacity of the product. However, there are obvious limits to the use of combinations but, as more research is done and as antigens become purer, the theoretical limits are increased.

Other factors of safety as applied to the protection of the general public are the keeping of complete production and distribution records and labeling. These items will be discussed later.

The word "purity" as used in the law is interpreted to apply to the relative freedom from extraneous matter, whether harmful to the recipient, deleterious to the product, or otherwise in the finished product. Unfortunately, biologic preparations with a very few exceptions are not pure compounds. The active antigen in diphtheria toxoid is only a portion of the total solids present, and the essential virus in rabies vaccine is as nothing compared to the amount of brain tissue present. Even in the highly refined antitoxins, or antiserums, where the protein present is almost exclusively gamma globulin, it is probable that not all of it is linked to the immune radical. Great advancements have been made and with present knowledge much

more could be and is being done. However, production costs must be considered along with any benefits derived by the patient through greater purity. There is need only to mention in passing that biologic products must be free of all deleterious impurities of an entirely extraneous nature.

The third and last word specified in the law is "potency." As defined by the regulations, this is interpreted to mean the specific ability or capacity of the product to effect a given result as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended. It should scarcely be necessary to say that both the physician and the patient have a right to anticipate the prophylactic or therapeutic response from the use of a product which competent investigation has shown to be possible. To accept a product for license and to offer it for sale without the support of such evidence would, justifiably, leave the National Institute of Health and the manufacturer open to the most severe criticism from the physician and the public. Obviously, the amount and quality of either laboratory or clinical data which can be secured for the different products vary widely. Both the laboratory and clinical data supporting such products as yellow fever and smallpox vaccines, tetanus and diphtheria toxoids, and diphtheria antitoxin are of a character which can leave no doubt as to the ability or capacity of these products to effect the result claimed for them. They are as nearly perfect as can be obtained through the use of any known drug. Unfortunately, many biologics do not lend themselves to results of this high order. Many are moderately good and others are exceedingly poor, if not valueless. It is in the last category where differences of opinion exist and where honest criticism is leveled at the National Institute of Health by the public for permitting license in the one instance and by the aggrieved manufacturer for refusing license in the other.

What is to constitute acceptable evidence with these controversial products? If the use of the product were left entirely in the hands of the physician, serving either as public health official or as private clinician, the matter probably would

resolve itself. However, other influences and motives will not permit the answer to the question to be developed so easily.

In examining data presented to support the requirement of potency it would seem logical if the National Institute of Health placed the evaluation on several factors. Briefly stated, these should include the plan of study followed in developing the product. Was it adequately controlled, by whom conducted, and what was the investigator's connection with the future of the product or with the manufacturer, were the findings accepted for publication and, if so, what is the scientific standing of the publishing journal, were the initial findings confirmed by disinterested investigators, and, finally, does an independent examination of the claims for the product agree with well established scientific principles of the basic science involved? Unfortunately, not all data are acceptable evidence. There is much in published scientific literature which is written in an ink of confusion and inadequacy which fades rapidly on critical reading.

Even with the scientific knowledge necessary to insure that each and every lot of each product can be manufactured to insure *continued safety, purity,* and *potency* there are bound to be opportunities for errors. As insurance against the latter it is required that clear records be kept so that production procedures and the results of all tests on any lot of material can be examined. This is an excellent safeguard for the public and also a fine opportunity for the manufacturer to follow the success of each production lot.

LABELS

Each product must be ultimately put into a final container package for marketing. Such a container must be carefully labeled so that the physician is advised of the contents and its proper use. It is of obvious advantage to have standard names for each licensed product so that the physician can obtain a product by name irrespective of the manufacturer. Provisions are also made to allow the use of trade names so that a manu-

facturer does have some means of distinguishing the material of his manufacture. Since each physician cannot be expected to know the essential details of each biologic he is called upon to use, further information must be given. The enclosure or direction sheet accompanying each final container package serves this purpose. This enclosure is looked upon as being part of the label and should be limited in subject matter to:

(*a*) the name of the product;
(*b*) the composition of the product;
(*c*) a brief statement about the method of preparation;
(*d*) reference to scientific literature reports with particular attention to all views where the value of a product is controversial;
(*e*) dosage recommendations and method of administration in greater detail than label space will allow, and
(*f*) precautions as to use.

This type of enclosure can be very helpful to the physician.

The kind of container used may to some extent be important, dependent upon the product. At least this is a factor in certain continued potencies. In addition, there must be limitations on the container size based on human dosage since it is not reasonable to expect repeated entry into a container to be free of possible contamination.

FURTHER DETAILS OF LICENSING

The broad principles underlying the biologic control regulations have been discussed. If the reader should desire to make application for an establishment license it is generally accepted that such a request is based upon plans to manufacture some specific product. The physical facilities and equipment needed to produce tetanus antitoxin differ greatly from those necessary for a simple bacterial vaccine. In the former instance animal stables, bleeding and injection stalls, antitoxin purification space and equipment, and proper quarters for toxin production are minimum requirements.

In view of the above facts it is reasonable that the establishment and initial product applications should be made simultaneously. The desired information on the product application is essentially a brief description of the methods and equipment to be used in the manufacture of the proposed product. If the initial applications are in order the regulations then provide for inspection of the establishment by a qualified member of the Institute before the establishment license is granted.

There may be some feeling on the part of a prospective manufacturer with regard to disclosing details of a method. However, the Institute staff are highly ethical scientists so there should be no need for concern. Presumably such information is confidential according to the general terms of the regulations. However, certain exceptions are included, the meaning of which might be somewhat flexibly construed. There is, of course, no reason to believe that this would ever occur.

ENFORCEMENT OF REGULATIONS

Little has been said thus far regarding enforcement of the biologics law. It must be emphasized that the National Institute of Health is entirely a scientific institution and not a police agency. There are provisions in the regulations which require that each licensed establishment be inspected each year. This inspection usually serves as an opportunity for the friendly exchange of ideas between the scientific workers in the manufacturing laboratory and the representative of the National Institute of Health. The inspection itself is thorough but done in the spirit of a desire to improve the products of the manufacturer so that better and better products are available.

There are penalty provisions in the law itself for noncompliance. In general, individual product licenses or establishment licenses may be suspended or revoked, if, after due warning, the manufacturer fails to conform to regulations which insure the continued safety, purity, and potency of any or all products. There must in this connection be provisions for hearings and these are adequately provided. There are also

provisions under the United States Public Health Service which make it possible to remove incompetent members of the licensing agency.

VETERINARY BIOLOGICS

Veterinary biologics for domestic animal usage are covered by regulations similar to those embracing human biologics. The veterinary regulations are defined in the Virus, Serum, Toxin, and Analogous Products Act of 1913. This law is administered by the Bureau of Animal Industry under the United States Department of Agriculture. The licensing and operation of a veterinary establishment is in all respects similar to those procedures already discussed for human biologics. Further details of this law appear in a previous chapter.

15

Drug Certification

WALTON VAN WINKLE, JR.

IN an increasing number of instances, the manufacturer of a new pharmaceutical, particularly in the category of antibiotics, must concern himself with the certification of the product as to its identity, quality, or potency. The term "drug certification" is customarily applied to the examination and confirmation, by an agency other than the original producer, of batches of a drug, to verify their suitability for use. It differs from the "new drug" procedure—and parenthetically from Council-acceptance—in that it constitutes more or less a continuous process, concerned with individual batches rather than the preparation in general.

Although any authoritative group may, in theory at least, certify to the safety and efficacy of a drug, at present only the Federal Government—specifically, for the purposes of this discussion, the Federal Food and Drug Administration—performs this function, and then only in the case of certain types of substances, as we have observed. Obviously, in order that any system of certification provide the maximum protection against adulteration or misbranding for both the producer and the consumer, the agency charged with issuing the certificate must not only be competent but also independent and unbiased as well. The Food and Drug Administration has these qualifications.

To substantiate this last remark, it must be recognized that the concept of certification is not altogether new, despite its comparatively recent application to some classes of pharmaceuticals. Indeed, it is a development of over forty years standing. Thus the practice of certifying batches of coal-tar colors

originated early in the enforcement of the Food and Drugs Act of 1906. It is true that the statute contained no express provision for the certification of such dyes. Section 7 of the law, however, provided that foods would be considered adulterated if they contained any added poisonous or deleterious ingredient which might render the product injurious to health. In addition, authority was extended to prevent economic fraud in food products through means of coloring and staining. And in the case of confectionery, the statute bore a specific prohibition against poisonous colors and flavors.

Upon this slender legislative frame, the Department of Agriculture, as early as 1907—the year the law became effective—adopted a series of regulations and rulings to provide means of insuring the availability of colors safe to use in foods. This regulation, in fact, may be considered as the forerunner of all certification procedures now in force under the Federal Food, Drug, and Cosmetic Act.

The first step taken in inaugurating coal-tar color certification was to set up a list of *acceptable* dyes deemed safe and suitable for use in food products. Although this, in itself, marked a radical departure from previous practices, it was recognized that no assurance of freedom from toxic properties was possible unless the batches actually manufactured were certified as complying with the specifications of the permitted dye. Thus certification served as a verification of the manufacturer's processing of the coal-tar intermediates; it squarely met the ever-present problem of inaccuracies in compounding and treatment, of insufficient controls that permitted the encroachment of impurities, such as arsenic and lead, and of the other types of contamination that frequently rendered such dyes unsafe.

The certification procedure, as outlined in Food Inspection Decisions 76 and 77 (1907), encompassed the filing of affidavits by the manufacturer and his chemist, reciting tests that had been followed to establish the identity and purity of a particular batch of coal-tar color. These documents were submitted to the Bureau of Chemistry, the agency within the Department of Agriculture at that time enforcing the statute. Upon con-

firmation of the results reported in the affidavits by the Department's analyst, a lot number was assigned to identify the batch, which then became known as a "certified batch." Use of the color permitted the manufacturer to list on his label the statement "CERTIFIED COLOR," which soon acquired valuable consumer connotations.

It must be borne in mind that the entire system of certification, during that period, was on a voluntary basis. No legal compulsion existed that a certified color only be employed in foods. Indeed, where it was found that the dye contained deleterious substances, it was necessary to prosecute under the general adulteration provisions of the law. This has been changed in the present enactment; the use of a certified color, with rare exceptions, is a requisite to the product's legality.

COAL-TAR COLOR CERTIFICATION

The Federal Food, Drug, and Cosmetic Act now in force gives considerable implementation to the administrative practices relative to coal-tar color certification developed under the prior statute. As we have already noted, the voluntary features of the procedure have in the majority of cases been supplanted by the statutory requirement that only certified colors be employed in the preparation of foods, drugs, and cosmetics subject to the Act. So far as drugs are concerned, the only exception are coal-tar dyes intended *other* than for purposes of coloring only. This includes such drugs as methylene blue, acriflavine, scarlet red, and mercurochrome, which therefore need not be certified before use.

It frequently happens, however, that coal-tar colors are added to drug products for purposes of coloring only. These substances, of course, are required to be one, or more, from the list of dyes permitted to be used in drugs. In addition, they must be drawn from a batch that has been certified in accordance with the requirements of the Coal-Tar Color Regulations.

The procedure governing the addition of a new coal-tar color to the list of permitted colors and the process through which the

manufacturer must go are both complicated and drawn out. The double criteria of suitability for use and harmlessness for the purposes intended must first be met. This calls for extended pharmacological tests, somewhat analogous to those at times pertinent in "new drug" investigations. The color, once proved acceptable, is then added to the permitted list by amending the Coal-Tar Color Regulations; the procedure is prescribed generally in Section 701(e) of the statute, supplemented in detail by the regulations already issued.

Similarly, the practice of certifying batches of the dye is hedged with safeguards to assure the maintenance of its identity, purity, and freedom from contamination. Rigidly maintained sampling procedures are fixed by the regulations; data to be furnished the Food and Drug Administration in the request for certification are likewise specified. The certificate is issued only after the Administration's analysts have verified that the particular batch meets fully the required specifications of the color. The manufacturer, moreover, is called upon to maintain adequate records of the color's distribution and use; indeed, failure to do so may result in the termination of the certificate's effectiveness, and, in some instances, the withdrawal of certification service. Finally, it should be remembered that the labeling requirements of a coal-tar color differ somewhat from those imposed on the usual food and drug under the Act; and hence must have particular attention.

INSULIN CERTIFICATION

It is not perhaps commonly known that Banting's work in the field of insulin was patented by the University of Toronto. Licenses to manufacture the drug were conditioned on the assaying of each batch of insulin, and other forms of pre-distribution control. The patents expired on December 23, 1941; such control, of course, could not be continued or enforced.

The situation thus raised focused the attention of the Food and Drug Administration on the question of applying the certification procedure to a drug wholly unlike substances previously

subject to regulation. It was recognized that the health and well-being of diabetics made it essential that a drug of standard potency be assured. Nor did it seem feasible to rely upon the recognized enforcement methods contained in the law.

Because of the importance of the situation, the Congress was asked to amend the Federal Food, Drug, and Cosmetic Act to provide for the examination and certification of each batch of an insulin-containing drug by the Food and Drug Administration. So pressing was the matter, that the Congress acted, for once, with alacrity. The bill passed both Houses and, with the signature of President Roosevelt, became law—all within four days of its introduction. The amendment was designated as Section 506 of the statute; in it is found the first real provision governing drug certification.

The regulations promulgated under Section 506 of the Act have established the pattern followed in later certification regulations. It should be noted that the Insulin Amendment, and the regulations thereunder, could not be patterned after the coal-tar color provisions of the Act because of the difference in the uses to which colors and insulin are put. For example, in the case of colors, the certification is designed primarily to prevent the distribution of harmful dyes. The certification of insulin, however, is necessary to insure not only a safe but also a potent product.

PENICILLIN CERTIFICATION

The discovery of penicillin and the methods by which it could be produced on a large scale came at what might be considered a most opportune time. The enormous battle casualities of World War II were to be materially reduced by the application of this antibiotic. But the circumstances posed two problems. One, it became imperative that the armed forces be furnished with adequate supplies of this medication. The relative novelty of its nature and processing, however, made any large-scale production difficult. So, too, the vagaries of production, the instability of the product, and the many other un-

known factors called for some form of pre-distribution control by an agency not under the control of the producers.

Initially, it was thought that the provisions of Section 505 of the Federal Food, Drug, and Cosmetic Act, dealing with new drugs, might be interpreted to provide the requisite type of control. Indeed, at the time the first new drug applications for penicillin were allowed to become effective in 1943, applicants were notified that their continued effectiveness were conditioned on the submission of samples from each batch of penicillin to the Food and Drug Administration for examination. Although the legality of this requirement was never challenged, it cannot be denied that it rested on a rather tenuous basis.

It was the purchasing specifications of both the Army and Navy, however, that crystallized the requirement that all batches be examined and passed by the Food and Drug Administration. These specifications also set up minimum standards which the penicillin was to meet before acceptance. Here, therefore, was a form of certification in which the purchasing agency authorized another to carry out the procedure.

The practice thus instituted virtually insured that all penicillin would be subject to pre-distribution control since production of the drug was so limited that the greater portion of it was taken by the armed forces. Under this arrangement, however, the Government bore the cost of certification, whereas the Federal Food, Drug, and Cosmetic Act provided that the cost of certification of coal-tar colors and of insulin be paid by the manufacturer.

Early in 1945 it became evident that penicillin production would soon be ample to supply not only military needs but in addition all civilian requirements, and, in fact, permit considerable quantities to be set aside for export. Indeed, the end of the war in Europe so reduced military procurement that the major portion of each month's production was diverted to civilian use. In consequence, it was obvious that Army and Navy purchasing specifications no longer would serve to protect the bulk of the penicillin produced. The Food and Drug Adminis-

tration's certification of all batches prior to distribution would accordingly lapse.

Careful consideration was given the situation. With commendable frankness, the Administration consulted with various trade groups. The conclusion was eventually reached that the vagaries of penicillin production, the difficulty of its standardization, the instability of some batches, and other factors so set penicillin apart from other drugs that, for the fullest public protection, a form of pre-distribution control was advisable. A substantial portion of the industry indicated its acceptance of this view.

Since pre-distribution control could not be established under the existing provisions of the Federal Food, Drug, and Cosmetic Act, an amendment to the Act was introduced in Congress. There was no substantial objection to the legislation from industry. Congress rather quickly enacted the bill into law on July 7, 1945. The amendment was designated as Section 507. One unique provision of the law distinguished it from the Insulin Amendment after which it was generally patterned. The requirement for certification of penicillin-containing products may be withdrawn at the time that the Federal Security Administrator concludes that it is no longer necessary for the protection of the public.

STREPTOMYCIN CONTROL

In the latter part of 1945, streptomycin became available in very limited quantities. This is another antibiotic whose production is complicated to the same extent as penicillin. In addition, it is difficult to free batches from toxic contaminants. It would therefore appear, on the surface at least, that there is as much reason for requiring the certification of streptomycin as there was in the case of penicillin.

But when certification was suggested to the drug industry by the Food and Drug Administration it met with vigorous disapproval. It was argued, for example, that streptomycin, in view of its toxicity, was subject to the new drug provisions of the

Act, differing from penicillin, which had been proved to be safe, bringing it out of the "new drug" category. The provisions of the new drug section, it was submitted, were adequate to provide pre-distribution control of the antibiotic as a new drug, without additional amendments to the Act. However, careful analysis of Section 505 by Administration lawyers convinced them that none of its provisions could be relied on to furnish a true form of continuous pre-distribution control. Of course, during the period in which streptomycin production was insufficient to meet the demand, control had been exercised by the Food and Drug Administration under orders of the Civilian Production Administration; this terminated, of course, with the liquidation of that agency.

The matter was finally resolved by amending Section 507 of the Act to include streptomycin and its derivatives within the same framework of certification applied to penicillin products; this law was approved on March 10, 1947. The procedures affecting penicillin and streptomycin certifications are now embraced in one set of regulations.

PHILOSOPHY OF DRUG CERTIFICATION

Type of product requiring certification. Although it is obvious that the primary purpose of drug certification is to provide the medical profession and the public with drugs which are both safe and efficacious, nevertheless, without certification, the pharmaceutical industry has been accomplishing this same objective successfully for many years. Why, then, is certification of any drug considered necessary? What added benefit accrues to the user when a drug is certified? To understand the law and regulations regarding certification and simplify compliance, an appreciation of the fundamental philosophy underlying certification is essential, particularly as the Food and Drug Administration views it.

It is at once apparent that not all drugs now on the market are in need of certification. Indeed, the present provisions of the law provide adequate protection for the consumer in the

case of most drug preparations. Certification, therefore, would appear to be necessary only under unusual circumstances. It should, moreover, be applied exclusively to drugs differing in important respects from those for which it is conceded that certification is not required.

To justify the imposition of the certification procedure, first of all, a drug must have therapeutic importance. One of questionable value would not be worth the expenditure of time and money for certification, and this is also true of any drug, it is apparent. Indeed, to certify a drug of questionable value would, by the very act of certification, make it appear, under present criteria, to be of extraordinary importance, thus tending to lend official sanction to dubious claims. Moreover, it would not be possible to certify efficacy where the drug could not be demonstrated to be of value in any disease. Therefore, the first requisite to certification is that the drug be possessed of material therapeutic value.

However, therapeutic substance goes beyond a demonstration of the value of the drug in a disease condition. In addition, the control of the particular disease must constitute an immediate and pressing public health problem. The fact that the drug is efficacious only in minor conditions or those which are self-limiting and without serious sequelae mitigates against certification. Furthermore, the disease for which the drug is offered must occur with sufficient frequency and affect a substantial portion of the population. To illustrate, a drug might be efficacious in the control of plague or yellow fever, admittedly serious diseases; it would not, however, necessarily call for certification because neither yellow fever nor plague is a major public health problem in this country.

But not all drugs answering these specifications are in need of control through certification procedures. For example, although the sulfonamides, quinine, and many others meet the tests of drugs having real therapeutic importance, no one has suggested their certification. It is evident, therefore, that still other factors operate in those instances where certification appears justified. One of the most important of these is the pos-

sibility of contamination, or even association, of the drug with advantitious toxic materials. A drug toxic *per se* has predictable actions; but one whose potentialities for harm are due to instability or peculiarities of productions may have unforeseen and unforeseeable effects. The *unpredictability* of toxic effects, then, is one of the principal factors to be weighed in determining the need for some form of pre-distribution control of a drug.

An unstable drug, tending, under certain conditions, to decompose with the formation of toxic by-products, makes it necessary to test each batch for stability. Instability of this character, naturally, assumes more than ordinary importance in a drug having the degree of therapeutic importance discussed in preceding paragraphs. For public protection, in such instances, an independent testing agency should, if it seems advisable, examine each batch of the drug under conditions of distribution and use.

It sometimes occurs that the process of preparing a drug may result in the simultaneous production of deleterious by-products, not commercially feasible to remove. Batches so contaminated, of course, may have to be discarded. The public is afforded added protection if each batch is given another scrutiny by an agency other than the producer in order to be doubly certain that no toxic batch is released into the channels of commerce. This has already proved of value in the case of streptomycin where the Food and Drug Administration has refused release to batches found to be contaminated with histamine-like material, even though the batch was originally approved for distribution by the manufacturer.

Just as the toxicity of a drug preparation may, in some circumstances, be unpredictable, so may its therapeutic effects. Here again, instability or extraneous material may be responsible for such variations in potency. Where the drug is truly important medically, it is imperative that each batch possess the activity claimed on the label at the time of use. The time lost in treating the patient with an ineffective preparation may, indeed, spell the difference between his survival or death. Unpredictability of potency may, therefore, call for the application

of certification procedures on broad grounds of public safety. Further justification may be found when the means for assay of potency depends upon biological assay or procedures of disputed accuracy or upon intermediate methods still under investigation with a view to improvement.

Another factor which must be considered in seeking justification for drug certification is the state of existing knowledge concerning production methods. This aspect is particularly applicable to antibiotic drugs produced by biological processes. Where the methods by which the drug may be most satisfactorily and economically produced are the subject of intensive study, variations in these may be made continually and to such an extent that only occasionally are consecutive batches produced by identical methods. Furthermore, production means proving satisfactory in pilot plant operations may be wholly unsuccessful when applied to large-scale production. Often, in fact, these methods are only developed on the basis of actual experience in full-scale production. The lack of completed knowledge concerning the best means of production may result in product variation requiring careful control of each batch before distribution. Certification provides an independent check on such controls without hampering experimentation on production methods.

Many drugs may be produced with a minimum of special equipment and may be controlled by ordinary laboratory procedures. Others, such as insulin, penicillin, and streptomycin, necessitate special, costly, and complicated installations operated by men especially trained in particular production technics. Furthermore, the control procedures differ considerably from those ordinarily and routinely employed. The development of a drug of true therapeutic importance—particularly if it is unpatentable—encourages many different firms to produce it. If it be one requiring special facilities and technics for its production and control, disastrous results may follow attempts to manufacture it by those inadequately equipped from the standpoint of facilities and personnel. Certification may be justified, under these circumstances, to prevent the entrance

of inadequately equipped and inexperienced firms into the field. Although this would seem to be an unwarranted creation of a monopoly, such measures can be justified on the ground that their object and result is to protect the public health.

From the foregoing discussion, it is readily appreciable that certification procedures are justified only under certain limited conditions and for a very restricted class of products. It is not necessary, of course, that all of the criteria mentioned be met; however, a substantial number of these factors must be present before concluding that the existing safeguards found in Federal and State statutes are inadequate. In sum, where certification is proposed for a drug, it must be examined as to its properties, methods of production, and extent of usefulness and toxicity. Any decision regarding the type of control to subject the product should be reached only on an individual basis. It follows, therefore, that requirements for certification of classes of drugs may not be justified even though a particular preparation in that group may warrant such action.

Relation of certification to new drug section of Federal statute. The relationship of the new drug provisions of the Federal Food, Drug, and Cosmetic Act to drug certification requires examination primarily because of the arguments at one time advanced by some legal representatives of the pharmaceutical industry that the provisions of Section 505 would permit the equivalent of a certification procedure in the case of some new preparations. The contention is based upon an interpretation of paragraphs (d) and (e) of this section. Thus, Section 505(d) provides that:

> If the Administrator finds, after due notice to the applicant and giving him an opportunity for a hearing, that . . . (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality and purity; . . . he shall, prior to the effective date of the application, issue an order refusing to permit the application to become effective.

It was urged that the Administrator could find the facilities and controls to be inadequate if the new drug application did

not specifically state that samples of each batch of the drug would be submitted to the Food and Drug Administration for examination and that the drug would not be distributed until the applicant had been notified that such examination revealed the drug satisfactory for use. If such samples were not submitted prior to distribution, it was argued that the effectiveness of the application could be suspended under the provisions of Section 505 (d)(2) since the application would contain an untrue statement of a material fact.

The legislative history of Section 505 clearly shows that the Congress did not contemplate a continuing pre-distribution control of new drugs when the section was drafted. Furthermore, Section 505 (d)(3) clearly refers to facilities and controls under the control of the applicant and does not extend to controls exercised by outside agencies. In addition, Section 505 is concerned only with the safety of a new drug whereas, as will be discussed, certification implies examinations of a broader scope. In short, the object and philosophy of drug certification clearly extend far beyond that contemplated by the framers of the new drug provisions of the statute.

The Insulin Amendment did not, it should be noted, specifically exempt new insulin preparations from compliance with provisions of Section 505 of the Federal Food, Drug, and Cosmetic Act. By administrative decision, however, the Food and Drug Administration does not insist on an application for new insulin products. This waiver is based on the fact that the requirements for certification duplicate those specified in new drug qualification, going further, in fact, by demanding demonstration of the efficacy of the product. It may be observed that the Penicillin and Streptomycin Amendments specifically exempt these products from the purview of the new drug provisions.

Implications of certification. Certification of a drug by any agency, particularly by the Government, carries with it the obvious implication of "approval" of the product. At the risk of misleading the consumer, "approval" of this nature cannot be given to one attribute or characteristic of the drug and not to all others. Clearly, there would be little point in certifying the

safety of a drug if the certification did not also extend to its usefulness and the claims made on its behalf. Certification must deal, therefore, not only with safety but with identity, stability, efficacy in treating or preventing disease, and claims made in the labeling and advertising. In short, certification must be an "all or none" procedure.

General vs. *product certification.* The amendments to the Federal Food, Drug, and Cosmetic Act, providing for drug certification, have dealt with individual products. However, the question of whether Congress shall be asked to enact new legislation each time a drug appropriate for certification is developed or, on the other hand, whether a general amendment providing for certification of *any* drug when evidence adduced at an administrative hearing shows the need of such measures, has been the subject of much debate. The viewpoint of the Government is well expressed in a letter from the Federal Security Administrator to the General Counsel of the American Pharmaceutical Manufacturers' Association, dated July 19, 1946. It was written in response to a request for a statement of views regarding a proposed amendment to the Act to provide for the pre-testing and certification of new drugs presenting problems similar to those involved in the production and use of insulin and penicillin. The Administrator supported the proposal as necessary to the protection of public health and endorsed it heartily. He pointed out:

> It seemed to me that a general provision for certification of such drugs as insulin, penicillin, streptomycin and new products presenting similar problems would not only be more compatible with the structure of the Act but would be more certain of safeguarding both the interests of the public and of legitimate manufacturers than would a continuing series of specific amendments enacted as each new drug in this category is developed.

The Administrator realized fully that the Government cannot and should not undertake pre-testing services on drugs generally. On the contrary, he agreed that it was to be limited to apply only in the following instances:

(1) to new drugs as that term is defined by the statute;
(2) to new drugs which, like insulin, penicillin and streptomycin, are considered highly efficacious in the treatment of serious diseases that are suffered by a significant number of people;
(3) to such drugs where controls in manufacture and in assaying the finished products present such difficulties and hazards as to make it likely that even the most careful manufacturers will occasionally produce lots failing to meet standards appropriate to safety and efficacy of use.

The important key to the necessity for certification, the Administrator emphasized, is the difficulty inherent in the production and assay of the drug. Thiouracil, for example, does not present such difficulties; hence, it would not be included. Moreover, certification of individual products would be discontinued when technological advances overcome these complicating factors and the public health no longer required pre-testing control.

It was acknowledged that the scope and importance of future developments from investigations of the therapeutic values of substances produced by the metabolism of micro-organisms and other living tissue could not be foreseen. Thus, the commercial production of penicillin was followed in only two years by that of streptomycin. And myriads of organisms remain for study to determine their therapeutic properties. Indeed, the impetus to research in this field by the discovery of penicillin and streptomycin from work on only a few organisms emphasized the likelihood that many spectacularly beneficent drugs will be discovered within the next few years. Nor did the Administrator believe that it would be possible to extend the needed controls to these new products through the new drug section alone, or to provide for the requisite protection to consumers and to legitimate industry through legislative action with respect to each product as it is developed.

Again, the need to apply certification controls might arise while Congress was not in session; even when in session, more-

over, its attention is too frequently preoccupied with other affairs to permit prompt and effective action.

It was not the Administrator's view that pre-testing legislation relieved the drug manufacturer of any responsibility whatsoever. If anything, it emphasizes his responsibility. Nor did he hold that governmental testing is necessarily more accurate than that of the well-equipped drug manufacturers. The point he insisted on was that where the hazards to the control of potency and other factors upon which the safety and efficacy of insulin, penicillin, and streptomycin depend are as great as they are, and where human health and lives are so definitely at stake, a second checking of these drugs before distribution is a minimum of the insurance the public has a right to expect.

Despite the argument presented at length, the drug industry appeared divided on the question. The opponents of the "general amendment" argued that it would be too easy to issue regulations for the certification of drugs for which such control is not essential. They believed that Congress should consider the need for certification of each individual product as the case arises. It was the contention of this group that a "general amendment," as proposed, placed legislative responsibility in the hands of an executive branch of the Government and might thus lead to restrictive and bureaucratic control of the pharmaceutical industry. One cannot be wholly unsympathetic to their arguments.

The proponents of the "general measure," on the other hand, urged that the development of new drugs proceeds so rapidly and the time required to secure congressional approval of legislative proposals might be so prolonged, that serious consequences might ensue during the waiting period. Administrative hearings might be held immediately upon the presentation of a problem permitting decisions to be reached quickly. A greater flexibility was provided for dealing with emergency situations. Precedent for this type of control is contained in Section 404 of the Act which provides for emergency permit control of foods. Another argument in favor of a general amendment was that in congressional consideration of new legislation, extraneous fac-

tors might enter the discussions; thus, a powerful lobby might prevent or promote enactment of legislation. When dealing with questions of public health, attention should be focused on facts and decisions should be made by experts, a situation not always true of legislative committees. Administrative hearings are less subject to outside influences; the legality of their decisions, moreover, are usually subject to judicial review. Furthermore, it is easier to terminate certification under a general amendment when the facts warrant such action; useless laws are not left on the statute books; nor is it necessary to request repeal of amendments by the Congress, as might be necessary under statutes providing for individual product certification. Lastly, repeated requests to Congress for specific amendments to the Act provide an opportunity for the enactment of legislation often promoted by selfish groups and designed to weaken other provisions of the law.

ADVANTAGES OF CERTIFICATION

Consumer advantages. The certification of a drug product by a governmental agency has certain advantages, both to the consumer and to the producer. The most important is obviously the added public protection afforded by certification as compared to the usual methods of drug regulation. Certification is designed to *prevent* the marketing of unsafe or inefficacious drugs. Most of the other regulatory provisions of the Federal Food, Drug, and Cosmetic Act are punitive in nature; they penalize a violator *after* distribution of the drug. Such a system of enforcement does not necessarily prevent serious or fatal consequences from either accidental or deliberate violations of the law. Certification, on the other hand, is more apt to assure that these situations do not occur—a sort of locking the barn door before the horse is stolen.

Another advantage of an indirect nature which may accrue to the consumer is the reduced cost of administration of the entire regulatory program. Although certification itself is far from inexpensive, and is obliquely reflected in the price of the

product, there is less necessity for expensive court actions, or other regulatory procedures against violators of the general provisions of the law. The net saving in the cost of administration of the law that results may more than offset the added expense of certification.

Manufacturer's advantage. An advantage in the interest of the manufacturer lies in the prevention of so-called illegitimate competition. This can be brought about in two ways. Refusal to certify batches of drugs from firms not properly equipped or adequately staffed will bar competition with high quality products by inferior, and perhaps unsafe products. In addition, since certification extends to the representations made for the product, ethical producers do not have to compete with irresponsible distributors who market their product with exaggerated or unwarranted claims. Although this is cited as an advantage to the producer, it is also an obvious benefit to the consumer.

Another advantage of drug certification to the manufacturer is the greatly decreased likelihood of accidental violations of the law with resulting legal actions. Certification implies that the Government has examined the drug and found it is not adulterated or misbranded. The Government, in a very real sense, shares the responsibility for the product with the manufacturer, an advantage worthy of careful consideration.

DISADVANTAGES OF CERTIFICATION

Increased Government regulation. An objection to governmental certification of drug products which has been cited as a serious disadvantage is the increased interference in private enterprise by the Government implicit in such a procedure. Industry, and particularly the pharmaceutical trade, is already under close regulation by various governmental agencies. As a matter of policy, the industry resists attempts designed to increase such regulation. However, the proponents of certification argue that considerations of public health and safety must come first and only secondary consideration can be given to the

wishes of private individuals or firms. The industry counters this by reference to the record of achievement its members have made under less restrictive control.

Time factor. Another objection raised is the time during which the drug must be withheld from distribution after it is produced and before it is certified. This delay creates a storage problem, and, in the case of a scarce item or one subject to seasonal demand, may interfere with its availability when needed. Actually, however, only the storage problem deserves much consideration, and this is not a serious one. Under an efficient administration, certification can be rapid, taking only as long as is required to do the necessary laboratory examinations. Obviously, under an inefficient administration, the time factor might become important, but past performance by the Food and Drug Administration should leave little cause for apprehension on that score.

Cost. Certification is expensive and the cost must be borne either by the Government or by the manufacturer. Certification legislation now in effect provides that the cost be borne by the latter. Although the fees paid by the manufacturer represent the direct cost of certification, there are, however, indirect costs such as the expenses of storage and record-keeping. Both are, of course, added to the price of the product and are paid for by the consumer. Hence, another disadvantage of certification is the increased cost of the drug. Experience has shown, however, that this item does not augment the retail price of the drug by any substantial amount; indeed, the added protection afforded the consumer seems well worth the small addition.

Delay of scientific progress. The most serious criticism which has been leveled at the certification procedure is that it may tend to "freeze" progress. It has been argued that the difficulty of changing regulations or of convincing the administrators of the law that a modified product or new process should be admitted to certification stifles any incentive to make improvements. If this criticism is valid, it certainly depreciates the eventual value of drug certification. However, an examination of the experience under the Penicillin, Streptomycin, and Insu-

lin Amendments shows that this is not so. Thus, globin insulin with zinc has come on the market since the Insulin Amendment was enacted. Furthermore, crystalline penicillin and several new dosage forms of this drug have been developed after the original regulations under the Penicillin Amendment was promulgated. Clearly, in these instances progress has not been unduly hampered, nor has the initiative of the industry been dulled.

In sum, it is believed that a fair appraisal of the advantages and disadvantages of drug certification shows that the advantages outweigh the disadvantages.

MECHANISM OF CERTIFICATION

The Statute. The statutory language used in the three amendments to the Federal Food, Drug and Cosmetic Act is extremely broad. In general, it provides for the certification of batches of products containing the drug in question and empowers the Administrator to promulgate regulations defining terms and setting forth the conditions precedent to obtaining and maintaining certification.

Section 502(k) provides that a shipment or delivery of insulin shall be deemed to be misbranded ". . . if it is, or purports to be, or is represented as a drug composed wholly or partly of insulin, unless (1) it is from a batch with respect to which a certificate or release has been issued with respect to Section 506, and (2) such certificate or release is in effect with respect to such drug." Section 502(l) places similar restrictions on the distribution of penicillin and streptomycin. Since these provisions characterize unauthorized products as misbranded, all the enforcement procedures are applicable, including seizure, criminal prosecution, or injunction. In addition, Section 301(i) prohibits the misuse of any stamp, tag, label, etc., which might be authorized by these sections, or the regulations issued thereunder.

The Regulations. Generally speaking, the regulations adopted deal with the following aspects of certification:

(1) definition of the drug;
(2) mechanism of obtaining or requesting certification, including samples, etc.;
(3) standards of identity, strength, quality and purity;
(4) tests and methods by which compliance with such standards are determined;
(5) conditions placed on the "effectiveness" of certificates after issuance;
(6) maintenance of records;
(7) special labeling requirements;
(8) special packaging requirements;
(9) distribution;
(10) fees.

Any detailed discussion of the different regulations issued under the Insulin, Penicillin and Streptomycin Amendments is impracticable; their frequent amendment suggests the advisability of consulting the current requirements in any particular instance. Since the regulations are based upon the known scientific facts concerning the products, and that knowledge, especially with reference to antibiotics, is in a state of flux, they are subject to constant change to reflect newer developments. In general, however, the regulations follow the pattern shown above.

To assure proper coverage, the regulations must define each product with preciseness. Indeed, a product not meeting the exact definition is not only ineligible for certification, but need not be so processed, at least until the regulations have been amended to include it.

The regulations also provide, in detail, a mechanism whereby manufacturers may request certification, or obtain exemptions when certification is not necessary. They likewise specify the amount of, and manner of obtaining and submitting, representative samples of the product to the Food and Drug Administration. In some instances, forms are provided by the Food and Drug Administration for submission of requests or samples; in

others, the manufacturer makes his request by letter, incorporating protocols of his examination of the batch involved.

The standards of identity, strength, quality, and purity prescribed by the regulations are, it may be noted, the *minimum standards* necessary to insure the distribution of a safe and efficacious product. As manufacturing techniques improve and new scientific discoveries are made, these standards may be raised by appropriate amendments.

Generally, the tests and methods of assay are prescribed in detail in the regulation. Again, these are subject to frequent changes as scientific knowledge regarding the products is increased. It is interesting to observe that the manufacturer is not required to use these particular tests and methods of assay, although his product must be able to meet all the standards prescribed by the regulations when tested by the methods there given. Ordinarily, the tests prescribed are those employed by the Food and Drug Administration.

The conditions under which certificates retain their effectiveness relate chiefly to the expiration date to appear on the label, the alteration of labeling, and the selling or otherwise disposing of the article contrary to the regulatory requirements.

The regulations also specify any labeling requirements not imposed by other provisions of the law or which differ from or supersede the general labeling requirements. Thus, storage, temperatures, expiration dates, caution statements, and similar data may be prescribed as circumstances warrant. In the case of insulin, for example, specific colors for the labels of different kinds and strengths of insulin are prescribed.

In order that the integrity of a certified batch of a drug may be preserved, the regulations provide for some form of sealing of the individual containers so that tampering with the drug, which would cause the certificate to expire, may be detected.

It has been the practice of the Food and Drug Administration to consult with the affected industry in drafting regulations. Often valuable suggestions are received from such conferences; these are incorporated into the regulations. This practice assures the drafting of workable regulations and serves to prevent

the inclusion of provisions which might favor the process or methods of one firm but make it difficult for another firm with a different but equally satisfactory process to meet the requirements of the proposed regulations.

Procedure. In applying for the certification of a new product containing a drug for which certification is required, the procedure is similar to that followed in submission of a new drug application under Section 505 of the Federal Food, Drug, and Cosmetic Act. Besides demonstrating the safety of the product by appropriate scientific evidence, there must also be included in the initial request for certification convincing scientific evidence that the product is efficacious in the conditions for which it is offered. A description of the manufacturing process and controls, together with all labeling, must likewise be submitted. Of importance is a complete description of all methods used to assay the drug and determine its identity, quality, and purity.

In applying for the first time for the certification of a product for which regulations have already been promulgated, information on safety and efficacy usually need be limited only to a showing that the product has the same properties as those products already being certified. However, detailed information on manufacturing processes and controls are required to be submitted; and, of course, sets of the complete labeling are an essential enclosure.

Subsequent certifications of individual batches of a drug are made on the basis of protocols submitted, showing the results of the manufacturer's tests and assays and the total amount of drug in the batch, and the quantities of various sizes or dosage forms made from the batch. After examination by the Food and Drug Administration to verify compliance with the regulations a certificate is issued.

As required by the regulations, a representative sample of the batch must be submitted to the Food and Drug Administration with each request for certification. The regulations usually specify the method of collecting the sample and the quantity to be submitted. Obviously, every precaution should be taken to insure that the sample is truly representative of the batch.

Fees. Fees are assessed for the certification service. Although these are based broadly on the calculated cost of performing the service, they are assessed in different ways, depending on the drug being certified. In general, however, the amount of the fee is proportional to the size of the batch and to the difficulty of the tests which must be applied to the samples. Only experience by the Food and Drug Administration can determine whether or not the fees proposed will be adequate to cover the cost of certification. This is illustrated by the one increase in fees assessed for certification of penicillin when approximately nine months' experience revealed that the cost of the service exceeded the income from fees.

Exemptions. Because of certain trade practices, it is sometimes necessary to provide exemptions from certification under certain conditions. In theory, the final distributor should be responsible for compliance with the regulations. But in practice, the distributor may not have facilities for securing the necessary data; he must rely on the original manufacturer. Even though the manufacturer may be provided with an exemption from certification for shipments to the distributor, he may be required to submit the necessary data for the distributor's application for certification. Again, it is the practice of some firms to store drugs prior to distribution at branch warehouses or at places other than the site of manufacture; storage facilities may not permit them to hold the drug at the manufacturing plant while it is awaiting certification. Exemptions for shipment for storage have been granted in such instances. Some firms merely label or package goods bought from others. Since they are responsible for the certification, it may not be necessary for the original manufacturer to also secure certification; provision may be made for him to ship under an exemption.

Records. Complete records of the manufacture, tests, and distribution of each batch of a drug subject to certification are required to be maintained by the manufacturer. In general, the regulations require that these be kept for a period sufficiently long to cover the usual shelf-life of the article. Provision is

made for inspection of the records by authorized officials of the Food and Drug Administration.

Duration of certification. A batch of a drug is certified only for a given period of time after its production. The time at which a certificate expires is usually based upon the demonstrated stability of the drug under the customary conditions of storage and use. Shipment of a drug, after the certificate has expired, is prohibited by law.

LIMITS OF CERTIFICATION

Fear has been expressed by some persons that the principle of certification will be gradually extended to many more products until finally most, if not all, drugs will be subject to some form of pre-distribution control. An examination of the facts, however, makes this event exceedingly unlikely. Indeed, it would be difficult to justify such a step as either necessary or desirable. The record of the pharmaceutical industry in producing acceptable drugs with a minimum of accidents—possibly preventable by certification—clearly demonstrates that the present controls are adequate, further control being necessary only under unusual and peculiar circumstances.

Based upon the experience with the certification of insulin, penicillin and streptomycin, it would require a staff many times that now possessed by the Food and Drug Administration, together with physical facilities of gigantic proportions, to provide an adequate certification service for just a few of the more important drugs. Thus, the certification of penicillin alone requires a staff of over twenty professional persons and even more technical and clerical assistants on full-time basis. Purely from a practical standpoint, it is probably infeasible to provide certification service for more than a few products. Certainly these should be confined to those falling within the group discussed earlier in this chapter.

It does seem inevitable, however, that additional amendments to the Federal Food, Drug, and Cosmetic Act, to provide for certification procedures, will be enacted. Whether these will

take the form of a general provision to impose certification on any drug when the facts so require, or whether individual amendments relating to specific products will be sought cannot be predicted at this time. The principle of certification, however, appears to be established. Nor can it be denied that, administered wisely, and restricted to products whose characteristics call for this type of control, certification does afford the maximum degree of protection to the public and, incidentally, to the producer, against adulteration and misbranding.

16

Council Acceptance

AUSTIN SMITH

IN another chapter of this volume the factors governing the recognition and acceptance of a new so-called ethical drug preparation by the medical profession are discussed. Foremost among the steps that serve to inspire the physician's confidence in a pharmaceutical is, obviously, its acceptance by the drug evaluating body of the American Medical Association, the Council on Pharmacy and Chemistry, and its inclusion in *New and Nonofficial Remedies,* the publication sponsored by the Council. Nor are the advantages of the Council's seal limited to the doctor's approbation. The druggist is also familiar with the significance of Council acceptance and is predisposed to place considerable reliance on it; hospitals purchasing large quantities of medicinals frequently stipulate that they bear the seal; and municipalities and institutions are inclined to favor Council-accepted brands of drugs.

The logic of applying for Council acceptance of a new drug preparation is clear and unassailable. Essentially, the organized physicians of the United States have, through the medium of their national association, established an impartial organization for the principal purpose of appraising and evaluating the drugs being offered to the medical profession for its use. It is but natural that the average doctor, flooded as he is today with the advertising effluvia of what must appear countless drug manufacturers and distributors, tends to lean heavily on the findings and recommendations of the Council on Pharmacy and Chemistry for guidance. As drugs accumulate complexity of identity and action, moreover, reliance on the chemical, pharmacologic, and toxicological experience and knowledge of the Council's

members has become almost imperative; no one physician, however extensively trained, is qualified to pass on the efficacy and safety of all of the drugs he is today being asked to employ in his practice.

The advantages of Council acceptance to the manufacturer and distributor of drugs do not stop with these considerations. His competitive position against products not bearing the seal of acceptance is, in addition, patently enhanced. His advertisements for the accepted drug are permitted entry into important and respected medical journals. His professional prestige—always a factor of importance in drug marketing—is measurably increased. And not only are his therapeutic claims for the drug more acceptable to the medical profession, but it is also reasonable to assume that enforcement officials will be impressed, in some degree at least, with the fact that they have passed the Council's critical scrutiny.

In the light of the benefits accruing to Council acceptance, it may, with some reason, be asked why all such drugs do not bear the seal of acceptance of the Council. There are several reasons why this point has not been attained. In the first instance, it must be borne in mind that the activities of the Council are critical in nature; as an evaluating body, its recommendations would lose their force were they issued perfunctorily for every drug submitted or to every manufacturer. Thus, those firms whose facilities and controls fall below acceptable standards or whose advertising reeks of unscientific and extravagant claims can not expect to receive Council acceptance for their products. As a matter of fact, one of the Council's principal activities is to expose the latter type of article by giving widespread publicity to the speciousness of the representations under which they are sold.

But even when we exclude this category of drugs from our consideration, it is evident that there still remains a substantial number of preparations which do not find inclusion in *New and Nonofficial Remedies.* Speaking generally, there are two principal reasons why their manufacturers do not participate in this system of impartial drug appraisal and recommendation.

In the first instance, the drug—or its advertising—may be of a type that is not countenanced by, or does not otherwise comply with, the Official Rules promulgated by the Council on Pharmacy and Chemistry. Not only do these rules embrace the general policies that have been laid down to permit consistency in the consideration and evaluation of the articles submitted, and to encourage uniformity in assembling and submitting required data, but they also are designed to effectuate certain principles that must be regarded as basic if the program of the Council is to be of any value. For example, it is unthinkable that a physician be asked to prescribe for his patients a preparation whose composition is unknown to him. Accordingly, the first rule requires that the quantitative formula of the submitted drug be disclosed for general availability. Other rules are similarly concerned with advancing the safety of medicines and their intelligent use and application.

The second reason that may explain why many pharmaceutical preparations have not been presented for Council consideration, although probably of an acceptable character, rests, generally speaking, on inertia; or may be attributed to a lack of knowledge of the procedure and some doubt on the part of the manufacturer as to his ability to comply with the requirements imposed by the Council. It is only fair to admit that the type of information called for in an application of this nature is thorough and searching. Without probative data the Council could reach no conclusion as to the acceptability or lack of acceptability of any preparation. It may also be acknowledged that the more recently required statements regarding controls and facilities tend to increase the task of the would-be applicant.

Nevertheless, this should prove no real obstacle in the case of an honestly promoted product. Somewhat similar data, as a matter of fact, are required in a new drug application under the Federal Food, Drug, and Cosmetic Act, and have not shown themselves to be over-difficult to furnish. Certainly, moreover, it is not unreasonable to ask that a drug manufacturer, producing and distributing a pharmaceutical to doctors, adequately justify his therapeutic claims and similarly establish his com-

petency to manufacture it. Broadly speaking, this is all the application to the Council contemplates.

Other obstacles to seeking Council acceptance are either without substance or have, over a period of time, been met by amendment of the Official Rules. In the first category, for example, is the baseless rumor that an applicant must advertise in *The Journal of the American Medical Association,* or otherwise make a financial "commitment"; this and other false concepts have been dissipated in another chapter. The restrictions formerly placed on the use of protective names, which discouraged a number of applications, have now been raised to meet modern commercial practices. The fear that the Council, in giving publicity to a rejection of the application, may work considerable harm to the prestige of the manufacturer, is no longer completely warranted; for example, articles of questionable eligibility may now have their status determined before a formal presentation. Furthermore, there are many articles not worthy even of derogatory mention and little effort is made to call attention to them unless there arises need for such action; for example, a flood of inquiries because of national promotion of the products.

Lest the tenor of the foregoing remarks give the impression that the Council is actively soliciting the presentation of articles for *New and Nonofficial Remedies,* it may, at this point, be explained that the Council feels that participation in its program is a matter of mutual advantage both to the medical profession and to reputable drug manufacturers. On the one hand, it will continue to give courteous and attentive consideration to the applications of drug firms that are able to meet its standards as formalized in its Official Rules; on the other, it proposes to maintain these standards on as high a level as may be necessary to advance the cause of drug therapy as it has so successfully done for more than four decades.

WHAT COUNCIL ACCEPTANCE MEANS

Probably everyone in the pharmaceutical field is acquainted with the terms *Council acceptance, seal of acceptance, Council on Pharmacy and Chemistry, N.N.R.,* and *New and Nonofficial Remedies.* Yet so familiar have the expressions become that some are apt to lose sight of precisely what is meant by the expressions in actual practice.

Elsewhere in this volume we have observed that the Council on Pharmacy and Chemistry was created in 1905 as a standing committee appointed by the Board of Trustees of the American Medical Association. Its members are eminent in medical fields such as medicine, pathology, and pharmacology; in addition, it is fortunate to be able to enlist the services of a roster of distinguished consultants.

Among its activities, the Council each year publishes an edition of its publication, *New and Nonofficial Remedies.* This volume contains descriptions of preparations and articles which have been examined and accepted by it for inclusion therein. The monographs in the book provide data regarding actions, uses, dosage, tests, and standards of these products. Also included is information concerning official drugs, including those intended for manufacturing use for which there are no formulary standards, which the Council feels is of assistance to doctors. In this last connection, it should be borne in mind that the official compendia are silent as to the therapeutic effects and pharmacological actions of the drugs they describe.

It must be emphasized that acceptance of an article for admission in *New and Nonofficial Remedies* does not imply that the Council recommends its use by the medical profession. Generally speaking, its only significance is that the Council has found that it does not conflict with its Official Rules.

ARTICLES INELIGIBLE FOR ACCEPTANCE

There are broad categories of drugs and pharmaceuticals that are ineligible, for one reason or another, for inclusion in *New and Nonofficial Remedies.* For example, drugs (except biologicals) that have had recognition in either of the official compendia for more than twenty years will not generally be considered. It is assumed that the medical profession has become wholly familiar with the therapeutic uses of such drugs and continued information regarding their actions need not be perpetuated in the pages of *New and Nonofficial Remedies.*

Moreover, until an application has been permitted to become effective for it under the "new drug" provisions of the Federal Food, Drug, and Cosmetic Act, the Council will not accept a *new* pharmaceutical unless it is quite evident that the product will not be barred from introduction into interstate commerce. The reason stated for this attitude is that the Council restricts acceptance to articles that are available on the market.

Also ineligible for inclusion in *New and Nonofficial Remedies* are articles belonging to any class of preparations already rejected by the Council. Of course, where new evidence is available to overcome the previous objections this rules will not necessarily bar consideration. The bibliography index of *New and Nonofficial Remedies* contains a cumulative list of references to reports of the Council specifying drug preparations previously refused acceptance and those on which unfavorable action has been taken; in case of doubt, reference should be made to this enumeration. If doubt still exists, an inquiry directed to the Council office may prove helpful.

Another category of preparations not eligible for acceptance include those advertised to the public which the Council considers unsafe for administration by the general population without medical supervision. Thus far the Council has characterized as safe for public use:

(*a*) antiseptics for prophylactic application for minor injuries of the skin;
(*b*) laxatives not prone to abuse;
(*c*) antacids and analgesics that can be safely used for the temporary relief of symptoms.

But even these classes of preparations may be ineligible if their labeling fails to contain adequate directions for their use and suitable warning against their abuse.

Finally, articles of nonmedical significance or that are not intended for the diagnosis, prevention, or treatment of human diseases are not considered eligible. Thus, a drug designed primarily for veterinarian use does not come within the purview of the Council. Nor do instruments or devices, as such, that do not directly involve consideration of some medicinal or pharmaceutic substance.

The foregoing statement of ineligibility does not, by any means, open Council acceptance to all other articles not listed. As a matter of fact, before submitting any preparation for inclusion in *New and Nonofficial Remedies,* a careful study of the Official Rules should be undertaken to determine whether it qualifies. Where eligibility is questionable, the manufacturer should communicate with the Secretary of the Council to ascertain informally the probable eligibility of the article.

THE OFFICIAL RULES OF THE COUNCIL

The principles and policies of the Council governing the acceptance of a preparation or an article for inclusion in *New and Nonofficial Remedies* have been formalized in seven concise rules. Their very brevity, however, calls for some degree of elaboration and explanation in many cases; otherwise their application might prove difficult and elusive. With this thought in mind, the Council has supplemented the rules with detailed explanations and interpretations. These serve as the basis for the ensuing discussion.

No discussion of the Council's rules, however, will be intel-

ligible unless we emphasize that "acceptance" by the Council of any drug contemplates a continuous process—not merely the status of the article at the time the application is submitted or the preparation adopted, but its handling and promotion throughout the entire period of acceptance.

Composition. The first rule imposes the requirement that the quantitative composition of preparations and articles submitted to the Council for consideration be made known, and that the Council be permitted to publish it. In formulating this rule, the Council has taken cognizance of the fact that intelligent prescribing requires that the physician have access to full information as to the composition of the drugs that he is called upon to use.

Before the enactment of the Federal Food, Drug, and Cosmetic Act, this rule was effective in sweeping away much of the secrecy that afflicted medicines on the market. Today, of course, it has only a minor effect on drugs moving in interstate commerce which are required by the Act to bear a statement of active ingredients on their labels, and, in some instances, a declaration of the amount of potent substances in a given quantity of a mixture. This rule merely extends a quantitative statement to every important ingredient in a mixture.

Similarly, the Federal law calls for a label statement of the "common or usual name" of the drug. The Council, in essence, affirms this requirement by insisting that a definite chemical substance or a mixture must carry a descriptive name satisfactory to the Council on the label and in the advertising. Where the preparation is without a name, or the one submitted is unacceptable, the Council may propose a title for consideration.

The general character of any vehicle, and the identity of preservatives or of any other substance—whether added or inherent as an impurity—must, in addition, be stated if there is any possibility that these may affect the therapeutic action of the preparation. This does not, however, make it necessary to publish the details of the working formula on the label.

The rule is tightened, though, in the case of preparations intended for parenteral administration. These pharmaceuticals

must have declared both the identity and the amount of any preservatives, the statement to appear in the labeling, and preferably on the individual container label of the ampul or vial, although when this is impracticable, the information may be stated on the carton label or individual package insert. By preservative, the Council means any substance employed to preserve the identity, strength, quality, or purity of the solution or combination. Thus, not only are bactericidal or bacteriostatic agents required to be stated in the labeling, but also stabilizers, antioxidants, buffers, and similar chemicals.

Since benzyl alcohol in amounts of one per cent or more acts as a local anesthetic and constitutes a potent therapeutic agent, when present in the preparation this ingredient must be included as part of the name, for example, as "SOLUTION SODIUM MORRHUATE 5% WITH BENZYL ALCOHOL 2%." The Council also requires that chlorobutanol be included in the title of those preparations containing more than 0.5 per cent of this ingredient.

Following the tenor of the Federal law, constituents without effect on the pharmacologic action of the preparation or which have no effect on the tissues of the body need not be submitted in detail; however, their nature and quantity must be disclosed to the Council so that it may judge for itself their inertness. Moreover, the Council may require that they be declared on the label in such a way as to make their nature or purpose evident.

No article will be accepted unless all data required of its composition are fully and truthfully furnished. Deliberately false statements concerning the product forfeits acceptance of the product.

Identification. Identity of any pharmaceutical is, of course, essential to the control of its quality; it is reasonable, therefore, to ask the manufacturer of the drug to furnish comprehensive data on this score. Rule 2 calls for suitable procedures and criteria for determining the composition or standardization of the submitted preparation or article to be furnished.

Where a chemical compound is the subject of the application, this information must broadly include tests for identity, amount,

and purity; for simple pharmaceutical mixtures, however, it may be sufficient to supply only methods for determining the presence and quantity of the potent ingredients. Reference to tests described in standard journals or other authorities may serve in lieu of extensive statements. Such vague and inconclusive phrases as "physiologically standardized" or "assayed" are insufficient, however, and, indeed, are apt to be misleading unless the standard and method have been published in detail adequate to permit independent verification.

Advertising to the public. One of the cardinal policies of the Council is directed at unwarranted lay advertising and is embodied in Rule 3 in a refusal to accept preparations and articles promoted to the public for use in the treatment of disease except in specified instances. This principle reflects established medical opinion that indiscriminate self-medication by the public involves grave consequences such as misdirected and inadequate treatment, failure to recognize serious disease until it is too late for effective treatment, and the spread of infectious diseases which in this way may be hidden from a responsible physician. These dangers to the public are implicit in lay advertising. Furthermore, the practice is subject to further condemnation because, by describing symptoms, it frequently suggests to the minds of people that they are suffering from the disease involved. Thus identified, it may also lead to the unconscious and innocent formation of a drug habit, and, finally, it may institute allergic reactions and develop sensitivities in a relatively large part of the population.

It is recognized, of course, that these objections do not apply with equal force to all drugs. Admittedly, in some instances more good than harm is likely to result from advertisements conveying truthful information, honestly presented, to the public. Such articles, if properly promoted, are eligible for admission to *New and Nonofficial Remedies.* These include preparations in the following groups:

(a) Disinfectants, germicides, and antiseptics, provided they are promoted only as prophylactic applications to superficial cuts and abrasions of the skin.

(*b*) Laxatives promoted in such a manner as is not likely to lead to their abuse.

(*c*) Other preparations and articles which, in the opinion of the Council, can be safely used by the public for the relief of symptoms, such as antacids and analgesics.

Each group is required to carry adequate and acceptable labeling statements and to limit claims to truthful dimensions, such as "FOR THE RELIEF OF MINOR ACHES AND PAINS," in the case of analgesics, and "FOR THE TREATMENT OF OCCASIONAL CONSTIPATION" for laxatives.

With the exception of these specified categories, and others that subsequently may be recognized, any article promoted to the public for the treatment of disease is precluded from admission to *New and Nonofficial Remedies*. Advertising to the public is not restricted to promotion in newspapers, magazines, radio, films, or similar devices, but, in addition, includes labeling, circulars, and placards which may reach the patient. This rule, it must be emphasized, imposes no restriction on the legitimate methods of bringing a remedy to the attention of the medical profession, such as by advertising in journals, labeling, circulars, and other printed matter distributed exclusively to physicians, dentists, pharmacists, and veterinarians, provided it does not invite or encourage use by unqualified persons. Moreover, advertising the name of a firm, as being a reliable one, is permissible in any advertising medium, public or professional.

We have reviewed the reasons why the Council objects generally to the naming of diseases in labeling, recognizing the practice as facilitating unnecessary and frequently unfortunate self-medication. Of course, if therapeutic indications should be necessary for proper directions for use of articles advertised directly to the public the Council would consider their statement unobjectionable in the case of preparations it accepts for promotion to the public. However, it condemns their appearance in the labeling of all other pharmaceuticals.

In its limitation on advertising, the Council has further ruled that where an item suitable for self administration is dispensed in its original container, any permanently affixed device identi-

fying it to the consumer constitutes advertising to the public. Thus, bottles with the name blown into the glass and other means of permanently stamping a name or initial or other distinctive mark on the container, its stoppers or seals, or on the article itself is deemed violative of this rule. On the other hand, readily removable labels are not objectionable nor is this rule applicable to parenteral preparations, which, indeed, should have permanent labels. The firm's initials or name on the trade package is also permitted if it is not suggestive of the article.

The Council is particularly opposed to the use of an accepted article to advertise other preparations not accepted by it. For example, it objects to the mailing of circulars for accepted and unaccepted preparations in one envelope where any possibility of misleading the recipient exists. It also objects to an inquirer being concurrently flooded with advertising material for non-accepted products when he specifically asked for information on an accepted item. In combination mailings, products which have been accepted by the Council and those which have not must be clearly distinguished, for instance, by the initials N.N.R. Advertising material, circulated exclusively to dealers, is, however, not subject to this last rule, nor are catalogues.

It is well to remember in this connection that any practice of using acceptance of one article in a way that promotes the exploitation of others that are opposed to the principles of the Council—unrecognized lay medicinals, for example—may be considered evidence of bad faith, authorizing the cancellation of acceptance of all preparations of the offending firm.

Similarly, the Council will not accept an item, or continue its acceptance, if the same article, or one essentially alike, is also being marketed as a therapeutic agent domestically by the same firm but under another name not recognized. However, no objection is raised to the use of a statement, such as "THIS SUBSTANCE IS ACCEPTED BY THE COUNCIL ON PHARMACY AND CHEMISTRY OF THE AMERICAN MEDICAL ASSOCIATION UNDER THE NAME. . . ." when a Council accepted article is sold outside the United States under another name. Incidentally, the Council

does not regard the acceptance of preparations marketed solely outside this country as within its scope.

Therapeutic Claims. As we have seen, accepted articles must confine their therapeutic claims to those stated in *New and Nonofficial Remedies* for the drug, unless additional representations have been approved by the Council. It is rather pertinent to bear in mind, in this connection, that conclusions made in articles appearing in *The Journal of the American Medical Association* may not, by reason of their publication, be incorporated in the claims offered on behalf of an accepted drug. Manufacturers and their agents, moreover, are responsible for any statements made or quoted in their advertising concerning the therapeutic properties of their products. Such claims must not only be compatible with demonstrable facts, but new claims that are not in harmony with already recognized authority or are unsupported by acceptable evidence are not allowed. Therapeutic claims that exceed, or substantially modify, those made at the time of acceptance must, as we have noted, be submitted to the Council for review before being used.

Particular attention should be given to claims for nontoxicity. These are admitted only when they do not conflict with known facts. The Council has cautioned physicians that a claim of lack of toxicity means only that toxic effects have not as yet been recognized with the doses that have been studied. Frequently such apparently justified conclusions are ultimately reversed by extended experience. The same reservation applies to statements that a particular drug is nonirritating.

The Council has carefully propounded the character of acceptable clinical evidence. The applicant is required to submit objective data with sufficient citation of authority to enable the Council to confirm the facts and establish the scientific value of the conclusions. The amount and nature of the supporting data that may be necessary depend generally on the inherent probability of the claims made. Thus, no support is needed for a self-evident claim; but when it runs counter to the accepted data on the subject very strong corroboration is essential. The acceptableness of evidence is, moreover, largely

determined by its quality; multiplication of inaccurate observations does not thereby render them of probative value. In addition, clinical evidence should be furnished in sufficient detail to permit an appraisal of the care with which it has been gathered and the legitimacy of its conclusions. Obviously, comparative trials facilitate and, indeed, are frequently essential in reaching a judgment on this score. Suspicion attaches to observations that are not described with enough particular to permit verification. As may be expected, the credibility of the data and the justification of conclusions reached are weighed in relation to the reputation and experience of the investigators, and especially their degree of bias, technical ability, and critical discernment. Anonymous communications or observations gathered without adequate facilities are rarely, if ever, accorded any worth as evidence.

Although the Council will comment on claims made in advertising material, it endeavors only to indicate the type of representations acceptable and the nature of the objectionable statements rather than to edit advertising copy word for word. Consequently, while it is willing to designate the general character of the revision that may be required, it will hold the firm responsible for compliance with the objections. In addition, the company is expected to observe the spirit and intent of the Council's criticisms in the copy that may not have been specifically censured.

Moreover, new advertising must be submitted for Council examination on preparation and before its use. However, material merely reprinted from that previously accepted by the Council need not be so reviewed unless it presents new claims; in the latter instance it should be accompanied by supporting evidence for Council consideration before release. Since claims find reflection largely in such advertising, failure to comply with this requirement may act as sufficient ground for a rejection of the article.

Finally, references to medical literature in the advertising of an accepted product are required to include not only the name of the investigator but also the year of publication, although a

full citation of the publication is permissible and preferred. Nor may the personal signature of a physician be used on the label or in the advertising of a product; this implies personal supervision and tends to create a misleading impression of therapeutic value, as, for example, that it is individually and specifically prepared for the user or his patient.

Protected Names. The exigencies of pharmaceutical manufacture and intelligent prescribing are resolved in the rule that trade-mark names for medical articles are acceptable only if the Council considers their use not to be harmful to health, and if the common or generic names are not unduly subordinated to such trade-marks in the labeling and advertising of the product.

So far as trade-mark or "protected" names are concerned, the Council is of the opinion that medical practice is best promoted by the use of a generic name for each drug, and not by the use of a different "protected" name for each brand of the drug. If nothing else, this avoids any needless tax on memory and the possibility of confusion and error. Nevertheless, it recognizes that the developer of a new remedy is entitled to designate it by a restricted name if only to protect his investment and expense. Consequently, the Council will accept a protected name from the discoverer of a drug or the firm first introducing it. Experience has shown, however, that any restriction to one protected name tends to prolong a monopoly unduly and, moreover, prevents Council acceptance of competing brands which, except that they employ other protected names, would ordinarily be acceptable. Accordingly, it will now accept several trade-mark names for the same article provided the article is not official, in which case the names must have been in use before the drug became official. The common or generic name of the product must also be given on the labeling and in the advertising and cannot be unreasonably subordinated to the protected name. In cases of this nature, the accepted drug may be identified by adding the generic or official title to the protected one, as, for example, "LUMINAL, BRAND OF PHENOBARBITAL," and "BENZEDRINE, BRAND OF AMPHETAMINE."

In selecting trade-mark names for drugs intended for Council consideration, other factors must also have attention. Thus, misleading names or those suggestive of diseases, pathological conditions, or therapeutic indications ordinarily are not acceptable, although serums, vaccines and antitoxins, following recognized custom, may bear titles suggesting their purpose.

It is the Council's opinion that, in marketing unoriginal pharmaceuticals, the producer's legitimate interests are sufficiently served by identifying them with his name or his *general* brand mark. A brand mark accordingly may be used, provided that it is not limited to, or utilized to distinguish, an individual product. Its significance must be confined to denoting proprietorship only.

Protected names will be acceptable for pharmaceutical *mixtures,* as a matter of fact, only under exceptional circumstances. An original combination marking a distinct improvement over available preparations may be so characterized, but it is rare that pharmaceutic preparations involve sufficient novelty warranting such action. The Council is inclined to weigh any decision in this connection against its preference that mixtures should be so named, if possible, as to remind the doctor of the potent ingredients, and that mixtures are usually best prescribed when the ingredients are adjusted to meet the individual case. There is no prejudice, however, against the marketing of common pharmaceutical preparations or mixtures even though they might not be acceptable for inclusion in *New and Nonofficial Remedies.* The Council may also recognize coined names for mixtures that were in continuous use before its establishment in 1905; and titles of mixtures named under the reasonable assumption that they constituted chemical entities, if they are not otherwise objectionable. There are times, in addition, when mixtures are best made, economically and from a standpoint of what might be called essential pharmaceutical elegance, by a drug or pharmaceutic manufacturer. In such instances the Council will give special consideration to the need for, and usefulness of, the preparation. It will not,

however, recognize a coined name for nonofficial dosage forms of official substances.

There are several rules governing name coinage for pharmaceuticals. Generally speaking, the Council favors coined names indicative of the potent element or constituent in the preparation. So, too, to avoid confusion, it will not accept coined names for salts that do not indicate the components of such salts, for illustration, "ARTIFICIALINE HYDROCHLORIDE." In such instances, the unqualified name, "ARTIFICIALINE," is acceptable only for the base.

Similar difficulties are apt to be encountered where a brief coined name is concocted for a product in its original form; for example, an elixir of a new hypnotic described as simply "ALIPHAL." Should the manufacturer subsequently decide to distribute the substance in powder form also, an entirely new name would become necessary, thus causing confusion to physicians and the trade. Consequently the Council holds that coined names for such substances are admissible only if they also describe the type or dosage form of the preparation, such as "ELIXIR OF ALIPHAL," or "ALIPHAL POWDER"—not "ALIPHAL" without qualification.

The use of numerals or alphabetical designations in, or closely connected with, drug titles tends, the Council feels, to remove the emphasis from, and, in many cases, to supplant, the name, thus leading to confusion and careless prescribing. Accordingly it will not, as a rule, recognize any name in which a numeral or letter is an integral part. An exception may be made where its use seems desirable because further improvement of the product is anticipated. Except in price lists and catalogues, moreover, numerals and letters should not appear in direct connection with the title of the product, but, if used, should be clearly separated from, and subordinated to, it by type size and position, if the latter is feasible.

Patents and Trademarks. To help determine the status of the article and its submitted title, the Council requires that it be furnished, in the case of a product patented as to process or identity, with the number of the patent. Similarly, the registra-

tion name and number of a registered trade-mark must be supplied; and if the label is copyrighted, copies of the entire label so protected must be submitted. Where the article is registered in a foreign country under a different name, this information is also essential; this enables the Council to identify the preparation more readily in the foreign literature.

Unscientific and Useless Articles. The Council has served for over two score years as a bulwark against the irrational type of formula that so frequently characterized drug manufacturing until recent years, and still persists to an unwarranted degree. One of its tenets, accordingly, is that it will not accept an article if, in its opinion, it will not be in the interests of rational medicine and the public.

This attitude is predicated generally on the premises that useless and worthless drugging is almost certain to be harmful. It is broadly drawn and applied not only to bar from Council acceptance the irrational formula but also all articles without definite therapeutic value; compounds and mixtures containing an excessive and unnecessary number of active ingredients and those of no probable assistance to each other; and preparations involving dangers of toxic effects out of proportion to their therapeutic value.

THE APPLICATION TO THE COUNCIL

As we have remarked earlier in this chapter, a number of manufacturers of drugs otherwise acceptable have been discouraged from making application for Council acceptance by the character and detail of the data required by the rules. Others, perhaps less averse to the task but with little perspicuity, have tried their hand at the preparation of an application, coming up with documents that call for all the ingenuity and patience of the Council's staff to decipher and unravel. Neither of these situations is warranted.

The only purpose of the application is, of course, to convey facts about the submitted product for the Council's consideration. The data furnished should, patently, be unambiguous,

concise, detailed, and explicit. Although its presentation calls for no literary ability, it does necessitate, in the first instance, a clear and careful analysis of the nature of the product, its manufacture, and its marketing, and secondly, its disclosure in lucid English.

The Council is informed about the product only through the medium of the application and the samples and exhibits. As a matter of fact, it will not ordinarily inspect factories, its concern being only with the finished product, although if such action appears advisable, its representative may visit the factory or office to obtain first-hand information concerning the manufacturing establishment, its available facilities and controls, the nature of its laboratory and experimental facilities, and the scientific personnel and investigative projects. However, as indicated, this course is infrequently adopted and reliance is placed principally upon the intelligence obtained from the pages of the application.

In an effort to channelize the information thus submitted, the Council has divided it into a number of different categories; these, in turn, are supplemented by explanatory comment to assist the applicant. The applicant who follows the outline thus suggested will simplify his task considerably.

Broadly speaking, the application comprises two general types of information, the one, the written portion, which must be furnished in duplicate, the other, the physical exhibits. The former, in turn, may be broken down into:

(1) The description of the product
(2) The description of the control procedures for the product
(3) Additional information required of a new applicant
(4) Statements and agreements with the Council

The physical material that the Council requires in giving consideration to an article may be enumerated as:

(1) Three trade packages of each dosage form submitted
(2) A sample of each active ingredient contained in the product
(3) Twenty-two copies of all labeling material

(4) Twenty-two copies of all advertising distributed or intended for distribution

The physical exhibits described call for little explanation or elaboration. Generally, consideration is expedited if the labels required are mounted on letter-size paper so that twenty-two separate sets of labels are available for examination. By labeling, of course, is meant all containers, packages, cartons, leaflets, circulars, and other package enclosures. In submitting samples of the articles and of the active ingredients, sufficient quantities should be furnished to permit the careful analysis made of the substances by the Chemical Laboratory of the American Medical Association.

THE DESCRIPTION OF THE PRODUCT

As its heading implies, the description seeks to elicit all material information about the product. The applicant's task is eased and directed by the subheadings furnished in the rules. Under no circumstances should the text deviate from, or be drawn without regard to, this enumeration; rather each should be carefully answered in the order designated.

Name of Product. To be supplied under this heading is the protected trade-mark or coined name for the article, if it has one; otherwise its common name may be given. In the latter instance, it should conform with the official formulary designation or the generic title adopted by the Council. We have already discussed the rules of the Council regarding acceptable nomenclature; the coined name must, of course, comply with these requirements. In addition, the applicant must here furnish a brief statement of the significance of the name and the reason for its choice, together with the date it was first employed publicly to designate the product. Care should be taken that the name given and its word order corresponds exactly with that shown on the labeling and in the advertising submitted.

Synonyms. Where a protected name has been stated in answer to the previous question, the official or N.N.R. title that may also be used for prescribing the drug should be set forth here.

If such a name does not exist as yet, the applicant may submit, for consideration by the Council's Committee on Nomenclature, one or more suggested non-protected names suitable as a generic designation. If the product is being marketed under an official, Council adopted, or common or generic name, any other appropriate synonym is satisfactory. Where there is no synonym, or the applicant is not interested in utilizing one, this subheading need not be answered.

Definition. Actually this requires a formulary description, either in chemical terms or in composition. Thus, if the article represents a distinct chemical entity, its scientific name, together with its structural chemical formula, so far as is ascertainable, should be submitted. A mixture of any kind should be defined by its formula, *i.e.* the finished product composition, setting forth a quantitative statement of its composition, including preservatives, vehicle, base, and excipients. The statement should be set forth both in percentage form if this be appropriate, and in metric measure. Here, too, the data should be compared with the labeling submitted to verify that the Council's rules have been followed.

Preparation. This portion of the description should embrace a general statement of the manufacturing processes. Although details of the processing may be omitted, sufficient information must be included to enable the Council to assure itself that there will result a product of the identity, strength, quality, and purity claimed for it. Particular attention should be paid to the statement of all control procedures used to detect errors in manufacture and to insure a satisfactory product. The data furnished should include the requisite information for each dosage form submitted. At a later point in this chapter, the description of facilities and controls is given more attention.

Properties. Required in the identification of the product are data regarding its properties. The information supplied should, where applicable, embrace appearance, odor, taste, and, indeed, any characteristic physical or chemical property—such as melting and boiling points, solubility, important incompatibilities.

Tests. Considerable attention should be given to compliance

with this requirement. Methods described should be phrased in accordance with the style of *New and Nonofficial Remedies* or the *United States Pharmacopoeia.* In case the product is a chemical substance, adequate tests for identity, for strength, for quality, and for purity—together with methods of assay—must be submitted. The statements should also include specified upper and lower limits of acceptability for the assayed ingredients. Similarly, methods for identification and assay of the principal active ingredients should be furnished for pharmaceutic mixtures. Substances requiring biologic assay, such as some vitamin preparations, must, in addition, be accompanied by protocols of several typical assays, signed by a reputable biological chemist or other qualified assayist. If the article is one that is represented as, or because of its manner of use must be, sterile, the methods utilized to determine this fact should be given, including the method of sampling, the bacteriologic method, the frequency of examination, and other pertinent data.

Pharmacologic Action. In those instances that the application deals with a preparation already accepted for inclusion in *New and Nonofficial Remedies,* it serves as sufficient compliance with this point to refer to the statement of pharmacologic action set forth in that reference. Where the article is not so listed, general information concerning the absorption, actions, toxicity, and fate or excretion of the preparation should be furnished, particularly as these relate to the mode of administration of the drug involved. The Council, incidentally, has published certain criteria to serve as a guide in the planning of experiments and the examination and evaluation of results for anti-infectives, including antiseptics, bacteriostats, and germicides, antifungal agents, and contraceptives; these are available on request. Where a product of these categories is submitted, data thus considered appropriate must be furnished in detailed form and twenty-two copies supplied as a supplement to the information given under this heading. Where the data are extensive, the Council permits a filing of an abstract. Similar reports and copies are demanded of a new drug.

Therapeutic Indications. A brief statement of the diagnostic,

prophylactic, or therapeutic purposes of the product is required at this point in the application, corresponding generally to the actions and uses already given in the current *New and Nonofficial Remedies,* wherever applicable. Claims that exceed these, however, must have the support of the pharmacologic or bacteriologic data previously supplied and of careful and extensive clinical studies. The latter should embrace a summary of the various conditions treated, the number and type of cases treated, the dosage, frequency, and duration of the administration of the drug, the therapeutic effects, and any untoward reactions observed. The actual clinical data, including a bibliography, should be furnished as a separate supplement, accompanied with twenty-two copies of each protocol, reprint, or other suitable reproduction of the evidence. When this is extensive, however, it is permissible to submit the detailed reports merely in duplicate, together with twenty-two copies of a suitable comprehensive and unbiased summary or abstract. Care must be exerted to reconcile the therapeutic claims appearing in any advertising with the indications and data here furnished.

Dosage. Wherever possible, the dosage and method of administration recommended in the current *New and Nonofficial Remedies* should be given. When the product is a new dosage form of an accepted article, or is one not previously recognized by the Council, a detailed statement of the dosage and administration for the drug must be furnished, including mention of any necessary precautions peculiar to its mode of application.

How Supplied. All dosage forms, sizes, and package forms of the article intended for Council consideration should be listed at this point. It is necessary to state also whether or not the active ingredient is marketed in bulk.

Manufacturer. Not only the name of the firm responsible for the labeled finished product must be given but also the names of the manufacturers of all ingredients contained in the article.

Patents and Trademarks. If the drug is patented, the United States patent number should be furnished; if imported, the number of the patent in the country of its origin is necessary. Similarly, if the article bears a registered trade-mark, its number

is required. In the case of foreign registrations, the name or names under which it is registered should be given.

The foregoing embraces the "description" of the product as it is contemplated under the Council's rules. It will be noted that in cases where a brand of the drug has already been admitted to *New and Nonofficial Remedies,* the task of the applicant is relatively simple. It is only where the proposed preparation is new to the pages of this compendium that elaborate protocols of laboratory and clinical evaluations must be furnished. Patently this is a reasonable requirement. Earlier chapters of this work serve as a valuable guide in assembling the type of data essential to satisfy the Council's critical appraisal of the real worth of a pharmaceutic.

THE DESCRIPTION OF CONTROL PROCEDURES

Although the statement of the control procedures should appear in the application under the heading "Preparation," the comprehensive nature of the information required makes it advisable to treat the subject separately. As drugs gain in complexity, controls obviously attain a position of importance in production. This is particularly true in the case of the new synthetics; nevertheless we would be wrong to confine this scrutiny and care only to chemicals coming under this category. Sterility controls are essential also in the production of parenterals; and as drug plants expand their activities and lines, the need of safeguarding each batch produced is immeasurably increased. The processing of biologicals frequently calls for aseptic treatment and, of course, for precise methods of assay.

With a growing appreciation of the importance of control facilities, therefore, the Council in 1947 amended its rules to require the fullest exposition of the procedures employed in producing drugs offered to it for consideration. To simplify compliance, it elaborated the nature of the data required into thirteen subdivisions. The mere reiteration of these headings should suffice to indicate the type of information for which the Council is looking.

(*a*) Precautions to insure proper identity, strength, and purity of the raw materials.

(*b*) Precautions to preserve sanitary conditions in space allotted to storage of raw materials.

(*c*) Whether or not each lot of raw materials is given a serial number to identify it and the use made of such numbers in subsequent plant operations.

(*d*) Method of preparation of formula card and manner in which it is used.

(*e*) Manner in which weights and measures of each individual ingredient are checked when preparing formula.

(*f*) Whether or not the total weight or volume of each batch is determined at any stage of the manufacturing process subsequent to making up a batch according to the formula card and at what stage and by whom this is done.

(*g*) Methods of maintaining sanitary conditions within the manufacturing plant and avoiding contamination of the drug with filth, dust and extraneous material.

(*h*) Precautions to check the total number of finished packages produced from a batch of the drug with the theoretical yield.

(*i*) Precautions to insure that the proper labels are placed on the drug for a particular lot.

(*j*) The analytical controls used during the various stages of the manufacturing, and packaging of the drug, including a detailed description of the collection of samples and the analytical procedures to which they are submitted. If the article is one which is represented as sterile, the same information should be given for sterility controls.

(*k*) An explanation of the exact significance of any control numbers used in the manufacturing, processing and packaging of the drug, including any code numbers which may appear on the label of the finished article.

(*l*) Additional procedures employed which are designed to prevent contamination and otherwise insure proper control of the product.

(*m*) Are representative samples of each lot of the drug examined by any other laboratory (government or private) prior to distribution? If so, by whom?

ADDITIONAL INFORMATION REQUIRED OF A NEW APPLICANT

A firm submitting for the first time an article suitable for inclusion in *New and Nonofficial Remedies* is required to furnish additional information in order to permit the Council to arrive at some conclusions as to the manner in which it conducts its affairs, the scientific personnel it employs, and its general policies, foresight, and professional outlook. Like other material contained in the application, it must be supplied in duplicate.

First of all, the Council requires a list of all products sold by the applicant for medicinal use in humans. This may be satisfied by submitting two copies of a catalogue, price list, or other informative tabulation.

Also to be furnished is a statement of the laboratory and control personnel of the firm. This may be drawn in brief biographic form, giving the name, duties, educational background, and technical experience of each member of these departments.

The Council also asks for a general statement of the policies of the applicant, its scientific aims, its methods of marketing drugs, either for the public or for the professions, its future plans in these connections. It must be evident that the manufacturer seeking Council acceptance is equally interested in participating, in an active fashion, in the objectives of the Council. This should, in short, serve as an averment of his intentions in this respect.

STATEMENTS AND AGREEMENTS WITH THE COUNCIL

In addition to the above information, the new applicant is required to implement his tacit agreement to abide generally by the Council's rules by a properly authorized statement to this effect. Two covenants of this character must be filed with the

application. Ordinarily, they may in form follow the context of the rules, being signed by an officer of a corporation, a partner, or the owner, as may be appropriate. The statements read:

(a) That the applicant agrees to notify the Council promptly on the discovery that an error has been found in the compounding of any of its Council-accepted preparations, either by the firm itself, or by a Government or outside agency, that causes the article to differ from its standard of identity, strength, quality, or purity.

(b) That the applicant agrees to abide by the rules of the Council as applied to brands of his articles that may be accepted for inclusion in *New and Nonofficial Remedies,* and to submit to the Council before implemented all future proposals for changes in the composition, labeling, advertising, or market status of such products.

From time to time the Council may add other explanatory comments to its rules, but basically the objectives will remain as they have for over forty years—the advancement of rational therapeutics. One thing is certain: The Council is not vindictive in its approach to this problem. Nor are its decisions arbitrary and capricious. At any time a manufacturer, or any other individual, may feel free to dispute a decision or to offer suggestions. In fact, such an invitation is presented in the Preface of each edition of *New and Nonofficial Remedies.*

17

Product Development, Promotion, and Marketing

ROBERT A. HARDT

PRODUCT DEVELOPMENT

NORMALLY the term "product development" connotes applied research whose objective is to develop new, and improve existing, products. In recent years, however, its significance has been broadened to include also the more non-technical aspects of the subject, particularly those related to marketing. Consequently, a more modern concept of the expression views it as activities directed at the coordination of technical and non-technical aspects in the development of new products and improvement of already marketed products usually entrusted to a particular executive or department. Primarily, its function is to initiate the work of other departments, to correlate and evaluate the data thus procured, integrating the scientific with the commercial factors. In short, it coordinates all efforts undertaken in the preparation of marketable products from the conception of the idea to the initial distribution and sale of the finished products.

Generally speaking, in the pharmaceutical industry product development departments serve to sound out and interpret the needs of the medical, dental, pharmaceutical, and veterinary professions and direct the integration of applied research with sales. In some companies this organization is responsible directly to the management; in others, it is associated with the sales department; in still others, with the scientific department of the firm.

The product development department in preparing mem-

oranda for the sales or general management suggesting new products or improvement in existing products usually makes a sincere effort to outline their market possibilities. These reports, in addition, generally explore the existing need for the product as well as the marketing advantages it should possess. Of course, these thoughts need not be highly technical or extensively developed; they should, however, serve as a guide to the applied research laboratories in planning projects.

It should be borne in mind that this practice must always be a "two-way street." The laboratories' receptivity to new ideas should not affect or emasculate their own original thinking. That is to say, the laboratories should exchange suggestions for new projects with the product development department; the community of brains is certain to bring about desirable and productive results.

One concept of the functions of the product development department has been described in detail by Dahl and may be summarized as follows:

> Product development is more than technical development—there are many elements which contribute to the creation of a product other than its formula. Market research, purchasing, production, packaging, labeling, costing, pricing, medical, and legal factors all play a part in the evolution of a new product, and many of them *precede* technical development, if the latter activity is not to have faulty direction. There is a need for more of "what, why, when, and how" in technical product development which can only be supplied by proper and *early* evaluation of certain of the non-essential aspects.
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> The product must first have its market and field of use outlined in sharply definitive terms, for the setting up of the product objective must be based on facts and not on somebody's intuition.

Yonkman has observed that:

> . . . the functions described by Dahl should be invested in a single individual and it is well recognized that this individual must be carefully chosen. He must be almost superhuman in the sense that he must be very well grounded in many phases of pharmaceutical activity. He must have a keen appreciation of research and must be quite cognizant of the various types of problems confronting production, sales and advertising. Then, too, it is absolutely manda-

tory that he must be most personable and a fellow easily gotten along with. He is not only going to have to stroke the fur of many people in the wrong direction upon occasion, but he also will obviously become the target of many darts. He will have to be well armored with a rugged constitution, letting the chips fall where they may. But an individual with a really democratic and diplomatic approach and one endowed with the above attributes and capacities will certainly be a remarkable asset to any pharmaceutical organization.

WHAT PROMOTION COMPRISES

Since our discussion will show the relationship between *product development* and *promotion,* it is perhaps advisable to define this last term as we have done in the former case. Originally the word "promotion" described activities concerned largely with the printed word in advertising. In addition, exhibits and sampling were included in this category. Later, promotion also embraced personal interviews with physicians, dentists, and veterinarians. For some obscure reason the representative who made these calls was referred to as a "detail man." In Europe and a few other countries he was known as a "medical visitor." As Mr. Jones points out in another chapter, however, the term "detail man" has persisted in this country despite efforts to substitute a more accurate, descriptive expression such as "professional service representative."

Actually, the representative who makes calls on professional people with the object of inducing them to use or prescribe the product of the manufacturer is a salesman. While he may not always openly attempt to obtain orders, and indeed endeavors to be of genuine service by acquainting the prospect with his firm's products, he follows, or, at any rate, should follow, the principles of good salesmanship. Thus, the function of the "detail man," "medical visitor," "medical service representative" or "professional service representative"—however designated—is that of selling, a high type of selling, to be sure, and one much more subtle than that of the ordinary salesman of commerce whose business is to get an order for more prosaic goods or commodities.

It will thus be seen that "promotion," as used in this chapter, embraces all selling, advertising, and professional service activities, and may be broadly defined in pharmaceutical industry parlance to describe all efforts undertaken to create or increase sales or the use of a firm's products, whether done by the written or spoken word. It includes the following activities:

1. Selling the product to distributing outlets or users, such as pharmacies, wholesale druggists, physician's supply houses, and hospitals.
2. Promoting the use of the product to the medical, dental, and veterinary professions through the personal interview method.
3. Advertising in medical and professional journals.
4. Direct mail promotion.
5. Attendance or exhibits at medical conventions.
6. Sampling the product to interested professional users.

PROCEDURES IN DEVELOPMENT AND PROMOTION

Inasmuch as product development is, for the purpose of this chapter, concerned with policies rather than details, it is well to review a number of points which arise in considering the proposed product. Questions usually requiring answer include:

1. Does a need for the product actually exist?
2. In introducing the product, does the manufacturer actually make a contribution to therapy?
3. Has the firm played a leading role either through laboratory or clinical research in developing the product?
4. Can the efforts of the firm be better directed by concentrating on another type of product where it has more "know-how" or in which there is reason to believe it can play a more dominant role?
5. Is the firm actually offering an improved product?
6. Is the improvement sufficiently worth while to make the product more useful than competitive products?

If the responses to all of these questions is in the affirmative,

no one can dispute the right of the firm to market the product. If, however, one or more answers are in the negative, then the management of the firm should undoubtedly think twice before adding the product to its list.

The reason for such a decision must be apparent. Therapy is changing rapidly. No one can be unaware of the fact that the number of medical specialties is increasing with alarming rapidity, to some extent, unjustifiably. Duplication of specialties is a problem not only to the physician and the retail pharmacist, but to the manufacturer as well, who, once having decided to market a product, is burdened with the problem of promoting it in a highly competitive market. When eight or ten similar products differing only in name are placed on the market within a period of a few months, there is certain to be a serious problem for all concerned—the manufacturer, the wholesaler, the retailer, the physician, and the hospital. Considerable duplication could, however, be avoided were manufacturers to ask themselves the above questions before deciding to place another product on the market.

Painstaking thought and consideration of all sales factors in the early phases of product development will frequently assist materially in reducing the mortality of products once they have reached the market. When a drug is rushed into distribution with the idea that any of its sales weaknesses can be corrected later, the prognosis is not a very happy one. All too often the new product which is moribund with sales anemia after its first year of life has reached that state because short-cuts have been taken in its development, or sales advantages sacrificed to production convenience. For example, a new product's preliminary market testing may uncover the fact that it is preferred by both physician and patient in capsule rather than in tablet form. However, the marketing firm has better facilities for tableting than for capsuling. Despite indications that the product has a greater chance to succeed in capsule form the decision is made to market tablets and an important sales advantage thus lost. The principle to be remembered is that physician and patient

preferences are too important to be ignored no matter how good the product may be.

The time to correct sales weaknesses is before the product is introduced because if they appear after it is on the market the psychological effect on both seller and user is serious; in fact, no matter how speedily the correction is made, the damage to sales is often very substantial.

Once the decision to market a new product is made, it is the function of the product development department to plan and follow the progress of the following steps and procedures:

1. Clinical and laboratory testing.
2. Submission to the Food and Drug Administration.
3. Decisions on market forms and package design.
4. Development of cost and pricing schedules.
5. Ascertainment of the potential market and preparation of sales estimates.
6. Determination through purchasing department of whether ingredients and packaging materials are available.
7. Determination of whether it is advisable to market locally, sectionally, or nationally, or to test merely in certain areas.
8. Determination of whether the product has a potential market in foreign countries.
9. Determination of whether clinical data are adequate for successful promotion.
10. Decisions on the advisability of sampling the product and suggestions as to form and size of samples.
11. Decisions on method of distribution.
12. Arrangement for the creation of educational material for representatives.
13. Furnishing data for the preparation of copy for package inserts, leaflets, and journal advertising.
14. Collaborating with medical department in reviewing data submitted by outside consultants.
15. Determining when the product is ready for marketing and timing its introduction.
16. Collaborating with the management on deciding whether

it is advisable to present the product to the Council on Pharmacy and Chemistry of the American Medical Association.

17. Determining whether all possible promotion features have been "built into" the product.
18. Analyzing selling points of products which are directly or indirectly competitive and decide whether, on basis of this analysis, the proposed product has reasonable chance for success.
19. Collaborating with the management in deciding whether the product should be marketed under a trade-mark name, a generic name, a descriptive name, or its proper chemical name. If the decision is to use a trade-mark name, coordinate the activities in evolving a name and arrange for its registration by the patent department.

PRODUCT NAMING

The problem of the product's name is one which requires the most careful consideration. Cousins and Wadsworth have lucidly described the problem in their book *Trade Names:*

The christening of a new product is vastly more difficult than the naming of a newborn infant, and the indecision of a fond parent is a trifle compared with the disputation which commonly takes place in a sales department about to market a new article. In the case of an infant it is merely a case of picking one's fancy from names already current. For the commercial product, however, the name must usually be an entirely new one in the class of article concerned.

Whereas thirty years ago it was fairly easy to find a suitable name which was not already in use, today the names already on the register in a particular class may run into thousands so that the chance of finding one which does not bear an unfortunate resemblance to an existing name is much reduced. It is not now uncommon for a preliminary list of about twenty names to be reduced after a preliminary search to about five, and for these five to be comparatively poor ones.

The reason for this is not that good names do not exist, but that casual searchers have to work along the same lines. They draw conscious and subconscious analogies from existing names, and thus reach the same results as those who preceded them.

In the pharmaceutical industry manufacturers have submitted to legal search as many as eighty-five coined names before finding one which bore no similarity to names already registered or in use. Even before deciding on the name, the manufacturer should decide on its type; this decision will vary depending upon such factors as the nature of the product, the method of promotion, and the general competitive situation.

There are those who strenuously argue that all new pharmaceutical products should bear an exclusive coined trade-mark name. They reason that the manufacturer will probably spend thousands of dollars over a period of time in promoting the sale of the drug and is, therefore, entitled to the protection which a trade-marked name gives. Although this is a valid premise, nevertheless, such a blanket statement fails to recognize advantages inherent in other types of names, and loses sight of the fact that mere ownership and use of a name, no matter how good it may be, does not convey leadership in sales however it assists in the struggle for product leadership. It is well, therefore, to consider the advantages and disadvantages of the six general classes of names used:

1. The invented trade-marked word which is not descriptive. This type is also referred to as the fanciful, semi-fanciful or arbitrary name. Such names are sometimes formed by telescoping syllables of descriptive titles or components of chemical names; usually they have no special significance to the physician. *Examples:* Amniotin, Alurate, Benadryl, Merthiolate.
2. The generic non-trade-marked name. *Examples:* Insulin, Neoarsphenamine, Sulfathiazole, Penicillin.
3. The semi-descriptive or descriptive non-trade-marked name. *Examples:* Poison Ivy Balm, Vitamin B Complex Capsules, Liver and Iron Capsules.
4. The chemical or pharmaceutical name of the substance. *Examples:* Mannitol Hexanitrate, Digitoxin, Acetylcholine.
5. Collective names (invented trade-marked names) which are

used by more than one manufacturer. *Examples:* Sobisminol, Dicumarol.

6. The names or synonyms found in the official compendia. *Examples:* Thyroxin, Elixir Terpin Hydrate with Codeine, Oleovitamin A Capsules.

The advantages and disadvantages of each of these classes may be summarized as follows:

The invented trade-marked word which is not descriptive. This type is usually used to designate new compounds whose descriptive title is too long to write or remember. It is also frequently employed when the product represents a mixture containing a number of active ingredients.

The invented word has the advantage of exclusive use; provided the name is used properly and frequently, indeed, it becomes a valuable property to the owner. However, considerable publicity and promotion are required before a new name becomes familiar to the professions. Frequently, the name acquires no worth beyond the total sum spent in promoting the sale of the product and popularizing the title.

Moreover, the extremely large number of such names now in use have caused physicians increasing difficulties in remembering the names of many specialty products. Some members of the medical profession, in fact, display annoyance when a new product is introduced under a trade-marked name because their memories are already severely taxed. Often, too, the selection of names is neither helpful nor necessary. Physicians are justifiably critical when a trade-marked name is assigned to a product not sufficiently different from other products of the market to give the manufacturer the right of christening.

The generic non-trade-marked name. This class should possibly be selected for a product which does not differ from other products of the market or is possessed of only slight advantages. To illustrate, when penicillin products were introduced to the American market efforts were made by some manufacturers to establish trade-marked names, in most cases, without success. This was because the name penicillin had become so well estab-

lished generically that physicians logically fell into the habit of writing for "penicillin" in one form or another, followed by the name of the manufacturer if there existed a preference for some particular brand. Indeed, some firms who introduced penicillin preparations under exclusive names changed to generic names after concluding that they were making little headway in establishing a trade name for such a well-known substance. Very few penicillin products have done well under a fanciful name.

On the other hand, some vitamin B complex preparations were successfully introduced under trade-marked names although it still remains true that others were equally successful under the descriptive or generic title. A good rule where a manufacturer follows other manufacturers into the market with a product is to use the generic name if the firms initially introducing the product have adopted trade-marked names. Generic names in this case have the advantage of more common use and publicity; consequently if brand-preference talking points exist and are recognized by physicians, the manufacturer's name will frequently be specified. In this respect, sight should not be lost of the activities of the Council on Pharmacy and Chemistry to encourage the use of generic names, and of the response of the medical profession and many organizations to this encouragement.

Semi-descriptive or descriptive non-trade-marked names. Names in this class have been used successfully by some firms because the name indicates the nature of the product and, therefore, less effort is required in establishing it. Such names, however, have the disadvantage of being vulnerable to competition because they do not enjoy the protection of a trade-mark registration, although in some instances other manufacturers will not copy them out of a sense of fairness to the originator of the descriptive or semi-descriptive name.

However, since there is no legal obligation to honor the name, the decision can only be made with the thought that the semi-descriptive name will survive against competition because of the convenience it offers in the initial introduction of the product.

Chemical or pharmaceutical name. The chemical or pharmaceutical name of the substance, if a short one, should invariably be used unless there are well-defined differences or advantages in the product being marketed over the usual product on the market. On the other hand, if, for example, a compound has the chemical name 2,2-dimethyl, 3-diethyl-amino-propanol, the medical profession could hardly be expected to write it, let alone remember it, and an invented designation would be justified, particularly where the manufacturer is the originator of the compound. However, a manufacturer contemplating the marketing of digitoxin, a relatively short name, would do well to consider using that name, particularly since the product was originally introduced under an arbitrary name. To use another would only add to the confusion.

Collective names. The few collective names now being used in the pharmaceutical industry have the advantage of uniformly designating the products of manufacturers who are licensed by the inventor. This method eliminates the necessity of introducing different names for the same product.

Official names or synonyms. A manufacturer is seldom, if ever, justified in applying an invented name to a drug capable of being designated by the names or synonyms found in official compendia.

The situation with respect to invented trade-marked names is further complicated by the fact that it is often necessary to assign both such a name and a secondary invented trade-marked or generic name to the same product. This is frequently essential for proper legal protection as well as to comply with the rules of the Council on Pharmacy and Chemistry of the American Medical Association. This, however, increases the number of invented names to a very great extent and points up the need for eliminating additional names whenever it is possible to do so. One has only to speak with physicians to realize how strongly they feel on this subject.

The choice of a name for a new product frequently leads to a discussion as to whether the product is actually a specialty. This is not always an easy matter to decide, primarily because

the word "specialty" is not precisely defined. There are also several classes of specialties which, in general, can be described as follows:

Classical specialties: Patentable or original compounds which offer distinct advantages over existing products and which make a definite contribution to therapy.

Non-exclusive specialties: Original, but non-patentable, compounds or mixtures. These specialties do not have the benefit of patent protection, but do have the advantage of prior introduction. They usually are subjected to competition as marketing proceeds.

Competitive specialties: These merely duplicate preparations already in existence although they may offer some advantages in economy, convenience or effectiveness. Their distribution depends almost entirely on marketing skill for success.

MARKET RESEARCH

Once the decision to market a new product has been reached, methods of promotion should be carefully analyzed and a plan made which is most suitable and adaptable to the product. This analysis will seek to determine whether the major emphasis should be placed upon the personal interview method, journal advertising, direct mail, or sampling, or a combination of several of these. This may call for scientific market research involving the measurement of the effectiveness of various promotion methods.

The application of market research methods to the marketing of pharmaceutical specialties is still in its infancy. A number of manufacturers are, it is true, making serious efforts in this direction, but the problems differ widely from those found in the sale of packaged goods over the counters of retail stores. The methods usually employed are as follows:

1. Research of markets by using available statistical data on distribution of diseases, income groups, distribution channels, extent and type of competition and market potential.

2. Product research, mainly by testing acceptance of new products. This is usually done by projecting interview answers of a representative sample of physicians on a nationwide basis and interpreting the findings.
3. Research of policies, such as trade practices, distribution policies, discounts, and price structure.
4. Sales analysis.
5. Testing of effect of advertising and public-relation program, media research.

These methods, are of course, subject to considerable error, especially by inaccurate field work, confusion regarding sample selection, lack of inventiveness in proper technics and also because few market research experts have the proper knowledge and experience in market research methods and statistics and the pharmaceutical background necessary to interpret the results. On the other hand, there are a few pharmaceutically trained men who do have this knowledge and experience. As a result, some industry leaders take the position that the time and effort spent on these procedures are hardly worth while. There are others, however, who feel that it is only a matter of time until experts who have worked out successful market research methods for other industries, will accomplish the same for the pharmaceutical industry. They believe that the scientific evaluation of commercial activity is here to stay and they are preparing to be guided by these methods.

PROMOTION METHODS

Once a good product has been developed there remains the all important problem of its promotion. The established methods used in promoting the use and sale of pharmaceutical specialties have been treated in other chapters of this book. While many orthodox methods and procedures are available, there still remains a diversity of opinion concerning others; there is, moreover, always room for innovations.

Most pharmaceutical and medicinal specialty manufacturers

employ one or more of the following established promotional methods:

(a) Journal advertising
(b) Direct mail
(c) Detailing
(d) Sampling

Since few, if any, budgets permit heavy concentration on all of these methods, it is customary for most firms to select one for major emphasis or the spearhead in their program, supplementing it with the others. Thus, detailing, or the personal interview method, is perhaps the most effective when done well, but is also the most expensive. Consequently, a firm having a large staff of representatives usually finds it necessary to curtail its budget somewhat for the other activities.

Good sales have been built for individual products by using one method alone or by using a combination of several of those listed above. Under present-day conditions, however, it is essential that any method selected for the promotion of a product be executed well; competition for the physician's attention is increasingly keen.

Today thousands of detail men carry the message of their products to physicians. Many of these men are so well-trained that doctors welcome their visits. On the other hand, there are many poorly equipped men whose visits are largely a waste of the physician's time. This group is making it difficult for the better-trained to see prospects.

Medical journals are filled with advertising and here again there is strong competition for the physician's reading time. In order to attract attention to a journal advertisement, manufacturers are frequently obliged to employ considerable ingenuity in illustrations, topography, and copy. The physician's mail is filled with letters, brochures, blotters, leaflets, abstracts, file cards, medical publications, samples, and reprints, and consequently the possibility of waste is very great, many physicians finding it impossible to scan more than a small portion of their mail from pharmaceutical manufacturers.

Thus, it will be seen that all methods of promotion have their advantages and disadvantages. However, there are certain basic requirements for each; this is particularly true of direct mail. Although the subject is discussed in greater detail elsewhere, we might point out that there are four essential factors in the production of effective mail campaigns: planning, art, copy, printing.

There is usually some doubt in the mind of the advertiser confronted with the bills as to whether the high cost of good art is always justified. While it is true that the essential pattern of repetition and continuity in the campaign frequently requires the most liberal portion of the appropriation, nevertheless the modern idea is that better art in business literature builds prestige as well as sales. Robinson has summarized this idea interestingly and with great clarity:

> Many progressive advertisers are now using fine art, in addition to the highest type of commercial art, to provide a prestige-building background for their advertising. While this development has gained considerable momentum in national magazine advertising, it has probably attained its most impressive proportions through direct mail formats and techniques.
>
> As a group, ethical pharmaceutical companies are generally credited with having initiated this trend. What is even more important, they have continuously, and with keen discernment, fostered its evolution.
>
> The reasons are not hard to find. It was discovered that physicians, with their high average I.Q. and long professional training, are extremely susceptible to the appeal of dominant illustrations measuring up to a superior standard of artistic and professional competence. Moreover, the medical viewpoint is predominantly perfectionistic: with mail advertising the critical attitude of the average doctor penetrates to the very core of every presentation. To be acceptable it must be authentic to the minutest detail; restrained in tone; deferential to the doctor's knowledge of, and experience with, medical products.
>
> Most doctors are eager students of medical trends, but the demands on their time are extremely heavy. In one year they received an average of 1,285 pieces of advertising literature . . . all competing for this limited time! It is, therefore, not surprising that the use of better art combined with intriguing layout has proved highly

rewarding in identifying progressive pharmaceutical manufacturers with products of uniform excellence.

The leaders in this field have for years been keenly aware of these reactions. Through such magazines as *Scope, What's New, Seminar* —publications that successfully compete in art-work and typographic technique with the "flashiest slicks"—and a wide variety of other direct mail literature, they have gradually etched new trade names on the minds of physicians. This literature has opened thousands of doors to sales representatives, and has frequently been a dominant factor in influencing medical men when writing prescriptions.

High quality art-work well designed and, above all, well reproduced, has proved most productive in this field to date. The spectacular growth of a number of companies that have used this very simple formula proves this point. But the trend toward better art is "catching on." Many companies advertising industrial and commercial products have found that the universal appeal of good art can be used as a business asset, especially among groups of average high intelligence. And these groups include, besides doctors and other professional men, virtually all major executives, regardless of the type of business they are engaged in.

Most experienced promotion directors will agree with this statement. Indeed, no one can successfully refute or even challenge this point of view. However, it remains for each individual manufacturer to determine whether his budget for the promotion of his products will permit or justify the cost involved. Particularly is this true if the advertiser must decide between a high quality of art and a reduced number of mailings to the point where continuity and adequate repetition are sacrificed. The ideal situation is, of course, attractive and superior material *and* a sufficient number of pieces over a long enough period of time to obtain the desired result.

There is a similar trend toward improvement in the quality of copy and the copy approach. Brewer has described this trend well:

Realizing that physicians are deeply interested in acquiring professional knowledge long after their college careers have concluded some pharmaceutical manufacturers have changed their method of attack. No longer do they rely on merely publicizing the company name or that of their products. They build up sound, extensive research facilities; seek the counsel and cooperation of institutions

and leaders; with this scientific background they prepare literature comparable to that found in standard text books and add considerably to the distribution of authentic information which helps the physician in his daily practice. More and more of this type of advertising literature, brochures, symposia and books will find a place on the shelves in the busy doctor's office.

Haberman has referred to a "Growth Cycle" in the promotion of pharmaceutical specialties:

This Growth Cycle involves six stages of development:

1. The doctor must hear the name of the product.
2. He must know what he's going to use it for.
3. He must become convinced of the clinical effectiveness and safety of the product.
4. He must try it for the first time.
5. He must begin to use it routinely.
6. After a while he must find additional clinical uses so that he can prescribe more of the product—oftener.

COMPONENTS OF DIRECT MAIL PROMOTION

There are a number of more or less standard promotional pieces used by pharmaceutical manufacturers in direct mail promotion. A number of these are also distributed by detail men as they make their calls on physicians. Promotional material of this nature varies considerably as to format. The following are used to a considerable extent by many firms in the industry:

Publications and house magazines: These publications are similar in many respects to medical journals, although, of course, the advertising they contain is restricted to the publishing manufacturer. Usually sent free to all physicians, their objective is more institutional in character than immediate product promotion. They contain review articles of general interest, abstracts from the current literature, color as well as black-and-white photographs, schematic drawings, news of new products, illustrated specialized articles, editorials, medical scrapbooks, questions and comments, and laboratory technics. The inside front cover, and both sides of the back

cover are used to carry individual product advertising. These publications are attractively printed on good paper, and many of them make use of original paintings. They may be issued monthly, bimonthly, or quarterly. Among the most popular of these publications are Abbott's *What's New,* Upjohn's *Scope, Roche Review, Squibb Memoranda,* Sharp & Dohme's *Seminar,* Lilly's *Physician's Bulletin,* and Parke, Davis' *Therapeutic Notes.*

One of the principal advantages of these publications, in addition to institutional value, is the fact that their advertising pages are not in competition with other manufacturers. A disadvantage is the fact that the physician receives a great many such publications and competition for his attention is keen. Also, the preparation of these publications involves considerable costs for composition, printing, and mailing. Few manufacturers, moreover, can produce them without a sizeable medical department, a staff of highly trained medical writers and extensive library facilities.

House literature: These are descriptive booklets usually devoted to one product or to several products which naturally fall into a group. They describe the product in detail following a pattern such as:

(a) History
(b) Chemistry
(c) Pharmacology
(d) Clinical use
(e) Indications and contraindications
(f) Advantages and points of superiority
(g) Description of forms in which product is supplied
(h) References

These booklets are included in mailings, distributed by representatives, and frequently used to answer specific inquiries from physicians, residents, internes, and medical students. They are not expressly intended for general distribution to physicians, although they do prove of considerable value to retail and hospital pharmacists who must answer inquiries from doctors.

Mail broadsides or brochures: These are more profusely illustrated than house literature and contain information in more

condensed form. Designed to convince the physician that it is in his interest to use the product offered, they, as a rule, are organized for quick reading. The cover display is usually one of two types:

A. *Direct*: Using the name of the product with its principal indication or its classification . . . Hematinic, Cardiac Glycoside, *et cetera.*
B. *Indirect or teaser*: The art work being designed to present a figurative story or a meaning metaphorically implied but not expressly stated.

Return cards are frequently used with the brochures; these are for the convenience of the physician in requesting a sample or more detailed information.

Service material: Valuable, or at least interesting, service material is furnished in a number of forms including the following:

(a) Paper or stiff-cover manuals on specific subjects
(b) Anatomical drawings or photographs furnished complete or in series
(c) Handbooks
(d) Reference books
(e) Descriptive catalogues with therapeutic indexes
(f) Medical journal abstracts
(g) Monographs
(h) Diabetic diet calculators
(i) Slide rule conversion tables
(j) Printed prescriptions
(k) Reprints

Service material is, in many cases, received so well that it is filed for reference and retained for long periods of time. It serves to remind the physician of the manufacturer and those of his products directly or indirectly related to the type of service material furnished. Service material is usually costly and, in many instances, is wasteful because it may be distributed to physicians who have no special interest in the subject to which it refers.

Blotters: Blotters are commonly used because they remain on

the physician's desk for a longer period of time than the average piece of promotional material. One of their disadvantages is that the space available for advertising is somewhat limited; another that many physicians receive them in such large quantities that the copy is not always read even though the blotter is used.

3" x 5" file cards: Many physicians now keep a card index therapeutic record, the most popular size for the card being 3 x 5 inches. A number of manufacturers furnish such cards with condensed information concerning the product; some are die-cut with guides. They may also be distributed as complete sets by the detail man.

Samples: There are three common methods of furnishing samples to physicians:

(a) Distribution by the detail man during or after the discussion of the product in the physician's office.

(b) Unsolicited samples sent to all physicians or certain specialists. These are frequently mailed with printed material in envelopes or metal-edge boxes with platforms.

(c) Samples mailed on request from the physician or the physician's secretary. This method requires special handling and individual addressing which sometimes slows down the delivery of the sample for several weeks. Delay of this sort is unfortunate because it may be just long enough to allow the physician to forget that he had requested the sample. In many such cases the value of the sample is lost.

Sampling is an effective promotional procedure, but entails considerable waste, particularly when the physician has no interest whatever in the item. In some sections of the country, for example, samples have been collected in a medical building and sold or given to vendors making a business of sample salvage and subsequent resale in one way or another. Despite these obvious disadvantages, no substitute has been found for the act of seeing, feeling, and sometimes tasting a product before it is used or prescribed.

DISTRIBUTION

Distribution policies are tied more closely to the development and promotion plans of a company than most people suspect. An efficient and fair distribution policy can do much to implement the promotion program of the firm. The actual sale of the product is frequently made or lost "in the last thirty inches" —the pharmacist's counter. Distribution systems are, moreover, complex—almost as complex as the products which require merchandising.

The pharmacist's profession has been gaining strength simultaneously with the growth of the pharmaceutical manufacturing industry and the medical profession. The educational background of the retail pharmacist has improved as his services have been modernized to meet present-day medical needs.

As a consequence, the influence of the pharmacist with the physician is greater than ever before. He can be and is frequently of considerable assistance in promoting the use of a pharmaceutical specialty. It should be remembered that the manufacturer reaches the physician and the patient through four major outlets:

1. The wholesale druggist
2. The retail pharmacist
3. The hospital pharmacist
4. The physicians' supply house

Furthermore, in some sections of the country manufacturers sell directly to physicians. While there is considerable volume of business done in this way, most firms prefer to make use of trade channels. However, many manufacturers sell directly to hospitals on the same basis as retailers.

Distribution through the wholesaler is required where it is not economically sound for a manufacturer to distribute directly. A few firms find it advisable to limit their distribution to the wholesaler; others combine distribution through the

wholesaler with direct sales to larger retail pharmacies and hospitals. Wholesalers can be placed in four classifications:

1. Full line service wholesalers
2. Full line mutual wholesalers
3. Short line jobbers
4. Special service distributors

The manufacturer must decide whether it is desirable to concentrate distribution through one or more of such wholesalers or to spread his efforts over all four types. Therefore, a brief description of the services rendered by the four classes of wholesalers may be of interest.

Full line service wholesaler. This type of outlet carries most general drug store lines, such as prescription specialties and chemicals, proprietaries, chemicals, drug sundries, cosmetics, and other miscellaneous articles. The service house is the largest single creditor of most drug stores; it may employ thousands of salesmen.

The mutual wholesaler. These houses are usually a service wholesaler with the difference that the ownership is distributed among a number of stockholders, mostly retail pharmacists. The stockholders receive dividends at intervals. Mutuals sometimes distribute goods to non-participating members as well.

The short line jobber. This dealer is so characterized by the fact that his warehouse facilities are somewhat restricted that in consequence his lines are not complete. He often sells for cash or does not provide an extensive credit service.

Special service distributors. This may be recognized as a new type of wholesaler. These firms carry only prescription specialties and feature fast delivery service. Obviously, they can only operate successfully and efficiently in large metropolitan centers.

Retailers acting as distributors for the pharmaceutical industry may be classified as follows:

Retail pharmacy. This may be one of four types: the ethical prescription shop, the prescription and general line store, the merchandising store, or the hospital pharmacy.

Chains. Chain drug stores may operate from three to several

hundred stores. The larger chains offer warehouse service for the purpose of pooling their purchases. In recent years some chains have made a determined effort to increase the professional and prescription business of their stores.

Physicians' supply houses. These houses distribute such articles as surgical instruments, bandages and sutures, x-ray and office equipment, and pharmaceuticals and biologicals. Pharmaceutical products which lend themselves to office use by the physician are frequently sold through this outlet. There are a number of combination retail pharmacies and physicians' supply houses as well as a few combination physicians' supply and wholesale houses. Physicians' supply houses usually employ salesmen who call on physicians and hospitals.

Any plan of distribution should allow adequate profit to all classes of outlets. Inasmuch as both wholesalers and retailers deal with large numbers of manufacturers, the discount and pricing schedules should be as simple as possible. Although distribution policies are usually tailored to fit the individual manufacturer's problems, nevertheless, they can only be successful if they take into consideration the problems of the trade as well.

MEDICAL EXHIBITS

Most pharmaceutical manufacturers exhibit their products at state, sectional, and national medical meetings. The subject is discussed elsewhere in this volume, but a few remarks are not inappropriate at this time. In recent years with the development of new techniques for visual presentations many of the exhibits have become quite elaborate, some even making use of sound and animation. They are usually designed and constructed by professionals and are built in sections so as to permit flexibility in installation depending upon the size of the space. Most firms employ the technique of emphasizing some major theme which will attract attention, thus leading gracefully to discussion of the product or other products.

Representatives attending these exhibits are carefully selected and trained for their ability to converse with physicians seeking

information. Here again the competition for attention has become so keen that an exhibit must be extremely well planned and carefully thought out if it is to be worth while. The budgets of the larger manufacturers for medical exhibits will frequently run into six figures to cover construction, transportation, installation, servicing, maintenance, and attendants. Indeed, this promotional activity has become so highly specialized and complex that a number of the manufacturers maintain departments of exhibits and presentations. These departments also prepare the budget and handle the voluminous correspondence required in connection with the scheduling and contracting for exhibits. Similar activity extends to hospital, trade, and dental exhibits, as well as medical exhibits.

Not only are records kept of the number of physicians reached in the exhibits, but the doctors are frequently followed up for future interviews. The practice of sampling at exhibits has gone out of vogue to some extent because of the large number of exhibitors and the waste which often takes place when physicians do not carry the samples back to their offices.

Medical associations require that the exhibits be in good taste and cooperate with the exhibitor by making it possible for physicians attending the meetings to find time to visit the commercial as well as scientific exhibits. Interest in the meetings and attendance have grown in recent years to the point where it is no longer necessary for medical associations to solicit commercial exhibits aggressively. However, in most cases, the manufacturer must decide whether his budget will permit exhibits at all meetings or whether he must restrict himself to general or specialized meetings best suited to his product or line.

PUBLIC RELATIONS

Although many pharmaceutical manufacturers make no effort to develop consumer publicity, the very size of the industry and some of the firms in it makes communication with the general public unavoidable. Some drug houses have, as a consequence, recognized public relations as an important activity and a few

public relations departments have been established. In general, the functions of these public relations departments are about as follows:

1. Collaboration with the advertising department in preparing institutional advertising campaigns.
2. Collaboration with popular science writers in preparing publicity releases and stories about new therapeutic products.
3. Employee house organs.
4. Collaboration with the financial department in preparation of annual statements.
5. News releases to trade journals.
6. Preparation of material for speeches delivered to trade associations and service clubs.
7. Preparation of articles for trade publications.
8. Preparation of material for company histories.

The general public has become increasingly aware of the contribution made by the pharmaceutical industry to science in the treatment of diseases. The national magazines, moreover, are conscious of the fact that the public is interested in articles on medicine. Some of these publications, indeed, insist upon a medical or scientific article in every issue. While some of these prove dangerous because of their tendency to over-simplify and generalize, and, in some cases, to publicize therapeutic results prematurely, nevertheless, it is generally considered advisable to assist these writers rather than to ignore them. It has been found that proper assistance produces articles of a more accurate and more conservative nature than if the writer does not have access to information from the manufacturers. Public relations has become an important factor for the pharmaceutical industry and its members will be faced with increasing responsibility in this field. If the best job is to be done, the responsibility must be fully met. Otherwise, many opportunities will be lost.

18

Advertising

CHARLES S. DOWNS

As in many other fields, advertising is widely employed in the marketing of prescription and related merchandise. And when it is properly planned, prepared, and used, it performs certain sales tasks better, faster, and more economically than any other merchandising method. But it must be borne in mind that advertising is merely a sales tool, nothing more. Too frequently it is considered an end in itself. Actually it serves only as one of the means to the end of better distribution.

The objectives assigned to advertising and the kind of advertising that will best accomplish them cannot in every instance be categorically stated. Indeed, each product must be considered individually in the light of many factors. For example, the manufacturer must ask himself:

Is the product entirely new, possessed of dramatic effects that will draw wide attention in the medical press and at medical meetings, or is it one of only minor and prosaic advantages?

Is it a "bandwagon" product no different than that of competitors, marketed, perhaps, only to capitalize on established demand?

Is it indicated in the treatment of common, widespread conditions, or, on the other hand, is its potential use limited?

Is the bulk of the market for it found among general practitioners, or one or more groups of specialists?

Is the market for the product a seasonable one?

Is the product acceptable for inclusion in *New and Nonoffi-*

cial Remedies by the Council on Pharmacy and Chemistry of the American Medical Association?

Will the product be self-administered by the patient on the advice or prescription of a doctor, or will it ordinarily be administered by the physician, or his nurse?

If generally prescribed for self-administration, will prescriptions be written, or take the form of oral recommendations?

Is the product an exclusive formula of the manufacturer or distributor? Is it protected by patent to assure a monopoly for a substantial period?

Does the product have a trade-mark name?

Is the probable margin of profit sufficient to warrant expenditure of money and time in its promotion?

Does the product despite a limited potential sale and profit warrant advertising as a "prestige item" to reflect credit upon the name and other products of the firm?

What sort of competition must the product face?

With the answers to these and similar questions, the formulation of advertising strategy and plans is next in order.

For the entrant in the "ethical" marketing field, one of the first decisions necessary is the reliance to be placed on advertising, as compared to detailing, to develop the market. Nor is this a problem likely to be solved satisfactorily by blind adoption of any detailing-advertising expenditure ratio used by other firms. Indeed, that there is no single proportion generally accepted is demonstrated by the variety of practices followed. Thus, there are extreme instances of successful dependence wholly upon advertising. It may be mentioned, too—although consideration of the policy does not fall within the scope of this chapter—that there are equally extreme examples of profitable reliance completely upon detailing. But a much larger group of cases represent the successful use of almost every possible combination of the two means. Neither to be ignored are the

many failures that often characterize every gradation of procedure from one extreme to another.

Marking the difference between those marketing successes and failures—after making due allowance for variations in other factors affecting the consummation of sales—seems to be no more than the conscious or unconscious application of a rather simple formula by the successful organizations. This principle may be summarized thus:

> *Never use the costly tool of detailing for any sales operation that can be performed as well, or better, by the relatively cheaper medium of advertising.*

Other criteria also serve to guide the manufacturer in the selection of marketing media. Is the product an exclusive one? Does it possess dramatic and easily demonstrated advantages over all other products used in the treatment of the same conditions? Are clinical reports in the medical press extensive, highly favorable, and from authoritative sources? Is distribution rather easily accomplished? If the answers to all of these questions are in the affirmative, it is reasonable to anticipate that the product can be marketed successfully by means of effective advertising alone. Furthermore, in all probability, sales effort *should* be confined to advertising in those instances where the manufacturer has but one or, at most, a very small number of products, to bear the cost of detailing; or where the potential market is not large; or is controlled by a small, widely scattered group of physicians.

To the degree in which marketing conditions differ from those specified, dependence upon advertising should be reduced. Perhaps the circumstances are distinguished only by the fact that adequate distribution requires personal selling to appropriate trade outlets. Perhaps the advantages of the product and published clinical reports are such that many physicians can be persuaded to prescribe it only by personal sales presentations attuned to the attitude, reactions, and special needs of the individual practitioner. Again, the product may be identical with those of competitive firms so that the cultivation of per-

sonal friendships by detail men must be the chief reliance in building both distribution and sales. In any case, the formula remains the same: Fit the tools to be employed to the needs of the sales task. The application of this rule more often than not results in the use of some combination of detailing and advertising, since few products lend themselves to successful promotion solely by one means or the other.

When advertising is employed in combination with detailing, it should be designed:

To gain distribution and professional acceptance and use wherever this is possible. This course permits the detail man to concentrate his effort upon the more difficult prospects.

To win a more receptive audience for the detail man. This is accomplished by repetition of the name, advantages, and uses of a product, together with the company name. The resulting familiarity gives the product and company something of the character of old friends. Some of the prospect's friendly feeling thus created favors the detail man when he calls.

To enable the detail man to make better use of his time. Some knowledge of the product on the part of the prospect eliminates most introductory explanation by the detail man. Consequently, he may devote nearly all of the time allotted for his call to clarify points which the prospect may not fully understand, as well as to elaborate upon those in which the greatest interest is exhibited.

To offset skepticism toward the detail man's claims. Some prospects discount many of the statements of detail men as understandable over-enthusiasm. The same statements in print, over the name of a reputable company, are more likely to be accepted at face value. This is especially true in the case of products whose advertising is screened by one of the councils of the American Medical Association or the American Dental Association.

To give dramatic or sentimental expression to sales points.

Most detail men find it difficult or impossible to deliver an idea dramatically or sentimentally. Yet, even in prescription product promotion, drama and sentiment are sometimes the best of all means for emphasizing sales points. Advertising can and does use both approaches successfully.

To add in other ways to the effectiveness of detailing. Left with the prospect by the detail man at the time of his call, advertising can serve as an effective reminder of salient sales points touched on, and also as a memorandum for ready reference regarding use. Employed to follow up the detail man's call, it may be used both as a further reminder and to give additional information if this is needed. When it is scheduled to appear at intervals between regular detail calls, the force of often repeated visual impression is added to the verbal impressions achieved by detailing. The effect may be more than cumulative; it may be described as synergistic.

To reach professional men in areas where it is not economically feasible to send detail men, or to pave the way for the establishment of detail men in new territories.

To confound, beat, or meet competition with announcements of new prices or products, or any other news in which speed of dissemination is a factor that may affect sales.

THE ADVERTISING APPROPRIATION

A number of methods of varying value of fixing the advertising appropriation are in common use. The first is that of the hit-or-miss lump sum, its size determined by the collective judgment, guess, whim, penury, generosity, pessimism, or optimism of the management prevailing at the time the appropriation is made. Comment upon this procedure would be superfluous.

A somewhat better, though scarcely ideal, practice is to appropriate a percentage of the amount of total sales in a preceding calendar period. In some organizations this percentage figure is a matter of fixed rule, and does not vary from period to period.

Yet a better method is the appropriation of a percentage of

the volume of expected sales for some calendar period. This practice is further improved if provision is made for periodic upward or downward adjustment in the amount of money appropriated to compensate for the difference between sales expectation and realization.

A fourth procedure strongly supported in many quarters is appropriation of the sum estimated as necessary to accomplish a desired result in a given time. This, perhaps, is the best of all methods when the effect of advertising upon sales can be determined in advance with absolute, or nearly absolute, accuracy. When such determination is not possible, however, as is often the case when a combination of sales methods is to be used, its shortcomings become obvious.

Another course open to firms having a number of products to be advertised is to employ some combination of the methods just described. Here, a bulk appropriation is determined by one method, while another dictates the division of the total sum into individual product appropriations.

Whatever the choice of method, however, its operation should invariably be guided by the answers to the questions asked earlier in this chapter. By way of illustration, suppose that the product to be advertised is new, exclusive, carries a high profit margin, has outstanding advantages, and can be widely employed by the great majority of the medical profession. Such a product might well be given an advertising expenditure of thirty per cent or more of estimated sales for the first year. If the exclusiveness of the product is not protected by patent, so that similar products can be expected upon the market within a fairly short time, an even higher early expenditure may be in order. In such instances, the rapid and wide establishment of a trade-mark name in the minds of physicians may be an important competitive factor, and should be considered in fixing the amount of the expenditure.

On the other hand, older and well-established products, those with small markets, and highly competitive, small-profit items call for lesser budgets ranging downward, according to circumstances, to perhaps nothing at all.

In general, firms engaged in the ethical marketing of sizable lines embracing exclusive and nonexclusive specialty, as well as highly competitive, products, have total advertising appropriations ranging from two or three per cent of total sales volume up to twenty per cent or more. The average for specialty and semi-specialty drug products probably lies somewhere between ten and fifteen per cent.

TACTICS

After the matter of appropriation has been decided, the problem of employing the money to best advantage arises. Sound planning is essential, and here again the answers to previously propounded questions are of value.

The first factor to be considered is the audience to which advertising may be addressed most profitably, whether this audience be composed of physicians generally, of dentists, nurses, veterinarians, pharmacists, of one or more classifications of medical specialists, or of a combination of some of these groups.

Answers to the same questions will have already indicated whether or not the product is one that requires detailing to accomplish most or all of the actual selling. Obviously, this is as important in formulating strategy as in making other advertising decisions. For, if detailing is to carry the heaviest burden, any advertising done should be of quite a different character than if the case were otherwise. The aim of advertising in this event should be to provide the background for detailing. Such advertising should be planned primarily to create a favorable attitude in the minds of the profession, with very little actual selling attempted or expected. Its principal functions will be to gain attention and to remind. Brief, restrained copy is in order. Strikingly designed, but dignified physical formats will be found of special value. The use of excellent pictorial illustration may add much to the effectiveness of the advertisements.

Perhaps, however, the product lends itself to advertising intended to create a part, or even all, of the demand and sale. If so, the printed message must not only attract attention and, to a

limited degree, remind, but must also inform and persuade. Copy will be longer in most cases, and will attempt to induce an affirmative response.

In the latter event, another decision is required. Should the broad, primary or basic advertising addressed to prospects generally attempt to effect completed sales? Or should part of the effort of this primary advertising be directed toward securing inquiries from interested, but not wholly convinced, prospects? These would then be subjected to further sales effort through follow-up letters, circulars giving additional or special information, samples, detailing, or other promotion.

Circumstances vary to such an extent that no single answer can solve all of the questions. Certain suggestions, however, may aid in determining policy. In general, it may be said that the solicitation of inquiries for follow-up will serve no useful purpose when all of the following conditions exist:

(1) The product is exclusive and possessed of unusually striking and easily demonstrated advantages.

(2) Published clinical reports on the use of the product are extensive, uniformly favorable, and are receiving wide attention from prospects.

(3) Administration of the product is simple and safe to an unusual degree.

However, the more the factor of competition must be reckoned with, or the more the successful use of the product demands special educational effort among prospects, the greater is the need for solicitation of inquiries for follow-up.

One of the most common causes of advertising failure is lack of consistency and frequency. Too many advertisers overlook or underestimate the difficulty of changing established patterns of habit and thought. The result is printed promotional effort that is too weak or too scattered to bring about the change in a sufficiently profitable number of cases.

To appreciate the importance of regularity and frequency in achieving the desired results from advertising, compare this tool for a moment with personal selling. No firm would expect a detail man to sell every prospect on the first, second, or, indeed,

third call. Even less would be expected if the visits were spaced many months apart. Furthermore, account would be taken of the fact that successful persuasion of medical practitioners is more than ordinarily difficult in the case of the average drug product. The treatment of disease is a very serious matter—so serious that few physicians are likely to substitute a product of which they have heard infrequently for one with which they are already familiar through use.

It must be recognized, furthermore, that it is easier for a detail man than for advertising to win the prospect's attention and time. Some students in this field firmly believe that no one advertisement, however dramatic, is apt to be read by as high a percentage of prospects as would listen to a detail man.

How unreasonable it is, then, to attempt to perform the tasks assigned to advertising with one, two, or three, or even ten widely spaced messages costing only one-fiftieth to one-twentieth as much as detail calls!

It follows, therefore, that for results advertising must be conducted on both a regular and frequent schedule. The effect of advertising is cumulative. The first, second, and third advertisements may stir only a ripple of action. The fourth, fifth, sixth, and seventh advertisements may bring only a slowly growing response. All of the time, however, if the advertising is prepared on sound principles, it is becoming more and more deeply impressed upon the minds of prospects. Then, sooner or later, one after another of a high percentage of them reads one of the messages at a time when, for some reason, his pattern of habit or thought is ripe for conversion. He tries the product advertised, or takes the crucial step that leads to trial. If the product is good, he continues to use it, and competitive firms will, in turn, find it difficult to make him change.

But what if the firm has a number of products to sell and an appropriation which permits only a thin advertising coverage of each prospect? In that case, the best rule is to select the most promising product and advertise it every month or oftener. What if the appropriation is only large enough for once-a-year advertising of one product to the national market of 145,000

physicians? Then pick an appropriate area of 12,000 physicians, and advertise to them twelve times a year. The records of the most successful advertisers prove that concentration of this kind is by far the more profitable procedure.

MEDIA—SAMPLES

The president of one great pharmaceutical company said not long ago that if his firm were required to give up, one after another, its three major types of advertising to the medical profession, he would choose to abandon medical journal advertising first. Second to be dropped would be direct mail. Last to be given up would be samples. He then qualified his remarks so extensively as to force the conclusion that he considered all three media indispensable to a well balanced ethical advertising program. Nevertheless, the order of his choice indicates, inversely, the order in which the three media usually produce direct, traceable, dollars-and-cents results.

That there is a sort of sales magic in samples cannot be denied. This is a fact discovered a long time ago by ethical drug product manufacturers. In this field, probably more than in any other, the power of samples to make sales is proved. And year after year it continues to pay.

Place a sample in the hands of the physician, or, in appropriate cases, the dentist, nurse, or veterinarian. Let the prospect see, handle, taste, smell, or feel the product. The sample may be small, far too small in many instances to observe its effect upon even one patient. Despite this, the sample in many instances will do more than any other type of advertisement to register the name of the product and its uses in the prospect's mind. Practically the only ethical drug products whose sales will not be benefited greatly by sampling are the rare medicaments distinguished by advantages so great that in simple justice to the patient their actual use is called for.

The most convincing of all samples, of course, are those which demonstrate the effectiveness of the product. These include such products as sedatives, analgesics, vasoconstrictors for the

relief of nasal congestion, laxatives, and all other drug products of which samples of practicable size produce readily demonstrable results. Upon proper occasion, the physician or other practitioner may employ these samples by trial upon himself or one or more members of his family to evaluate the effect of the preparation. If results from this use are impressive, there is considerable likelihood that the product will be adopted immediately for use in his practice.

In other cases, the prospect may choose to put the product sample to trial upon one or more of his patients. In this event, again provided results are sufficiently good, the advertiser's chances of accomplishing his objective still remain high.

With certain types of drug products, including some which do not, as well as some which do, produce nearly immediate demonstrable results, sampling to the medical and allied professions exerts a further important influence in building sales. This occurs when the products sampled are those for which oral orders or recommendations to the patient commonly take the place of written prescriptions. Representative of such products are antiseptics for superficial cuts and abrasions of the skin, mild laxatives, antacids, relatively safe analgesics, certain vitamin and other nutritional supplements, emollients, and special foods for infants and invalids.

When a preparation of one of these types is indicated, many physicians—and in some instances, dentists—give the patient a sample of the product favored, and instruct him to purchase a trade package for continued treatment. Specialists in child practice are particularly notable for the extent to which they follow this procedure in prescribing vitamin products and food formulas.

The effect of this practice upon patients is a powerful stimulus to sales. For all practical purposes, the physician or dentist has given his personal testimonial that a certain drug is the best of its kind. And, since that physician or dentist is, to his patient, the highest and most respected health authority in his community, the implied testimonial carries greater weight than recommendation from any other source.

Nor is the effect of this testimonial necessarily confined to a single sale. If a similar need arises again, the patient will, rightly or wrongly, probably try the same product. Furthermore, if the product can be widely used and the patient understands that it is reasonably safe, he is quite likely to repeat his physician's or dentist's recommendation to members of his family and to friends. Some of these, too, usually are favorably influenced by this evidence of professional preference. The result is that a single sample is often responsible for placing the product in a substantial number of home medicine cabinets.

Of course, sampling can be abused unless it is limited to useful and harmless drugs. The physician should not be used to exploit the patient. However, two factors tend to preclude unscrupulous exploitation of professional distribution of samples to patients. First, the vast majority of physicians and dentists will not distribute samples of products promoted to the public in a manner offensive to the professions. Second, all really conscientious members of these professions are quick to recognize, and to refuse to distribute to patients, samples of products of questionable worth, or those whose even partially unsupervised use is attended by any appreciable degree of danger.

Samples may be distributed by several methods:

(1) Unrequested samples may be mailed out indiscriminately to suitable groups of prospects.
(2) Samples may be sent upon requests solicited in the firm's other advertising.
(3) They may be distributed by detail men.
(4) They may be given out at commercial exhibits staged at meetings of professional groups.

Both advantages and disadvantages distinguish each of these methods. Unsolicited sampling is costly and results in a high degree of waste. With properly chosen products, however, it has been proved repeatedly to be of tremendous value. While sampling only upon request may reduce initial production cost and waste, some of which is offset by increased clerical costs, this method may also result in uneven distribution of samples. The

latter shortcoming likewise marks distribution of samples by detail men except in organizations having complete and intensive detailing coverage of all areas they serve. If, moreover, competition or other factors make the rapidity of sample distribution important, detailing may provide too slow a method. A further drawback is that it is not always possible to make every detail man conform exactly to home office wishes in the matter of sampling.

However, one of the advantages of the method, especially in the case of expensive samples, is that the detail representative can gauge the interest of the prospect and confine distribution to cases where the sample investment is likely to pay the largest return in subsequent sales. Another advantage is that the effect of the detail interview itself usually is heightened by the representative's presentation of one or more samples at the proper time. The latter factor alone undoubtedly justifies extensive use of samples by detail men. Generally speaking, however, such distribution should be used in combination with other methods, rather than made the sole sampling outlet of the advertiser.

Much that may be said of the employment of samples in detailing may be repeated as to their gift at medical and related scientific meetings. Only one additional consideration needs mention in the latter case. This is the fact that prospects attending these meetings frequently find themselves burdened by the quantities of samples and other promotional material given out by commercial exhibitors. If this occurs too often the accumulation is quietly discarded, either in some obscure corner of the exhibition hall, the public washroom, or the prospect's own hotel quarters. The better practice for exhibitors is to have samples on hand for prospects who wish to carry them away, and also to offer to mail samples to those who prefer it. Because of the difficulties of cost and expenditure of time involved in any attempt to reach the majority of a firm's prospects through professional meetings, sampling at these gatherings is of value chiefly as an auxiliary method, or for testing interest in new products.

Samples may range from miniature to stock package in size. A single specimen or many samples of the same product may be given to a prospect at one time. In both instances the determining factors are the nature of the product and the advertiser's objective in distributing samples.

Samples supplying a small quantity of the product—for example, one-tenth to one-half that contained in the smallest trade package—are usually sufficient:

When their chief purpose is to enable the professional prospect to see, taste, smell, or handle the product.

When the samples are intended to demonstrate results, and a small quantity of the product suffices for each trial. A sufficient number of samples should be supplied to convince the prospect thoroughly.

When most of the samples will be given to patients in connection with oral prescriptions. Here, again, a quantity of samples is indicated. The number is best determined by consideration of the number of patients for whom the average prospect can prescribe the product, and the seasonal character of its uses. Prospects usually prefer to be supplied periodically at not too extended intervals, rather than to receive a large number of samples at one time. This course obviously benefits the advertiser also.

Large samples or stock packages will be found more useful:

When the object of sampling is demonstration of clinical effect, requiring substantial quantities of the product.

When the product is one which the prospect, or members of his family, might find useful for frequent or daily employment in the home. This would include such preparations as those used for minor first aid, or for symptomatic relief in common conditions such as "colds." Another example is provided by vitamin products taken regularly as a routine health measure. Both good will and frequently repeated impression of the

name of the product can be achieved by supplying adequate quantities for this use.

When the product is one whose name the prospect does not wish to divulge to patients. In cases of this sort it usually is much more convenient for the prospect to dispense small quantities from a large container than to open and remove the contents from a miniature package for each patient. Secrecy regarding product name is commonly practiced in instances in which the physician may feel there is a possibility of dangerous self medication if the name becomes known.

When the product sampled is one frequently administered by the prospect himself in his office or bedside practice, and is also used at his order in larger quantity in other outlets. His preference in the larger purchase may possibly be favorably influenced by keeping his office or bedside requirements constantly supplied. One example of products of this nature is the inhalant. The initial treatment may be given by the physician in his office. Although the amount of the preparation used then is small, a profitable volume of sales results if the physician, at the same time, writes a prescription calling for fairly frequent, repeated use of the product afterward. Another illustration is the skin antiseptic. These are commonly used in the practitioner's office, although very rarely in any quantity upon a single patient. Their greatest consumption occurs when they are prescribed for home use in dermatological disorders, or when their application is ordered upon the operative sites of patients about to undergo surgery. Other products in the same general category are drug preparations of which the prospect may personally give a single dose for quick effect, and then write a prescription calling for repeated subsequent use by the patient. In these and many similar instances, money spent in supplying the office and bedside administration requirements of prospects is often very profitably invested.

Ingenious and at times expensive containers, especially designed for office, pocket, or emergency bag use, are often

provided for large samples from which the prospect will dispense small quantities. Many of these are planned for permanent use, and so constructed that they may be refilled easily with additional quantities of the product sampled. Refilling is handled in some instances by detail men; in others by keeping a record of prospects having the containers and mailing refills at regular intervals.

One note of caution about samples: When they are offered upon request, it is highly important that all requests be filled promptly. Samples not sent until long after prospects have forgotten about asking for them greatly diminishes their advertising effectiveness. Advertisers should devise in advance some practicable plan for coping with any unusually large number of requests.

DIRECT MAIL ADVERTISING

Direct mail advertising is the acknowledged medium for obtaining maximum measurable response from prospects in the medical and allied professions. Is the purpose of the advertising to secure sample requests in large number? Does the advertiser desire inquiries for complete and detailed information on the application of his product under general and special conditions? Is the product one for which the advertiser seeks direct or indirect mail orders? Then direct mail advertising is the medium of choice. One of the reasons for its use is its economy in the long run. For while the initial investment in this form of promotion is ordinarily greater than with other advertising, the cost of each response secured is almost invariably lower with direct mail. Under some circumstances, indeed, its cost, in terms of results obtained, may also be cheaper even when the object of the advertiser is only to obtain wide dissemination for the important selling points of his product, rather than immediate inquiries.

These statements are contrary to opinions occasionally expressed by proponents of other advertising media, as well as by some members of the medical and allied professions. We have all heard the snap-judgment that the bulk of direct mail mate-

rial is consigned unread to the waste basket. However, there is ample evidence to prove that this is an unwarranted and untrue assumption.

There are, for example, the results of a survey made among American physicians by the school of business of a leading university. This investigation disclosed that more than sixty-eight per cent of medical men opened and inspected, at least cursorily, all mail advertising of medical and allied products. Among physicians in a very large city, ten per cent read all advertising mail received, while eighty-seven per cent read a part of it. In communities of less than 25,000 population, sixty per cent of the practitioners perused all direct mail addressed to them. An even higher percentage of readers of advertising mail was found among physicians in very small towns and in the South. This treatment of direct mail material was discovered to be only slightly lower among medical specialists as compared to general practitioners.

These findings are all the more remarkable when one considers that during the period of the survey an average of almost twenty direct mail advertisements a week was received by the physicians studied; in some instances, in fact, the figure exceeded forty.

This study demonstrates that direct mail advertisements are read. For evidence of response from such perusal we turn now to the highly successful experience of steady and frequent users of the method, among them the producers of some of the larger selling ethical pharmaceutical specialties. Most of these firms are understandably reticent concerning details in this regard when such are sought for publication. From those which are available, however, as well as from reports phrased in terms of general experience rather than of specific examples, certain conclusions emerge.

The first and most impressive of these concerns responses to two types of mailings which, together, make up more than fifty per cent of all direct mail advertising addressed to the medical profession. One of these is the printed broadside folder and reply card; the other is the form letter with which a leaflet and

reply card are enclosed. Our interest at the moment is directed toward the most common use of these types of mailings, the presentation of one or more of the most important selling points of some pharmaceutical specialty, and the solicitation of requests for samples, or for more information on the use of the product.

It must be admitted, first of all, that much of this advertising is conducted under the favorable auspices of the following conditions:

(1) The advertiser is a reputable, well known firm.

(2) The advertised preparation is a drug of some special interest to the medical profession.

(3) The product, although not exclusive, gives promise of being genuinely useful in a substantial number of cases in the average prospect's practice.

(4) Samples or literature offered are of a nature to appeal to many prospects as of interest or use.

Under such circumstances many pharmaceutical houses consistently receive a response of from seven to eight per cent and up from well prepared and designed form letters or circulars addressed to general medical practitioners. Indeed, one firm, with many years of experiece in the field, regards any response of less than ten per cent as a failure. The response, moreover, is substantially increased by such factors as unusually skillful preparation of the advertising, dramatic product advantages, or the offering of samples or literature of obviously more than ordinary value. In these instances, returns of twenty and thirty per cent are not uncommon nor are those of forty per cent and more unknown.

By way of comparison, sample or literature offers featured in medical journal advertising rarely exceed one to three per cent in replies. In terms of cost of inquiry, the average for competently prepared direct mail in the pharmaceutical industry generally amounts to one-half or less—often the latter—of the cost of medical journal advertising. In this connection it should be pointed out that the value of medical publication

advertising in producing inquiries is by no means the sole measure of its worth; its more important functions will be discussed later.

Why is direct mail advertising for ethically promoted drug products so effective in gaining responses from physicians? The answer probably lies in a combination of circumstances. One factor is the precision with which the advertiser of a drug or allied product can direct and confine his promotion to immediate prospects. In few other selling fields can the sifting of active from indifferent prospects—along the lines of almost any scheme desired—be accomplished in advance with so much exactitude.

Is the product one which offers advantages that make nearly every physician a prospect for its use in profitable volume? Any one of several firms, specializing in mailing work to the medical and allied professions, can immediately furnish a list of every prospect licensed to practice medicine in the United States. Is the product of interest only to certain medical specialists? Or only to dentists or to veterinarians? Or will it appeal to physicians generally with the exception of one or more groups of specialists? No matter. There are available mailing lists organized and classified to meet in detail every variation of need. If climate, competition, incomplete distribution, lack of full detailing coverage, or other factors suggest limiting advertising to certain geographic areas, these may be chosen in any desired combination of States, counties, and towns. If it be thought that professional prospects above this or that or the other age are likely to be wholly or partially retired in many cases, or "too set in their ways" to be interested in new products in a profitable number of instances, mailing list classifications can also solve the problem.

It follows that there need be no waste or unprofitable circulation with medical direct mail advertising. The more experienced users know this, and carefully channel its force so as to achieve maximum results.

The mechanical flexibility of the medium is undoubtedly another important contributing factor to the remarkable effec-

tiveness of direct mail in the medical marketing field. Evidence of the advantages of this flexibility is revealed by a study of any physician's mail. Here may be seen a range of advertising vehicles extending from the humble postal card—at times beautified by the commercial artist and printer almost beyond recognition—to elaborate and patently expensive books and brochures. In between are folders, letters, blotters, booklets, and house organs of nearly every description.

While it is not always fully exploited, the advantage of tailoring the advertising format to fit the needs involved is evident in much of this mail. When charts, graphs, anatomical drawings, or any other kind of pictures are important in the advertisement, the mechanics of direct mail require no compromise in the matter of their most effective presentation as frequently occurs in journal advertising.

Moreover, wide latitude for the exercise of ingenuity is extended in the use of devices for gaining attention. Full control of materials and reproduction processes make possible maximum attractiveness and readability. There is no danger that many thousands of prospects may see the advertisement in distracting or even ludicrous juxtaposition to others, although this is not a problem in the best managed medical journals. Again, if inquiries are desired, provision can be made for reply in the easiest possible manner. And advertising material which the prospect may find useful for future reference may be designed for easy filing in desk or cabinet. These advantages leave little room for wonder that direct mail promotion excels most other forms of medical advertising in its ability to bring written responses. For the same reasons direct mail is sometimes the medium of choice, not merely for exploitation of its inquiry-producing power, but, as previously mentioned, to obtain wide dissemination for the product's selling points. In certain instances this end is possible through use of the special formats and reproduction processes only available with direct mail advertising.

In yet another respect direct mail has been found to be unique. Thus, it has proved the only advertising medium capa-

ble of inducing orders by mail in volume for drug firms selling to physicians who dispense, rather than prescribe, the medicines needed by their patients.

One great temptation besets every user of direct mail with more than one product to sell. Unfortunately, moreover, it is a temptation which all too infrequently is successfully resisted. This is the practice of advertising a number of products in a single mailing. Repeated tests by advertisers have proved that in many instances just as soon as a mailing scatters the prospect's attention over more than one product, results in sales, inquiries, or remembered impressions decline. Should maximum results for each dollar spent be the objective, the mailing advertising one product is the way to obtain them. The only exceptions to this rule are catalogues, manuals for therapeutic reference use, mail order advertising featuring specially priced assortments of drugs, and house organs or company magazines. And, even in the latter case, it is advisable to advertise not more than a few products in an issue.

Most discussions of direct mail advertising lead, sooner or later, to the subject of styles or types of mailings. Is a form letter accompanied by a leaflet or booklet and, perhaps, a blotter, together with a reply card, more effective than a small broadside folder and reply card? Experienced direct mail users in the medical field are in fairly general agreement that no one mailing style can be said to be the most effective. The safest method is probably to tailor each mailing to fit the specific problem involved.

House organs have been the subject of considerable special discussion in recent years. Several of these publications have come to enjoy a relatively high standing among physicians and members of the allied professions, indeed, to such an extent that other company magazines suffer by comparison, both in quality of editorial content and physical appearance. Consequently, unless the advertiser is prepared to compete with the best in both respects, probably the most prudent course is not to embark upon such a venture.

Tests made by successful advertisers in the ethical drug mar-

keting field seem to indicate that the class of postage used makes little or no difference in direct mail results, except in a few special instances. It is not surprising, therefore, to find that only about three per cent of all advertising mail received by physicians, other than government postal cards, is mailed by first class postage, most firms employing third class mail.

Any summation of facts having the greatest bearing on the effectiveness of medical direct mail would include the following, although, it may be noted, their sequence is not necessarily the order of their importance:

Attractive, striking, or unusual appearance. Appropriate design, color, and pictures play an important part here.

Skillful presentation of the principal benefits that will accrue to the prospect and his patients through the use of the product advertised.

The need for the product in the prospect's practice.

The ease with which samples or more complete information can be requested, if obtaining such requests is one of the objects of the advertiser.

The reputation and prestige of the advertiser.

The last point listed is important, for it has been demonstrated that physicians give greater attention to direct mail from the better and more favorably known firms than to that from others. It is in the achievement of such reputation that the next advertising medium to be discussed plays one of its most important roles.

PROFESSIONAL JOURNALS

Professional journal advertising is the medium for achieving frequently repeated impression at lowest cost. It is the medium which accomplishes more for each dollar expended than other forms of promotion in establishing and enhancing the reputation of a firm and its products. It is the medium which makes all other forms of advertising more effective by causing the

prospect to remember, "Oh yes, well-known firm—products considered good," instead of "Now where have I heard the name before?"

The value of professional publication advertising in accomplishing these ends is simply explained. First, there is the factor of cost. The larger medical and allied professional publications provide advertising circulation of full-page messages at less than one-half the cost of advertising printed on government postal cards, the very cheapest form of direct mail promotion. More elaborate types of the latter, of course, multiply differences in cost—often many times.

But low cost circulation is without value to the advertiser unless his message is seen and read. For evidence that it is, reference is again made to the results of the university research cited above. In one of the studies conducted during this investigation, a selected group of medical advertisements, which had been previously published, was shown to a carefully chosen cross-section of the medical profession of a large city. Physicians included in the survey were asked to identify which advertisements they remembered having seen, and, of these, which they had read.

The study showed that the journal advertisements in the group had been seen, when published, by an average of more than forty-two per cent of all the general practitioners surveyed. This compares with an average of slightly above thirty-seven per cent of general practitioners who remembered the direct mail advertisements shown. Remembrance by specialists was considerably less, though still substantial, in both cases. Moreover, more than forty-seven per cent of the remembered journal advertisements had been read, the corresponding figure for direct mail advertising being about fifty-four per cent. Of course, certain advertisements in both categories ranked above the average for remembrance and reading; others were below.

Here is strong support indeed for the conclusion that the attention achieved by medical journal advertising is excellent. Nor should the great disparity between this medium and direct mail advertising in ability to draw replies mitigate against these

findings. For even if journal advertising is only seen and read, without producing traceable action in more than a few instances, the advertiser may still expect direct, tangible benefits from it. First and most obviously, it is the least expensive form of "reminder" advertising. A prospect can be reminded of the name and principal advantages and uses of a product two to six times for the cost of one direct mail advertisement. This alone is sufficient to warrant the wide use of journals, at least as a supplementary medium. Moreover, in those instances where printed promotion is expected to do no more than repeat a name or state advantages as a support for detailing, expenditures for space in medical publications probably should be the largest item in the advertising budget.

The second great advantage of the medium is, in many ways, the more important. It accrues to those firms whose messages appear in journals which exclude from their pages all advertisers and advertising that fail to conform to certain rigid rules and principles. These publications include all which adhere to the code of the Council on Pharmacy and Chemistry of the American Medical Association, as well as other journals which have set up rigorous rules of their own.

Representation by advertisements in these publications is almost tantamount to a certification of the firm's integrity, substantial character, and observance of high ethical standards in dealing with the healing profession. Prospects recognize that questionable firms with products of dubious worth are not permitted to advertise in these magazines. As a consequence, regular advertising in them promotes, as no other medium can, the feeling by the reader that the company, with its products, is included among those entitled to greatest respect in the field. Conversely, failure to advertise in such journals may be sufficiently conspicuous to draw conscious or unconscious attention, and thus introduce an element of doubt into the minds of prospects.

The significance of these points becomes clear when we realize that, in marketing medical products, the advertising of firms having the highest reputation and prestige receives most favor-

able attention by prospects. Advertising in journals of the type under discussion contributes to these attributes and thus the effectiveness of other forms of advertising.

In any discussion of advertising value, mention should be given to the reading of journal advertising by medical specialists. Usually these men are less responsive to all types of advertising than general practitioners. Nevertheless, specialists appear to observe and read more journal advertisements—not merely in their own special publications, but in magazines edited for the profession as a whole—than general practitioners do. This is a matter worthy of attention in advertising products whose principal appeal is to specialists.

Probably no other vocational field approaches that of medicine in the number of magazines published on regular schedule. In the United States alone there are literally hundreds. First in circulation and first, by far, in influence is the weekly *The Journal of the American Medical Association.* Next in circulation, if not in influence, are three periodicals supported almost entirely by advertising which, it may be remarked, is not too rigidly screened. These are distributed without charge to most physicians in the country. Then come a dozen or so general medical journals, of national or regional scope, but with much smaller circulation; more than fifty magazines edited for various classes of specialists; nearly forty State medical association publications; and, finally, a very large number of county and town or city medical society bulletins. Publications are less numerous, though still substantial in number, in the fields allied to medicine.

In making a choice among these journals, the advertiser should take into consideration not only the special factors involved in selling his particular product, but also the circulation, reputation, influence, and appeal of the publications most appropriate for his advertising.

Another consideration is the cost of journal circulation. Between many journals there are substantial differences in cost for each thousand readers. In the four publications of largest circulation, rates per thousand readers are lowest. At the time

this chapter is written, current prices for full-page advertising space purchased on contract for the use of twelve or more pages annually, are about, in the major publications, $3.50 to $4.50 per page for each thousand circulation. The comparable average rate for State medical association journals is not quite $12.00. Rates for magazines edited for specialists, and for many local and county medical society bulletins, amount to $20.00, and more, per thousand readers.

Obviously, advertisers, whose distribution area is limited or whose product appeals only to specialists, would be unwise to purchase circulation worthless for their purpose. It is equally obvious, however, that the larger circulation journals enjoying unquestioned prestige are highly economical media when a medical product's distribution is national and its appeal is to the profession generally. It must not be forgotten, moreover, that most physicians take great pride in their state and county journals.

The same principles of continuity and frequency applicable to other forms of medical product promotion apply equally to journal advertising. Most drug product advertisements in medical journals are full page in size. For the advertiser of limited budget, however, it is undoubtedly much better to advertise regularly with one-half or one-quarter of a page, or even smaller, messages, than to use full pages only occasionally. For the same reasons, regular advertising in one or a few journals is more effective than one-time advertisements inserted irregularly in many publications.

Color may not yet be as important in competing for the attention of medical journal readers as it is in direct mail advertising. The reason is that less than five per cent of medical direct mail promotional material is without color, while most journal advertising is still printed in black ink only. Competition for attention through the use of color does not appear to be as keen in the case of the latter medium. On the other hand, this may be advantageous as color would be strikingly noticeable when properly used in a mass of advertisements that are simply black and white.

The use of color in medical publications is growing, however, and its advantage in catching the attention of readers is undoubtedly great. Indeed, its value now for this purpose is probably many times that it will be in the future when, as seems likely, most journal advertisements will be printed in color. Today, an increasing number of magazines are offering advertisers the use of another color with black for presenting their messages. Usually the additional cost is not large, a fact which recommends the idea for consideration in many cases.

Another method of employing color in journal advertising is through the use of so-called "insert-advertisements." These are printed by the advertiser's printer, and are furnished to the journal to be bound into its pages. The stock used for these inserts is usually heavier than that employed in the body of the magazine. The result is that nearly every reader who casually thumbs through the magazine finds that it falls open automatically where the heavier paper has been inserted. This, together with an opportunity for the unlimited use of color, make insert-advertisements an important part of the programs of a substantial number of leading pharmaceutical manufacturers.

The value of special position in professional journals is the subject of much discussion in advertising and publishing circles. Special position space is that which, due to its location in the magazine, is likely to be observed by more readers for a longer time than advertising space elsewhere in the magazine. The advertising pages opposite the first and last pages of editorial content are examples.

Special positions sell at a premium rate, and there is usually far greater demand than supply. Some professional journal publishers are attempting to ease the pressure upon themselves by arranging editorial matter so that some of it appears near each advertisement in the magazine. Their usual procedure is to continue to sell the very best positions at higher prices, but to make no additional charge when the advertisements are placed next to reading matter in unspecified positions. Other publishers, most of them in the medical field, hold to the traditional

format of an advertising section front and back with the editorial material placed between.

In either case, special positions are of unquestionable value when they can be had. Certain advertisers have made notable use of them over long periods of time. But the importance of special position should not be overrated at the expense of the message itself. What the advertisement says and how it says it are always more important than the position in which it appears in the publication.

What should be the proportion of journal advertising expenditure to that for the other two major ethical media, sampling and direct mail promotion? The correct answer in any case is one that only the advertiser himself can provide. Any analysis begins with a sensible and critical appraisal of all known or discoverable elements affecting the sale of the product. It is only completed when, by experience, experiment, and the exercise of good judgment, the preliminary plans are molded into the form that most efficiently serves the particular needs.

CONVENTION EXHIBITS

Each year medical and allied professional groups hold nearly one hundred and fifty conventions at which producers of drug and other products incident to the practice of medicine may rent space for exhibition purposes. Despite the number of these meetings, and their large total annual attendance, however, conventions do not directly serve profitably as a major advertising medium except, perhaps, in a few instances. These generally exist for only those firms offering medical items for which direct, on-the-spot sales can be secured in money-making volume at conventions—books, instruments and other professional equipment, and possibly a few other products.

But for most companies in the medical marketing field, professional meetings do not provide sufficiently continuous and frequent coverage of prospects to qualify as more than a secondary and supporting advertising medium. For this reason,

budgets for exhibits should represent a smaller part of the total cost of most advertising programs.

This is not to say that convention exhibits are not without an advantage peculiarly their own. For it is true that no other medium provides such an opportunity for the simultaneous application of advertising and detailing effort to masses of prospects.

The advertising function is performed by the exhibit itself, aided usually by such supplementary material as appropriate promotional literature. In some cases, no more is attempted with the exhibit than to catch the attention of prospects through beautiful and striking appearance. With this type of exhibit, the selling effort is entrusted to exhibit personnel—whose expenses, incidentally, are properly chargeable as a sales, rather than as an advertising, cost.

Other advertisers go much farther toward making their exhibits aid in creating sales for their products. These firms, too, strive to make their exhibits as attractive in appearance as possible. But, in addition, a presentation of product advantages and uses is incorporated into the exhibit proper. Charts, graphs, pictures, case records, models, and actual demonstrations are only a few of the devices employed. The results, in increased attention value, multiplied impression of important sales points, and added prospects who can later be detailed, usually compensate for the additional cost of such exhibits.

Other stratagems may be employed by advertisers to draw prospects to their exhibits. Among the practices used are the distribution of useful small gifts, and even of lottery tickets on quite valuable prizes, to all prospects who stop. While it is clear that the number of visitors to an exhibit can be increased by methods of this type, nevertheless, their sole employment cannot be recommended as a satisfactory substitute for features of interest in the exhibit itself.

Because effective exhibits necessitate a relatively high advertising and sales expenditure in each case, most business organizations will wish to weigh all proposed convention commitments carefully and individually for probable value to be

gained. This is not especially difficult in the case of most conventions. The managements in these instances base their solicitations for the sale of exhibit space squarely upon the size and type of audiences to be provided. Exhibitors, in effect, buy circulation of a given kind; the sellers, of course, do all within their power to deliver full value.

In direct contrast to these offerings, other conventions hold out circulation to prospective exhibit space purchasers purely as a secondary consideration. Exhibitors at these meetings pay a high price for small circulation, to which is added of course the gratitude of the group holding the convention.

MOTION PICTURES

More than thirty years have passed since the production of the first medical motion picture. The first showing of a medical film for advertising purposes followed not long afterward. In ensuing years motion picture apparatus and technique have improved enormously, each advance contributing to the wider use of films.

By the outbreak of World War II these had almost achieved their present high standard of excellence. Color film had replaced the achromatic variety in many instances. Sound was increasingly employed. Slow motion, endoscopic and micrographic cinematography, and animated schematic or diagrammatic drawings were all in use. There was a brisk demand for worthwhile medical films for professional audiences. Some medical advertisers had recognized an opportunity for product promotion through films, and had produced a considerable number.

The full potentiaities of this medium were not widely appreciated, however, until dramatically demonstrated by the success of visual educational methods in speeding the training of millions of men in our war-time armed forces. The end of the war has been followed by a soaring demand for medical films of educational value. Medical and allied professional schools seek them for student instruction; practitioners, for all sorts of pro-

fessional group meetings. Furthermore, prospects do not object often to advertising in these films if it is deftly handled. Here is an opportunity upon which many firms are capitalizing. Those which are not will do well to give the medical motion picture the serious consideration it deserves.

Advertising films for medical and related professional audiences fall into three general classifications. First, there is the film in whose subject matter the advertiser's product plays no part. Thus, the picture may deal with an aspect of an experimental or clinical medical subject that the advertiser thinks will be of educational value or unusual interest to audiences. His benefit is the good will of prospects who see and perhaps hear him designated as the producer or sponsor of the film.

A second type of medical motion picture permits some product promotion. This is obtained through the presentation of a clinical procedure to which the use of one or more of the advertiser's products is incidental. This use is depicted in the film, not unobtrusively, but rather in a favorable light—often in a manner which shows certain product advantages. This type is probably the most widely followed pattern in films distributed under medical advertisers' auspices.

The third class of medical film is the most effective advertising vehicle of all when employed under the proper circumstances. The principal subject matter of a film of this sort is the use of the product itself. This includes its indications, contraindictions, dosage, correct method of administration, and the results of use. Only when the product meets certain conditions, however, will such a film succeed in drawing interested audiences. Either the product itself, the use to which it is put, or the technic with which it is employed must be new and of more than average interest to prospects. Furthermore, the film should afford a convincing presentation of the product's actual use.

An example of a product that lends itself to the making of such a film is an anesthetic which is attracting wide attention, either because it is new and offers certain advantages, or because it is employed in a new type of anesthesia, or is administered by

a new and improved technic. Here it will be readily seen that the product lends itself to the motion picture method of reporting. It will be recognized with equal clarity that the use and physical indications of the effects of many drugs cannot be as interestingly and convincingly presented.

A number of other factors influence the success of any type of technical motion pictures distributed by medical product advertisers. One extremely important consideration is that great care be exercised both that procedures pictured and their details shall not be open to serious medical or scientific criticism. This danger will be avoided as far as possible if films are made under the direction, or with the assistance, of generally recognized authorities in the medical or other fields involved. If these authorities will permit the use of their names in the films, so much the better; this will improve their reception and increase the demand for them. A somewhat similar aid to favorable reception is to gain and feature evidence of the approval of films by the proper boards or committees of such respected nonprofit organizations as the American College of Surgeons, and others. The American Medical Association maintains a Committee on Motion Pictures that provides information on available films; reviews them; and aids in the planning if this is desired. The reviews of this Committee are published, like book reviews, in *The Journal.*

The temptation to emphasize the advertising aspects of films should be resisted to the utmost. Obtrusive and obvious advertising defeats the advertiser's purpose by affecting audiences unfavorably. Subtle advertising, as experience has repeatedly shown, is the key to maximum results with films.

The use of color is required for successful presentation of the subject matter of some films. Color is being used also in an increasing number of instances in which it is not required by the nature of the picture. Color's contribution to the favorable effect of a film upon audiences is undoubtedly considerable, and its extra cost is probably justified in most cases where budgets permit.

The chief advantage of sound films is evident. An important

disadvantage, however, is that sound projection equipment often is not available for showings of such films to professional groups. This difficulty can be obviated only when the firm distributing a sound picture also furnishes equipment for its presentation. Nevertheless, the number of medical societies and schools that possesses sound projection equipment is increasing. Another objection to sound films is found by some companies whose motion pictures are usually presented by detail men. These firms feel that it is desirable for their representatives to be able to offer any indicated comment, and to answer any questions or comments that may come from audiences as the showing of the film progresses. It is easy, moreover, for the detail man to stop the projection of a silent film, reverse the machine, and show over again any part of the film that members of the audience might wish to view a second time.

Advertisers may choose one, or any combination, of three principal methods of distributing medical and related motion pictures. Sometimes films are lent by the advertiser directly to interested professional groups which arrange for projection. Another method is to furnish copies of films to the motion picture libraries maintained by various professional associations and societies. These in turn lend the pictures to interested groups. The third procedure is to supply copies to detail men who arrange showing and present the film in person. Here, again, the individual advertiser's choice of methods is the one best accommodated to circumstances.

Whatever this may be, one thing will nearly always increase medical motion picture demand and circulation. This is the use of a small amount of space in appropriate media for dignified printed advertising of the availability of the films.

NOVELTIES

Desk calendars, appointment books, automatic pencils, mechanical devices for making medical calculations, and other novelty or "remembrance" items are often employed as media for advertising addressed to members of the medical and allied

professions. Such gifts are frequently stamped with the recipient's name. They may be distributed at professional meetings, on calls by detail men, or by mail.

The usefulness of the gift is probably the most important consideration in this type of advertising. Indeed, if the novelty is not useful, it will seldom be kept. One that is unique, or at least unusual, will gain greater attention for the advertising it carries than an ordinary gift. Most advertisers would probably agree, moreover, that the effectiveness of novelty advertising for drug products is enhanced when the use of the gift is somehow related to the use of the specific product advertised.

Three circumstances restrict the use of novelty advertising in the medical market. One, as mentioned before, is that the needs of the patient are a far more significant factor than gratitude in the physician's choice of medicaments. Another point is that most medical men object to the display of drug, or other prescription product, advertising in their offices where it may be read by patients. Finally to be considered are the limitations imposed upon the advertising message by the physical character of many novelties.

As result, most novelty advertising in the ethical drug field is confined to publicizing the donor's name and a slogan, rather than one of his products. And, even when this is its object, advertising novelties can be considered of value only as minor and supplementary media. Certainly they cannot take the place of other advertising.

ADVERTISING TO THE PUBLIC

Two principal types of advertising to the public may be undertaken by firms marketing prescription and allied products.

The first is the advertising to laymen of products for which professional prescription use is sought. Toward this sort of promotion, the attitude of the medical profession as a whole is well expressed by a statement from the Council on Pharmacy and Chemistry of the American Medical Association:

Indiscriminate self-medication by the public involves grave dangers, such as misdirected and inadequate treatment, failure to recognize serious disease until it is too late for effective treatment, and the spread of infectious diseases when hidden from a responsible physician. All these are involved in the advertising of drugs to the public, with the further dangers of suggesting by description of symptoms to the minds of the people that they are suffering from diseases described, the dangers of the unconscious and innocent formation of a drug habit and the dangers of starting allergic reactions.

Most physicians would also concur in principle with the opinion of the Council that the dangers mentioned do not apply with equal force to all medicinal products, and that there are instances in which more benefit than harm may accrue from drug advertisements giving the public truthful information without misleading suggestion or emphasis. Generally speaking, such instances are confined to the advertising of products which physicians commonly recommend or prescribe orally, rather than prescribe in writing. As was mentioned earlier, such items include only disinfectants, germicides and antiseptics promoted for prophylactic use on superficial cuts and abrasions of the skin, mild laxatives, antacids, relatively safe analgesics, and a few others.

But professional agreement in principle regarding advertising of this nature to the public does not often signify approval of the promotion in fact. It is rare indeed that any drug item advertised to lay audiences is also recommended or prescribed by many medical or allied practitioners. The immediate and almost unconscious reaction of these men is to shun as a "patent medicine" most of those products advertised even with restraint and honesty to the public. This makes the dual promotion of drugs to the professions and the public inadvisable in all but an extremely few instances.

Another type of lay advertising which in recent years has come into rather wide use by medical product manufacturers is the so-called institutional variety. In this, the eventual object of the advertiser is to increase his product sales, of course. His methods, however, are so indirect that his purpose is often not

readily apparent to his public audience. Magazine, newspaper, or radio advertising may be used for his task.

Some institutional advertising is given over entirely to presenting the advertiser's organization as a firm in whose products the public may have the utmost confidence. If the advertiser is a manufacturer of toothpaste or other non-medical items, as well as of prescription products, one motive may be deduced with certainty. He is attempting to increase public confidence in his non-medical merchandise by increasing the statute of its maker. Of other possible purposes, more in a moment.

The most popular theme employed in the institutional advertising of medical product firms is that of building public confidence in the physician. Variations of the same idea feature the dentist, the hospital, the veterinarian, or the pharmacist. The pattern is much the same in any case. Basically, it is a presentation of the contribution of one of the professions in the war against disease.

One object of such advertising is clear. The advertiser is seeking the good will and favor of the professional man and woman featured in his promotion to the public. He is doing this by waging in their behalf an educational advertising campaign of the sort which they cannot, or will not, carry on for themselves, but from which they will benefit.

Of course, this may be the only purpose of the advertising in certain instances. In others, one may be forgiven for suspecting that it is not. It seems highly probable that most drug manufacturers doing this kind of advertising are motivated to some degree by the possible advantages of getting their firm names before the public without, however, running the risks involved in promoting specific products to that audience.

What are these advantages? One concerns oral prescriptions or professional recommendations by the doctor to a patient. Sometimes no brand name is specified, or two or three brand names may be mentioned; the patient is advised to purchase one of them. When such situations arise, advertising to the public may well be the determining influence on the decisions of patients.

Of far greater importance in the volume of sales involved, the same influence may also frequently determine the choice of brand of many of the products, such as an antiseptic, purchased by the public for self-medication. The scales are weighted still more in the advertiser's favor if pharmacists have been induced, by public advertising or other methods, to favor or recommend his brand.

No accurate, concrete estimate of the value of the various benefits mentioned here is available. It is certain, however, that institutional advertising to the public does not produce substantial results quickly. It is a form of promotion which, if employed at all, should be used on a long-term basis.

TRADE ADVERTISING

Wholesalers, retail pharmacies, and often physicians' supply houses are important links in the selling chain of all ethical drug product manufacturers, except those sold directly to physicians, dentists, veterinarians, or hospitals. In all other cases, if the trade distribution links are weak, the best of advertising and detailing campaigns will fail. Physicians and other practitioners will not long continue to prescribe what patients cannot obtain.

The task of securing and maintaining adequate trade distribution is one sometimes entrusted entirely to personal selling effort, sometimes to advertising, but far more frequently to some combination of the two.

In securing distribution for a new drug product, the usual procedure, insofar as advertising is concerned, is announcement of the product to the trade. This announcement to retail outlets usually includes not only such details as the product name, package sizes and supply sources, but also enough information about the use of the product so that pharmacists can answer questions often asked them by those who write prescriptions. The latter is important, for many medical men depend upon the pharmacist to supply any needed bits of information they may have forgotten.

Advertising of the new product to the appropriate profession commonly follows announcement to the trade. Coincidental with this professional advertising, further printed promotional material is usually addressed to the trade to keep it informed of the advertiser's activities in building prescription demand.

Expenditures for trade advertising of prescription products of an exclusive nature should not be large in proportion to those for professional promotion. It is probably a safe guess that most successful advertisers of ethical drug specialties devote not more than ten to fifteen per cent of their total budgets to trade advertising.

Trade periodicals are the most widely employed medium for drug trade advertising. However, when the advertiser's problems include that of obtaining orders by mail, direct mail usually will be found to give better results. A few manufacturers' house organs have accomplished enviable results in building trade cooperation and friendliness, but the majority of publications of this sort get scant reading by recipients.

"Dealer helps" are an important phase of trade advertising. With most prescription product manufacturers, these helps consist of advertising addressed to physicians over the retailer's firm name. Frequently, the dealer's service to medical practitioners and their patients is featured, along with the product under promotion. Usually the distribution of such ethical merchandising aids is left to the retailer himself. Some manufacturers, however, even go so far as to obtain a suitable mailing list of professional prospects to whom the manufacturer then addresses an entire direct mail campaign for the retailer. A successful effort of this sort is one of the best possible forms of insurance of warm and effective retail cooperation.

A number of manufacturers of ethically promoted drug products supply retail pharmacies with window, counter, and other store display advertising. Some of this features products ordinarily sold on oral prescripition. In other instances, the advertising stresses the value of the pharmacist's professional service to physicians and the public, with the manufacturer's name or trade mark as a secondary feature. The latter type of store dis-

play advertising is extremely popular with retailers, and seems to be growing in favor at the expense of the kind which features products.

EXECUTION OF ADVERTISING

The final measure of the success of advertising is the result produced—long-term as well as immediate. Unfortunately, results are not always what they should be. Advertising may, in fact, harm sales. It may have no discernible effect either way. It may increase sales, but to a lesser extent than it should.

When one of these events occur, the fault is not that of advertising as a tool, but of the persons responsible for the particular advertising involved. They may have overestimated their market, failed to gain adequate distribution, or made any of a dozen other mistakes which the best of advertising could not rectify. If it can be assumed that satisfactory personnel has been chosen to be responsible for advertising activities, one, then, may too often trace the failure to poorly executed advertising—which, unfortunately, may not be the fault of the advertising department.

This usually may be traced to one or the other of two common causes. The first is the feeling of too many people in other spheres of activity that they have an extraordinary insight into advertising. Top business executives, lacking professional training, seldom presume to interfere in the techniques employed for the solution of legal, engineering, medical, accounting, or laboratory research problems. Yet some of these same men, with no more special training in advertising, use the authority of their positions to dictate details of the procedures employed in the creation of their firms' printed promotion. If their judgment runs counter to that of advertising experts, the opinions of the latter may be brushed aside or over-ridden. Themes, appeals, copy construction and style, layout, illustration, use of color, even typography—all are prescribed with equal self-assurance by this type of executive. "I've always had a flair for this sort of thing," he will say.

The second common cause of poor execution is the delega-

tion of advertising to bright young men whose qualifications for the task are largely limited to a desire for a career in the "advertising game," coupled either with a facile pen, a plausible front, or kinship with a senior executive.

Few firms can afford the luxury of either practice. This is especially true in the ethical drug marketing field where the printed word accounts for a larger part of total sales cost than in many other industries. Advertising is a complex, technical business. It is neither easily nor quickly learned. Its success depends in high degree upon the special skill, technical knowledge, and seasoned judgment expended upon every phase of its creation.

Such is not a task for dilettante direction by top management. The latter has a number of functions vital to the success of a firm's advertising program. But with the exception of those ranking drug trade executives who have risen to their present positions through the practice of creative advertising, the upper managerial role is not to sit in judgment on the form of copy, layouts, and art work. Neither is responsibility for the creation of these elements one to be entrusted to some favored tyro, however brilliant. These are tasks for experts alone, as is research for scientists, and construction for engineers. Only when this is thoroughly understood is there any likelihood that advertising will be as consistently good as it should be.

Experts in this field may be employed as members of a creative advertising department organized within the framework of one's own organization. Or their services may be secured by retaining an advertising agency of which they are a part. The manner of their employment is not as important as the fact. Choose with care, judging a man by his accomplishments rather than by an arbitrary list of qualifications. Compensate him adequately, remembering that the real creative experts of advertising are few.

Then welcome him into the deliberations of your organization. Extend to him the kind of confidence that you bestow on your physician or lawyer. Let him have the benefit of your experience and the aid of your position in the business. Help

him garner all the facts about your financial, production and research problems, and policies relating to sales. Make available to him all data and reports bearing in any way, unfavorably as well as favorably, upon present and future product demand and use. Inform him fully about your margins of profit, methods and channels of distribution, discounts, and about any special bulk sales arrangements that you may have. Place in his hands all available records on previous advertising, its cost, effectiveness, and any obstacles, unusual problems and adverse reactions encountered.

When you or any member of your organization have what appear to be good advertising or selling ideas, they should be given to your advertising man. He knows that he does not have a monopoly on worthwhile ideas and will appreciate the effort to be helpful.

Scientific personnel whose work requires wide reading in medical and related fields can often give the advertising man valuable suggestions and information that will be of assistance in the formulation of publication advertising schedules. Although he may know publication circulation, he is interested in the character and influence of journals as well. He has a general knowledge of the latter factors in the cases of the well-known, well-established magazines. It would help him, however, to have frank technical opinions of the reader appeals of the many newer publications that have been launched, together with observations that may call to his attention any editorial improvement or deterioration occurring in older ones. In doing this, an attempt should be made to view the periodicals from the viewpoint of their general readers, not merely one's own. Remember that while you may not read the sensational newspapers, and that while none of your friends may do so, a million other people read no others.

In the preparation of house organs addressed to the professions, both articles written on agreed-upon subjects and suggestions by scientific personnel will be welcomed heartily. Your advertising man will also be aided if opportunities are arranged for him to meet key professional and trade figures. Other forms

of assistance that contribute affirmatively to better advertisements for your firm are many.

But, again, when it comes to actual execution—unless you are an expert and have the record to prove it—*Don't meddle!*

Being human, your man will err at times. But, as somebody has pointed out, the finest physicians and lawyers are wrong once in a while, too. The amateur physicians, lawyers and advertising men are wrong most of the time.

This should be remembered always. Management might also remember that what should be one of the greatest of all its advertising concerns is startlingly often neglected by executives whose attention centers on the form rather than the purpose of promotion. The neglect is of co-ordination and synchronization of sales-producing activities. These are not carried on entirely independently of each other in any company, of course. Nevertheless, there is frequently much too loose a synchronization of effort to achieve anything like maximum selling efficiency.

Many factors are involved. For companies with many products, decision is needed on the allocation of selling effort to be given to each, at least of the more important ones. For all firms it is important that there be developed basic advertising and selling strategies that will successfully meet competition in providing motives for professional use of the product promoted. Definite sales objectives, intermediate and ultimate, should be established. Through cooperative effort, plans and schedules for production, distribution, advertising, and detailing should be developed, correlated and synchronized to form a single integrated program for the attainment of the sales objectives.

This program and its component parts are now ready for consideration, possible modification and final approval by business high command. Adoption of the program should be followed by the presentation of all or appropriate parts of it, in orderly, detailed, timetable form, for the guidance of all concerned, including the outside sales organization.

In the development of such a program not all contingencies can be foreseen, it is true. Details and tactics may have to be changed from time to time. This, however, does not weaken the

great basic advantage of the plan. Stated as simply as possible, the advantage is this: The results of good advertising and effective personal selling are both substantially increased by this close coordination and synchronization of effort.

The establishment of such a program, continued adherence to it, and encouragement of the cooperation necessary for its smooth functioning are responsibilities of top management. Only when these responsibilities are fully met do advertising and detailing dollars yield full return.

19

"Detailing" the Physician

THOMAS H. JONES

DETAILING plays an important role in a marketing program of the so-called "ethical" drug preparation. If in no other way this fact is evidenced by its continued employment by nearly all pharmaceutical manufacturers with considerable success. The word "detailing" is used to describe the function of representatives whose task is to call upon physicians and explain the nature and purpose of particular drugs or other articles which are useful in the diagnosis or treatment of disease. Some companies prefer the designation "professional representatives" to describe the men engaged in this work, nor can it be denied that this phrase does have a more dignified connotation than "detail man." Whatever the name selected for the men engaged in calling on the medical and allied professions, however, their function still is to inform the doctor and the pharmacist of the therapeutic usefulness of their companies' products.

It is feasible, at times, to introduce a new drug product without employing the services of the detail man. A sales campaign consisting of well-planned mailing pieces, supported by advertisements in medical journals, frequently is successful in developing an active demand for the product. Nevertheless, the experiences of the most successful companies argue strongly in support of the inclusion of one or another type of detailing in all ethical marketing programs. As a matter of fact, despite the evident successful development of some pharmaceutical specialties without employing detail men, it is quite probable that the volume of sales in these instances would have been much larger if effective detailing had been combined with the other promotional efforts. The primary burden of medical journal adver-

tising and direct mail pieces is generally to plant and cultivate interest, so to speak, in a product. But usually detailing must be depended on to reap the harvest of that interest by converting it into sales volume.

The unique advantage of detailing, as against other forms of promotion, lies in the opportunity it affords the doctor to discuss the product with one equipped to explain its uses and value in understandable terms. It is true that the physician may have read about the drug; indeed, he may even have received a sample in the mail. But it is only when the detail man calls that the doctor has occasion to satisfy his curiosity about particular aspects of the new product or to discover information contained neither in journal advertising nor in the direct mail pieces. In fact, a detail man who has been properly trained is in a position to furnish immediate information that may often result in the doctor's prescribing a product, even, in some instances, while the representative is still in his office.

OBJECTIVE OF DETAILING

The task of the detail man, however, is not merely educational or abstractly professional. Indeed, the major objective of detailing is the development of the doctor's interest to the point where he will actually prescribe the product before him. For no matter how informed the detail man is or how well he explains the nature and purpose of the drug, no interview with the doctor can be termed successful unless it induces a prescription or sale. Of course, the prescription need not be written immediately, but, generally speaking, use of the product should follow the detail man's call, or the interview may be considered a failure. This aspect should be emphasized in training. The detail man should be impressed with the fact that the primary, if not sole, purpose of his call on the doctor is to develop prescriptions or recommendations for his company's products.

In the light of this criterion of successful detailing, the task of the detail man is neither easy nor simple. Persuasion rests on subtile and intangible factors. The detail man must first of

all be tactful in his approach. For example, the adoption of a pedagogic attitude is almost certain to offend, thus weakening or destroying any chance of obtaining the prescription cooperation. Nor is the function of the detail man to attempt to teach medicine to a practicing physician. On the other hand, proper training does permit him to develop a specialized knowledge of a limited number of drugs and their application in the management of disease processes. This background should equip him to render a genuine service in this field to physicians. And it is this ability that makes for success. Indeed, more prescriptions are written as a result of this type of assistance and cooperation than from any other effort.

QUALIFICATIONS OF A DETAIL MAN

As the company's personal representative, the detail man, of course, reflects on the general character of his firm. His is the opportunity to create either a favorable or an unfavorable impression of the company he represents. It is evident, therefore, that considerable attention must be given to his selection, training, and supervision. Usually the best qualified for detailing pharmaceutical specialties are men who are graduates in pharmacy or an allied science. Those with a background in the science of nutrition are adaptable for work with food specialties; while men with training in the field of engineering usually qualify to sell diagnostic or therapeutic appliances. Naturally, an automobile salesman cannot sell drugs; and the pharmacological equipment of the pharmacist enables him to discuss intelligently the forte peculiar to the detail man.

Qualified applicants can often be obtained by consulting the employment placement services of the various colleges. In addition, the firm's own representatives or supervisors may frequently be depended on to recommend suitable material. However, no detail man should be hired until a study has been made of the requirements of the work to be assigned and the requirements of the particular task. Nor is it possible to draft a pattern that will serve as a competent guide to selection for all companies

or all pharmaceutical products. There is no way, moreover, of determining in advance whether or not a man who has been successful with one company will be equally successful with another.

However, while no specific formula can be written as a guide for selecting men, general suggestions can be offered. The requirements to be considered may be summarized as:

1. Sales sense
2. Appearance
3. Educational background
4. Vocabulary
5. Honesty
6. Willingness to work
7. Willingness to cooperate
8. Stability

Of these qualifications, the fundamental requirement for successful detailing is clearly what we have designated as sales sense. So important is this attribute that its presence or absence should be established when the applicant is first under consideration for a position on a detail staff. Experience has proved that many men otherwise fitted by educational background, appearance, and personality to engage in detail work fail to produce results simply because they lack this ability to consummate a sale.

The first interview of the prospective detail man can give valuable information; a quick appraisal of an applicant can be made as he crosses the threshold of the office of the personnel manager. Is he well groomed? Is his personal appearance appealing? Such details frequently give some insight into the character and other qualifications of the individual for the position. Certainly, they are of prime importance in their own light.

After the applicant has been seated and made to feel at ease, his knowledge of words, and their application, can be ascertained during the general course of conversation. His response to seemingly casual but well-directed questions will not only do much to reveal his character traits and sincerity, but at the same time offers opportunity to measure his vocabulary, diction, and mental powers.

Educational background can, of course, be easily determined, both from the applicant's statements of his schooling and his

general manner. His willingness to work and to cooperate, as well as his stability and honesty, can be verified by his previous employers, if he has had business experience. Honesty, both of purpose and character, can similarly be judged, at least partially, by consulting his character and credit references. Earnestness and sincerity are frequently self-evident.

However, the most important qualification, sales sense, is often difficult to uncover. It has been shown, indeed, that some men who have been engaged in sales work for years are, despite this evident experience, almost totally devoid of this essential quality. On the other hand, there are men who, despite their previous occupation as teachers, clerks, or factory employees, have sales sense, many times without being aware of its possession. Thus, the applicant's prior training or occupation serves as an inconclusive criterion of his ability in this respect.

In an attempt to avoid the misplacement of various abilities, tests for ascertaining aptitudes have been developed; their usefulness is attested to by many authorities in the field of psychology. Today, in fact, many secondary schools offer students an opportunity to take a vocational aptitude test during their junior or senior years. For salesmen, moreover, sales aptitude tests are now given by several commercial institutions as an aid to management. These may be utilized at least to supplement a personal interview. Needless to say, a carefully planned application blank will be found helpful in evaluating the applicant for the position, although, as we have indicated, not too much reliance should be placed on these answers.

We have emphasized the need for sales sense because, in the final analysis, a good detail man must be a good salesman. He will be called upon to sell products to physicians, to hospitals, and to drug stores; he will frequently find that he must actively promote his firm's products; he is in general competition, at least, with the representatives of other drug companies, if only with reference to the time element. In short, if he is to be successful, he must be more than just a sales clerk; he must possess all the attributes and abilities of the efficient and effective salesman.

TRAINING

Once a decision has been reached to engage a man, steps must be taken to provide him with the first essential for success in his work—a complete knowledge of the firm's products. This can be imparted only by careful training in the plant and office. Studying the drug as it is actually made, from raw material to finished package, places a man in a position to discuss every phase of the manufacturing process, and should the need arise, to refute statements from any source designed to deprecate the firm, or its products.

After the man has reviewed the production processes and has gained a clear picture of the controls employed to insure purity, accuracy, and uniformity, he should be transferred to office training. Here he should be taught the story behind the company's products, their usefulness in therapeutics, and how to present them to physicians.

The best method of teaching is to approximate so far as possible the conditions under which the man will work in the field. Thus, all the objections to use which may arise in the course of the interview with the doctor or pharmacist should be ascertained. Whatever arguments are needed to overcome these objections and to present affirmative facts about the product should be supplied in office conferences.

Competition will be so keen in the years ahead that only the well-trained man will have a chance of success. It is imperative, therefore, that the training program be not stinted or restricted. On the contrary, it should be appreciated that there is no better way of securing the firm's future than by providing necessary funds to carry out a well-balanced, adequate training program of this nature. Among other things, the detail man should be taught:

(1) The proper manner to approach the doctor.
(2) How to secure his attention and interest.
(3) How to hold these.
(4) How to induce the prescription for the product.

He should, first of all, be instructed to approach the doctor in a courteous and businesslike manner. There is no need for him to be apologetic in any way, for his is a worthy message; otherwise he would not be calling on the physician. Confidence in his product should find reflection in his approach. The interview should be viewed as mutually advantageous. Attention can be obtained by making the opening statement meaningful and substantial. Listless or negative preliminary remarks are to be avoided. On the other hand, exaggeration should never be resorted to.

Once attention is obtained, it can be held by explaining in clear, concise language the type of the product and its purpose. Obviously, what the doctor is interested in are the conditions in which he may find it helpful. This discourse should generally be short in its opening phases, to be developed in answer to questions or as particular aspects are expanded. The presentation should not degenerate into a "lecture." Its vividness may be enhanced by illustrations of experience, by reference to recent medical literature, by emphasizing the advantages of the drug over others. A sample of the preparation may be utilized as a means of stressing one or more points. At the close of the interview, it is important to let the physician know where the product is available for filling prescriptions. A courteous request for its trial should close the presentation.

During the training period, men whose diction, enunciation, or voice quality is poor should be given exercises for self-improvement; similarly, vocabulary deficiencies should be corrected. If there is no one in the company's organization qualified to undertake these tasks, outside assistance should be obtained. It seems too obvious to repeat that the detail man should be trained in the fundamentals of proper speech. Nor should this basic training be deprecated; to quote the Earl of Roscommon: "Those things which now seem frivolous and slight, will be of serious consequence to you, when they have made you once ridiculous."

After training in the plant and office, the new man should be assigned to work in the field under the close observation of an

experienced representative. Thus, he may accompany an experienced man on the latter's calls until he feels wholly confident of handling interviews alone. Indeed, it is a serious mistake to assign a man to a territory before he has acquired the poise and confidence that can only be obtained by working with one with experience in detailing the company's line.

Even after a man has successfully completed his plant, office, and field training, he will need the understanding help of a good supervisor as well as the stimulating guidance of the sales manager or director. Training in itself does not—indeed, cannot—produce a finished detail man; time alone can accomplish this.

FORMULA FOR SUCCESSFUL DETAILING

It has been said that there is a formula for productive detailing that will practically guarantee success provided, of course, it is given a chance to work. That it is effective is evident—at least to the writer, who has found over a long period of years that only men who have not employed it conscientiously and well have failed as detail men. The formula is so elementary in its simplicity that some say it merely states fundamental truths that are commonly recognized as the ingredients which, put together, assure success. Despite the familiarity of its tenets, however, too few men practice these principles; this perhaps is the reason that much detail work is so unproductive.

For all interested in improving the quality of detail work, the formula that will tend to insure productive detailing may be summarized in the statement that the detail man must possess and exercise (1) knowledge of products, (2) enthusiasm, (3) a positive mental attitude, (4) courtesy, (5) tact, and (6) honesty.

Even men who have been on company pay rolls for many years fail to appreciate the importance of the first item in this formula. One with a thorough knowledge of his firm's products develops an enthusiasm for them which proves contagious. Indeed, he tends to believe in them so strongly and so honestly as to make others believe as he does.

The man with such knowledge and enthusiasm is almost cer-

tain to maintain what we have designated as a positive mental attitude. It has been said that "fields are won by those who believe in the winning." The detail man, so indoctrinated, will not be put off by the physician who refuses to see detail men. The refusal will inspire him to greater efforts; ingenuity may find a method of arranging the interview. In a surprising number of instances such unquenchable and buoyant efforts are successful, the writer has found.

Courtesy still returns its own reward. Simple courtesy, extended to an office secretary, may open the inner office door. Once there, the exercise of the simple virtues of courtesy and tact frequently opens the way for a return visit.

Of great importance is honesty. If the physician recognizes that he can depend on the detail man for truthful statements he usually will offer a sympathetic ear. If, however, he has reason to doubt the words of the visitor, the latter will no longer be welcome.

ESTABLISHING DISTRIBUTION

In one sense the primary task of the detail man is to establish distribution of his company's products. Indeed, before any physicians are interviewed, he should call on each wholesale druggist in his territory as well as all the leading retail druggists. It is not necessary, of course, to see every druggist in town before attending to physicians; it is advisable, though, to visit those stores concentrating on prescription business. Obviously, it is a waste of effort to call on a doctor and induce him to write a prescription for a drug if the product is not available at the retail druggist. To "stock" the jobber and trust to the retailer to order does not, it is evident, assure that the first prescription will be filled. It is frequently possible to persuade the "prescription" druggist to cooperate in the promotional efforts by stocking the articles being detailed. It can always be pointed out that the amount of free advertising the store will receive by being mentioned during calls on physicians will be worth many times the cost of the merchandise.

Once a stock of the product has been placed with wholesalers

and key retailers, calls on the doctor should be begun. Lists of prescribing physicians are available; these should be supplied to men going into a territory for the first time. It should be observed, however, that there have been many changes in physicians' addresses in recent years. It is advisable, therefore, to verify the addresses on the list by reference to the local telephone directory.

The knowledge as to whether the doctor is a specialist or a general practitioner is helpful in planning an interview and makes it possible to confine the discussion to appropriate subjects. For example, an orthopedic surgeon would show little interest in a presentation of the value of a drug in the nausea of pregnancy. The Directory of the American Medical Association will be found a valuable reference book supplying essential information regarding the background, hospital associations, and other professional connections of members of the Association.

Busy doctors are naturally the ones most difficult to see. However, since they usually are also the most important, every effort must be made to interview them. To be discouraged by stories that certain physicians are unapproachable or have a fixed rule never to see a detail man is frequently without cause. Even a so-called "busy" doctor will see a detail man representing a reliable company. Moreover, whether an interview will be granted depends in many instances largely upon the tact and intelligence of the detail man.

The best approach to the problem is to call at the office and enlist the help of the office nurse or secretary. While it is her duty, of course, to conserve the doctor's time, the good secretary also recognizes that a well-informed detail man can often be of real service in this respect by assisting the doctor to keep informed of current developments and new products.

It is well to remember, in this connection, that the detail man who places a value on his own time never overstays his visit. His presentation should be concise, even brisk. He supplies the information about his product, and thanking for the courtesy of the interview departs. One who abuses the privilege of the

interview by verbosity and idle chatter finds subsequent appointments difficult to make.

Should a personal visit to the office fail to obtain the interview, a letter, requesting an appointment, may succeed. Again, a doctor who cannot be seen at his office may often be available for interview during his attendance at a medical convention. Indeed, this opportunity is one of the principal advantages of medical conventions for the pharmaceutical company. Tact and courtesy at a convention booth, moreover, will frequently establish friendly relations, thus making it simpler to interview the busy doctor when he is back in his office.

A reputation for knowledge of his products, together with the ability to present information about them without wasting a doctor's time, is perhaps the most valuable asset that a detail man can possess. While it is important to have a reservoir of knowledge, it is obviously poor judgment and tactics to empty the reservoir at every interview. Brevity of presentation, in fact, will be found an asset, so long, of course, as essential facts are not omitted merely for the sake of a shortened interview.

WHEN TO LEAVE SAMPLES

Whether or not to give samples of the drug to the physician often presents a difficult decision for the detail man. As a general rule, samples should be left only if a special request for them is made. If they are proffered although not asked for, they generally find their way to the waste basket. Samples, however, can and do serve a useful purpose. Thus, they make it possible for the physician to test the patient's reaction to the taste of a product and, in the case of efficacious products, serve to demonstrate their actual worth. Needless to say, a sufficiently large sample should be left to permit an adequate test.

However, there seems no doubt that the practice of sampling is overdone. Some detail men, in fact, seem to depend on samples to do their work for them. Some of the most productive detail men use samples sparingly, yet succeed in creating a large demand for the product. Their reasoning is that samples dis-

tributed promiscuously give the impression that the product cannot cost much and hence is without too much worth therapeutically.

Generally, the doctor who requests samples should be given them, provided, of course, that the product lends itself to sampling. Some drugs are so expensive to produce, however, that even judicious sampling may prove too costly. In such instances, it is often advisable to have the home office forward a regular-size package, without charge, to the doctor. Records of these shipments should be maintained, and followed up by inquiry within a few weeks.

NUMBER OF CALLS PER DAY

One question frequently asked is how many calls a detail man should make a day. Perhaps a better question would be how many *interviews* should be averaged daily. It is entirely possible for one to have to make thirty calls in order to obtain ten interviews.

While the number of interviews will vary with the nature of the work, experience suggests that an average of eight or ten interviews with physicians daily is not too difficult to maintain. To these, of course, should be added calls made upon dentists, hospitals, and drug stores. If the representative is possessed of the will to work, the proper number of interviews will be forthcoming.

SELLING HOSPITALS

As a rule, a hospital will not buy a pharmaceutical specialty until a sufficient number of physicians on its staff are prescribing it consistently. For this reason all the members of a hospital staff who could prescribe should be interviewed. It is only by such coverage of the staff that business from hospitals can be obtained. One impression that should be dispelled is that hospitals will buy only when the price is low.

ANALYZING EFFORT

Since the cost of making a call on a physician is high, it should be confined to likely prospects, obviously. For example, it can hardly be considered profitable to call with a prescription specialty on many dispensing doctors. With the number of hours available each day for the work limited, calls should be made, so far as possible, on the doctors who prescribe, a list of whom can often be obtained from the prescription pharmacies in a community. Thus, by enlisting the cooperation of the pharmacist in selecting doctors to be called on, in this respect and others, better progress can be made.

THE IMPORTANCE OF REPORTS

Reports give the home office information useful in contributing to the progress of the business. Although it is true that representatives should not be overburdened by requiring unnecessary reports or inconsequential details, nevertheless, periodical reports bearing proper information orderly presented are essential.

Reports on the activities of competitors sometimes prove valuable to the office; needless to say, they should not be offered by representatives as excuses for their own failures. As indicated, the report should constitute an accurate picture of the situation prevailing. Trifling information of no importance is out of place in a business report.

HELPING THE MEN IN THE FIELD

It is the task of management to maintain the morale of the men in the field on a high level. This can, of course, be accomplished most directly by giving them saleable products only to detail. But in addition it is important to keep in close touch with them and their activities. A man left alone in his territory for too long a period will eventually grow listless and lose inter-

est in this work. Regular visits from a supervising representative or from the sales manager, a trip to the home office for retraining, all pay in sustained enthusiasm and increasing sales.

The day has passed when a sales manager obtains results by Simon Legree methods. Instead, good coaching has replaced whip-snapping; the ancient "ginger letter" has given way to a more thoughtful understanding of the daily problems of representatives and a sincere effort to help solve them. There was a time when it was considered a mistake for a sales manager to be friendly with his men. Today the wise sales manager knows every phase of his men's activities and their personal problems. He is thus better equipped to guide them to successful performance of their work.

20

Professional Acceptance

AUSTIN SMITH

THE professional acceptance of a drug is determined largely by the promotional efforts of its manufacturer or distributor. By professional acceptance, of course, is meant recognition of the value of a drug by the medical profession and particularly the drug evaluating body of the American Medical Association, the Council on Pharmacy and Chemistry.

Approximately 150,000 physicians in the United States are immediately and directly concerned with one or more phases of drug therapy and its effects on human individuals. Most of these are members of the American Medical Association. In addition —or rather to satisfy this interest on the part of the profession— the Association combines several offices that exert, in one way or another, an influence on the promotion of drugs, their use, and their acceptance by the profession. This influence is only natural since the principal objectives of the American Medical Association are "to promote the science and art of medicine and the betterment of public health." These objects are essentially similar, however, to those of any group or association truly interested in the prevention and treatment of disease. Nor is it quixotic to include among those groups drug manufacturers having a product to distribute—they, too, are very much interested in these same purposes.

The similarity is recognized, also, from the physician's responsibility, defined in the Principles of Medical Ethics as:

> A profession has for its prime object the service it can render to humanity; reward or financial gain should be a subordinate consideration. The practice of medicine is a profession. In choosing this profession an individual assumes an obligation to conduct himself in accord with its ideals.

Is this not the same responsibility for members of other professions and trades whose principles are likewise aligned to the rendering of service for humanity, the enforcement of which "should be conducted in such a manner as shall deserve and receive the endorsement of the community"? Indeed, is it not in full accord with the desires of everyone interested directly or indirectly in the welfare of the public? If nothing else, common sense suggests business practices that follow the dictates of those fully aware of the responsibilities of the medical and allied professions and in doing so thereby advance their best business interests.

COUNCIL ON PHARMACY AND CHEMISTRY

Among the organizations generally recognized as exerting considerable influence in this country on the promotion of drugs, and like products, is the Council on Pharmacy and Chemistry of the American Medical Association. Its activities, on the whole, also reflect the thinking of other groups interested in and responsible for examining and commenting on promotional activities, and for this reason alone it is entitled to a detailed description. Thus, the Council offers an advisory service for the Advertising Committee of the American Medical Association—responsible for advertisement in the publications of the Association; for the Advisory Committee of the Cooperative Medical Advertising Bureau—concerned with advertisements in most State medical journals; for the policy-making groups of other medical journals that follow Council policies; and for those who are charged with the purchasing of supplies for hospitals and other health centers. These are the individuals and groups who, as well as the practicing physician, ask "Is this drug Council accepted?" or "Is this drug in N.N.R.?" These individuals, indeed, are largely responsible for the drug industry's awareness of the meaning of professional acceptance.

ADVERTISING IN AMERICAN MEDICAL ASSOCIATION JOURNALS

No advertisement of a drug or other preparation, coming within the purview of the Council on Pharmacy and Chemistry, is accepted for inclusion in American Medical Association publications and in other publications that are operated under the same policies unless it stands accepted by the Council. Certain other principles govern the acceptance of advertising for American Medical Association journals. Thus, no advertisement will be accepted which, either by intent or inference, would result in deceiving, defrauding, or misleading the reader; extravagantly worded copy is subject either to revision or to rejection; disparagement of competitor's goods is not permissible; testimonials and quotations will not be published in advertisements unless permission of the authors has been secured, the publisher reserving the right to require evidence of authenticity of testimonials; and quotations from the Association's publications may be used in advertisements only with express permission in each instance. Products accepted by the Council may be accompanied by the Council seal.

For many years the office of the Council on Pharmacy and Chemistry has been charged with the duty of examining and determining the acceptability of all advertising copy for therapeutic agents submitted for insertion in American Medical Association publications. The primary object of this task is to make certain that the claims advanced in the proposed advertisement do not exceed those which the Council permitted at the time that it gave consideration to the drug concerned or those that the Council may have subsequently found acceptable.

In addition, the advertising copy is scrutinized for any other questionable features or imperfections which require correction. These include such items as extravagantly worded copy or sweeping superlative claims, statements disparaging competitor's products, typographical errors, objectionable illustrations, absence of descriptive synonyms for trademarked chemical compounds, and of satisfactory statements of composition for phar-

maceutical mixtures sold under protected names, and mention of therapeutic agents not eligible for inclusion in the advertising pages of these publications.

In its examination of submitted advertising copy, the Council office also seeks to maintain a reasonable degree of consistency among the claims advanced by various competitors marketing the same drug or the same type of drug. At the same time, the office examines the copy to ascertain whether sources of references are given for quotations, whether references are used which truly reflect modern thought thus avoiding the misleading implications of outdated or disapproved theories, and whether references are to works generally acceptable to authorities in the field under question.

While it is neither possible nor practical to present both sides of a story in an advertisement, it is important that the statements should not offer a false implication, present an unduly optimistic picture, or minimize normal harmful possibilities. Thus, copy should contain no phrases or partial quotations from published papers that by themselves distort the true meaning intended by their authors. A common evasion of this nature, for example, is to omit important words. And finally, the Council office examines the copy for mention of objectionable advertising booklets and other literature, material that has not been seen by the Council or that describes products not accepted by the Council and therefore not eligible for advertising, directly or indirectly.

These searches would be unnecessary were the same effort expended by those responsible for preparation of advertising copy. There is a notable trend today, however, to do this; in the long run, it is a profitable undertaking. Sound scientific advice, coupled with a critical writing eye, have tended to avoid purple advertising verbiage. Today, in fact, copy more nearly reflects acceptable facts, even the most conservative views. There is, of course, still room for improvement; experience must be looked to to bring about the necessary corrections.

COUNCIL ACTIVITIES

The trend of drug marketing may be observed in a description of the activities of the Council on Pharmacy and Chemistry. This body was organized in 1905 "primarily with the object of protecting the medical profession and the public against fraud, undesirable secrecy and objectionable advertising in connection with proprietary medicinal articles." Today the activities of the Council are defined thus:

> The Council publishes annually a book designated *New and Nonofficial Remedies* (N.N.R.), which contains a description of preparations and articles which have been examined and accepted by the Council for inclusion in that publication. The book provides statements on actions, uses, dosage, tests and standards of the preparations and articles that have been accepted. The book also contains certain official preparations and other articles, including drug substances for manufacturing use for which there are no official standards, which the Council is of the opinion should be included for the information of the medical profession.
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> The activities of the Council also include the preparation of special treatises, articles, status reports and books designed for the practitioner and the medical student, the giving of grants-in-aid for therapeutic research, the securing of therapeutic trial of promising new preparations, and the encouragement of basic research on fundamental therapeutic problems.

It is evident from the foregoing that the Council is no longer primarily a policing body. The reason is simple: there is less need today for this type of activity. The enforcement of laws such as the Federal Food, Drug, and Cosmetic Act, and the acquisition of outstanding scientific help for industry have not only changed the major activity of the Council but have permitted, even encouraged, the broadening of its scope. This extension of interest is significant, reflecting as it does what is included today in "professional acceptance"; perhaps more important, it indicates some of the current problems confronting both the profession and industry.

COUNCIL RULES

The Council considers articles for listing in *New and Nonofficial Remedies* according to a set of rules designed to elicit complete information and to permit consistent and fair application for all firms and their products. In substance, the rules provide that an accurate quantitative statement of composition must be provided; suitable tests must be available for identification; the article cannot be promoted to the public for use in the treatment of disease unless it is one of those agents concerning which the Council feels that information can be made available to the public (for example, antiseptics for first aid, laxatives, vitamins, and certain analgesics); therapeutic claims cannot be exaggerated or misleading and must be limited to those found acceptable for inclusion in *New and Nonofficial Remedies;* the name under which the product is sold may not be harmful to health, such as might be the case if the names were suggestive of diseases or treatment, and must be accompanied by an official or nonproprietary name or synonym; patent numbers and trademarks, if any, must be furnished; finally, the preparation must not be unscientific or useless.

Obviously, it is the right and duty of the physician to know the essential composition of the drugs he prescribes. He also wants to be informed whether the mixtures are unnecessarily complex, being mindful of the fallacy of prescribing unnecessary potent agents (a practice that can be harmful as well as uneconomical for the patient), and of prescribing routinely several drugs of different actions in fixed proportions in one preparation (since patients vary according to their needs for different drugs, each drug should be prescribed according to the needs of the patients). The physician also is justified in demanding that the claims offered on behalf of a product which he is urged to use be in line with demonstrable facts. Obviously, he is entitled to a truthful picture of what he can usually expect in administering the preparation to the average patient. It may be noted, in fact, that when the Council insists that advertising

material be kept within the prescribed limits, protection is being provided for the manufacturer, as well as the public and the physician.

The firm submitting a product must provide specimens of advertising material, specimens of the drug for laboratory examination, evidence in support of the efficacy and proposed claims, information on trade name and synonyms, definition, preparation, properties, tests, pharmacologic action, therapeutic indications, toxicology, dose, how supplied, manufacturer, patents, and trade-marks.

It is not in the interest of the professions for a company to market an article under two different names. Nor is it in their interests or, indeed, the public's, to market a substance with acceptable claims in the United States and the same substance in other countries with other claims simply because these countries do not possess adequate facilities to limit misleading claims. To enforce these principles the manufacturer or his agent should be held responsible for *all* statements made or quoted in any of the advertising concerning the therapeutic properties of its products. The rules are more fully discussed in a previous chapter.

CONSIDERATION OF A PRODUCT

The Council office submits the company's data, with other information in its files, to a Council member who serves as a referee. The referee prepares a report or puts in finished form a rough draft, prepared in the Council office by a professional consultant, and returns it to the Secretary, who, every two weeks, transmits such material to the other Council members by mimeographed bulletin. Accompanying this report are specimens of advertising material and other pertinent material which may aid the Council members in their decisions. Thus, each Council member has an opportunity to judge for himself the usefulness of the product, whether it complies with the Council's rules, and the report offered by the referee who, incidentally, is an authority in the field of the subject which he is asked to consider.

In the next issue of the *Bulletin* to Council members appears the discussion by all members who may be able to elicit information not available to the Council office or the referee. In the following issue of the *Bulletin* appears the vote to accept the product, reject, or hold in abeyance. A three-fourths affirmative vote of the voting members (a nonvoting member being one who may be ill, temporarily out of the country, or otherwise occupied) is necessary for the acceptance or rejection of a product. If a product is accepted, the company is notified immediately of the outcome of the Council's consideration. However, if any advertising claims must be revised or deleted, or more supporting evidence provided, before the product stands finally accepted, the firm is so notified. On the removal of these conditions the product then becomes accepted and a description is submitted to the editor of *The Journal of the American Medical Association* for publication; subsequently the description is transferred to *New and Nonofficial Remedies.*

If insufficient evidence is submitted by the manufacturer to justify the acceptance of its product at the time of consideration, the manufacturer is notified so that he may submit the lacking information. If he refuses or is unable to do so, the product may be held in abeyance for further investigation or may be immediately rejected. The manufacturer always is given opportunity to argue the Council's decision; he may, at any time, ask the Council to reconsider the status of a rejected product.

Occasionally, there is brought to the attention of the Council a new product which shows promise of usefulness but on which the experimental work has not been sufficient to make it ready for general use by the medical profession. In order to assure proper and controlled clinical study of such a product the Council issues a preliminary report on identity and standards, on the experimental work that has been done, and on the further study that may appear desirable.

With the exception of the continuance of acceptance of a drug, all the Council's actions, whether of acceptance, rejection or omission, are published in *The Journal of the American Medical Association,* and later in *New and Nonofficial Rem-*

edies, or in the *Annual Reprint of the Reports of the Council on Pharmacy and Chemistry.* This gives full publicity for all the Council's decisions to manufacturers and physicians alike.

Prolonged delays in acceptance procedures are almost always due to failure on the part of a manufacturer to submit the data for which he assumes full responsibility; for example, evidence or revised advertising claims. A product submitted with all necessary information, which does not violate the Council's rules, usually can be accepted within a period of from six to twelve weeks—surely not a very serious delay—the period varying with the product; if it is new, a longer period is required than if the product were merely an additional brand or dosage form to be considered. If necessary, as when a manufacturer wishes his product Council accepted prior to bidding in certain contracts, or when a hospital or other body is anxious to have an immediate report, the Council can, by means of special bulletins, complete consideration within two or three weeks. However, this is not a procedure that can be followed frequently as it would upset the routine which has been found most effective to dispose of Council considerations.

Occasionally, short delays are created by the referee being pressed at the moment with other duties. But as soon as these are removed the referee turns immediately to the Council problem. If he desires to prove or disprove certain claims by actual trial in his laboratory or clinic, a further short delay may result; but obviously such experimentation is of benefit to the physi- claims. Furthermore, delay is sometimes occasioned when the submitted preparation is of a nature that requires exhaustive chemical study. The Council members assume a grave responsibility in declaring a product acceptable or nonacceptable; consequently they require that the necessary data for careful consideration be available.

CLINICAL EVIDENCE

The Council insists that the manufacturer must supply evidence for therapeutic and other claims. The Council is not

equipped to initiate a clinical investigation of every drug submitted for its consideration. However, it does have the facilities of seventeen members to draw upon, the members' associates, and other outstanding authorities throughout the entire country who serve as Council consultants. A chemical laboratory maintained at American Medical Association headquarters also examines the chemical composition of every submitted product before it is admitted to *New and Nonofficial Remedies* unless there is adequate reason to waive such examination.

Clinical evidence should offer objective data with citation of authority enabling the profession to confirm the facts and establish the scientific value of the conclusions. The amount and character of the evidence required depend on the inherent probability of the claims; thus no evidence is needed for a self-evident claim, while very strong evidence is essential when the claim is contrary to the accepted data of science. The acceptability of evidence, moreover, hinges mainly on its quality rather than its quantity. For example, multiplication of inaccurate observations does not render them accurate. Of course, the evidence should be gathered in sufficient detail not only to permit judgment as to the care with which it was assembled, but also as to the legitimacy of the deductions. Comparative trials facilitate and are often necessary for such judgment. Indeed, observations that are not described with sufficient detail to permit verification are subject to suspicion. The credibility of the data and the justification of the deductions are influenced by the reputation and experience of the investigators as to disinterestedness, technical ability, and critical judgment. It may be remarked that observations gathered without adequate facilities are usually without probative value.

Occasionally, manufacturers, without previous experience with the Council, fail to understand what constitutes adequate evidence. The kind of evidence wanted is that which will stand up before any critical examining body, the kind a scientist would not be reluctant to present before a medical or other scientific group. Signed statements, even when they come from the best of men, do not constitute evidence if they are merely

testimonial in character; for example, several hundred signed testimonials are not equal to one or two good pieces of research.

When claims for nontoxicity are made they should not conflict with known facts. At best, a claim of lack of toxicity may only mean that toxic effects have not as yet been recognized; apparently justified beliefs concerning this point are often ultimately reversed by extended experience with the drug. The same observation is appropriate regarding the claim that the drug is nonirritating.

EXEMPTIONS AND REACCEPTANCE

Certain official agents, and combinations of official agents, are exempt from Council consideration if they are marketed with no unestablished claims and under the official name or synonym. A list of exempted articles may be obtained from the Council office and may be found in the preface of *New and Nonofficial Remedies.* Undoubtedly there are many who have noticed that *New and Nonofficial Remedies* contains some official agents as well as nonofficial ones. This is because the Council feels that there are many such preparations about which the medical profession is not sufficiently well informed; since the *United States Pharmacopoeia* does not provide statements of actions and uses, the Council makes these available in *New and Nonofficial Remedies, Useful Drugs,* and the *Epitome of the United States Pharmacopoeia and National Formulary.* Each year, moreover, *New and Nonofficial Remedies* is revised to maintain claims in accord with those generally accepted at the time of revision. This annual revision thus provides a reference to which the physician may turn for authoritative and up-to-date information on the therapeutic value of drugs.

Three years after acceptance each product is again reviewed to determine if it is still in keeping with the Council's rules; if it is, the agent is accepted for another three years. At the end of each interval of three years, or more often, it is re-examined.

COST OF COUNCIL WORK

The Council has never accepted, or permitted to be accepted, a cent of remuneration in any form for the consideration of products. The cost of maintaining the Council on Pharmacy and Chemistry, as well as that of the other American Medical Association Councils and Bureaus is borne entirely by appropriations made by the Board of Trustees of the American Medical Association. Nor is the Council influenced in the slightest by any proffer of advertising patronage to *The Journal of the American Medical Association* or other Association journals. Indeed, Council members are not advised by the Secretary of any information with respect to a proffer of advertising; hence, there is no possibility of their action being affected by this factor. Incidentally, if the Secretary learns of such an offer, the company is notified forthwith that it will have no effect on the Council's consideration. The Council is a scientific advisory committee and is able to maintain this status by being free of financial encumbrances.

"OVER-THE-COUNTER" ITEMS

The Council does not consider for acceptance every agent sold to the public. In the first place, to do so would be a tremendous undertaking. Indeed, no one body of moderate size could ever hope to give consideration to all the drug preparations that come and go. Of greater importance is the status of claims made to the public: Are such agents sufficiently effective to meet all the claims usually advanced? But aside from the truthfulness of the claims, are the preparations of a nature that should be in the hands of medically untrained individuals? The evils of self diagnosis and self treatment are, of course, evident, and this consideration is given close attention.

The medical profession has warned frequently against the hazards of self-medication involving, as it occasionally does, grave dangers of misdirected and inadequate treatment, failure

to recognize serious disease until too late for definitive treatment, and the spread of infectious diseases when hidden from a responsible physician. These factors all may be present in advertising drugs to the public, with the further dangers of planting the suggestion, by descriptions of symptoms, in some minds that they are suffering from diseases described, of unconsciously and innocently causing the formation of a drug habit, and of starting allergic reactions.

These possibilities do not apply in equal degree to all preparations; admittedly, there are instances in which some general good is likely to result from advertisements conveying information to the public, if it is truthful and does not mislead by undue emphasis or suggestion. The proper promotion of such articles would not preclude professional acceptance, but, in view of the potential dangers to the public, such cases should not only be carefully weighed, but should be confined to certain groups of drugs. Of course, "advertising to the public" includes all promotion of the article in newspapers, magazines, placards, or circulars which may reach the patient, radio, films, and similar devices. Obviously, it also refers to the labeling of drugs.

Such a limitation ordinarily imposes no restriction on the generally acceptable methods of bringing a remedy to the attention of the profession, such as advertising in journals, labeling, circulars, and other printed matter distributed solely to physicians, dentists, pharmacists, and veterinarians. However, promotion should not be designed to invite or encourage use of these articles by unqualified persons; hence, the rule against the naming of diseases and therapeutic indications in the labeling. On the other hand, this information may not only be necessary, of course, but a legal necessity for proper instruction in the use of articles sold directly to the layman; it is therefore permissible in the case of the preparations accepted for promotion to the public.

OTHER ASPECTS OF COUNCIL WORK

Some individuals have averred that the average physician is capable of judging the value of a product. Unquestionably, he

is trained to observe clinical responses. But has he the time and the necessary detailed knowledge of bacteriology, pharmacology, toxicology, endocrinology, and other special branches of medicine always to determine which patients might have recovered without drug intervention, which preparations are unnecessarily complex, which contain incompatible agents, which may have lost part of their effectiveness because of partial absorption into the container, or by oxidation, and the host of other factors that must be considered? Many of the manufacturers with products accepted by the Council would be the first to say no. Nor can it be denied that each member of the Council having spent many years of special study in some particular field is able to give quicker and more adequate answers to such questions.

The Council occasionally is asked if there is need for its existence because of the new food and drug legislation. The answer is in the affirmative. Thus, in considering a new drug application the Food and Drug Administration, under the terms of the 1938 Federal Food, Drug, and Cosmetic Act, is concerned primarily with the safety of the preparation. Indeed, if this agency attempts to question certain claims in the proposed advertising material, it may be reminded by the manufacturer that advertising material, not accompanying the market package, is outside its jurisdiction. Moreover, any action based on the consideration of claims for usefulness can only be initiated on interstate shipments after a new drug application has been made effective.

Several additional considerations render it impossible for the Food and Drug Administration to consider the labeling and to determine the composition of all types of drug products after they have appeared on the market: First, limitations of the facilities and personnel available for the enforcement of the Act; secondly, the attention the Food and Drug Administration is necessarily focused on the small segment of the industry always engaged in marketing products with wholly fraudulent or even vicious claims; and thirdly, the large number of pharmaceutical manufacturers and products marketed. Further-

more, the Food, Drug, and Cosmetic Act is applicable only to products in interstate commerce; many products as a matter of fact do not go beyond the borders of the State in which they are manufactured. Unfortunately, altogether too many State enforcement agencies have inadequate facilities to control these. Under the circumstances, for a considerable volume of therapeutic agents which the physician uses, the only definite assurance that the labeling and advertising claims for them are in accordance with sound medical opinion is the appearance on the package of the seal of the Council on Pharmacy and Chemistry.

Other agencies have analogous limitations. Thus, the Federal Trade Commission exerts little or no control over medical advertising directed solely to the physician; indeed, the law, for all practical purposes, exempts drugs so advertised. The Post Office Department reserves its action for schemes in which the mails are used for fraudulent purposes. Usually, articles mailed to the public are involved. The National Institute of Health is concerned only with serums, vaccines, toxoids, and analogous products in which are included certain antisyphilitic preparations; the scope of its action is necessarily restricted.

COUNCIL OBJECTIVES

Nostrums placed on the market in the seventies and patented German synthetics grew enormously in number in the early part of this century. Profits were immense and enticing. While a few of the compounds were of distinct value, the vast majority were simple mixtures of well-known drugs put out under fanciful copyrighted names and for the most part fraudulent in one way or another; many, indeed, were actually dangerous. Although a few were products of well-known drug houses, the majority were put out by men who knew nothing of drugs or their effects but who went into the business of manufacturing medicines as they would any other. Few hired competent chemical or medical advice, and as a result no statement was too silly or claim too extravagant to make. Those with a critical eye

may have seen through the flimsy material offered as "evidence," but by persistent and occasionally clever advertising many were duped into buying and using these mixtures. Truly in these earlier days medicine, in some instances, could have been defined by the disappointed patient and physician as "the art or science of amusing a sick man with frivolous speculations about his disorders, and of tempering ingeniously until nature either kills or cures him." As early as 1879, the American Medical Association adopted resolutions condemning the use of these secret and semi-secret mixtures, but it was not until 1905 that the Council on Pharmacy and Chemistry was formed.

Many of the original objectives of the Council have been firmly established, partly because of the increasing appreciation of its work by the medical profession, partly because of the more conservative and scientific attitude of the average drug manufacturer. As a result, the commercial production and distribution of medicinal products are on a higher plane in the United States than in any other country. But there must be close cooperation by all branches and representatives of the profession. "Pharmaceutical manufacture is largely a business; and as such it will be ready to defer to the demands of its customers—the medical profession." To be completely effective, therefore, everyone interested in progressive medicine must participate in the program.

An interesting observation is the degree to which the public has become Council conscious. The Council office not infrequently has queries from physicians asking if a product is Council accepted simply because their patients have made such inquiries. Many people in lay audiences addressed by members of the headquarters staff ask about Council acceptance in a manner indicating considerable familiarity with the Council and its seal.

MEDICAL COPY WRITING

The problem of professional acceptance is intimately associated with advertising. Preparing medical copy to satisfy the American Medical Association seems to be quite troublesome

for many copy writers; yet the task is not a difficult one. The late Charles S. Mohler, whose tragic death in 1946 ended an outstanding career as Advertising Manager and Assistant Business Manager for the American Medical Association, presented a paper in 1930 at a meeting of the American Drug Manufacturers Association describing medical copy writing in such a simple and sound style that it is suitable even today for reproduction. Accordingly, it follows, in part:

Medical Copy Writing

* * * * I shall confine myself here to advertising as it is related to drug products, and particularly those drugs sold to and through the medical profession. This kind of advertising, therefore, concerns two parties—the manufacturer, on the one hand, as the seller and the physician, on the other hand, as the buyer. It will help us to a better understanding if we study each of these two parties.

The Manufacturer's Function

* * * * The scientist may in the solitude of his laboratory bring forth an epoch-making discovery, but that discovery may die in the travail of birth, unless some one seizes the torch from his hands, fans it into the full flame of commercial development, and carries over to humanity its actual application.

The assembling and management of capital, the seeking out of raw materials, the erection and maintenance of manufacturing buildings, the installation of machinery and the development and direction of skilled labor are quite as necessary as the discovery itself. * * * *

Rights of the Manufacturer

In return for your efforts in manufacturing medicinal preparations and making them available when and where needed, the American economic system recognizes that you have certain rights. You have the right to individual initiative and business enterprise. You have the right to a just profit on your capital investment and your operations. You have the right to build up a name and a reputation for yourself so that a certain percentage of the medical profession may be expected to discriminate in favor of your products. Your advertising then, so long as it is truthful, needs no apology. It is simply one of the tools of modern business.

A Look at the Doctor

The other party to medical advertising is the doctor. What kind of man is he? Some say that, after all, the doctor is just an ordinary human being and should be so regarded by the medical advertiser. I agree. I go even further, and say that a great many of the difficulties or failures in medical advertising come from the very fact that the physician is *not* recognized as a human being.

The human being is different from the animal in that he expects a considerable degree of rationality in things presented to him. Advertising copy written for physicians must first of all display rationality, remembering that John Smith, M.D., is a professional man. He has been educated in medicine. Academic training and hard experience have taught him to think critically. His work is concerned with the most marvelous machine on earth—the human body, whose operation is governed by a thousand and one different factors.

Why the Doctor is Critical

That M.D. to whom you are addressing your advertising knows full well that a good mechanic can make two or three tests and be absolutely certain as to what is causing a knock in a motor. On the other hand, your M.D. knows that he may be called to attend a typhoid-stricken family, may apply every known resource of medical science and may have as a result two deaths, one near death, one mild attack, and two escaping the disease entirely. Such experiences as these make it plain why the physician is critically minded, why he is slow to accept generalized statements about the effects of medicinal agents. * * * *

The Doctor's Outstanding Urge

The second question about the doctor is this: What is the underlying motive that causes him to respond to medical advertising? What is his chief concern when he prescribes for a patient? Is a beautiful appearing product important to him? Is fine taste essential? Is low cost the deciding factor? No, all of these things may be of some consequence, but the one urge that transcends all others in the doctor's mind when he prescribes a medicine is to get successful results. The whole pattern of his professional life is made up of a succession of battles against the inroads of disease. In each of these struggles he is the commander-in-chief. Medicinal agents are one of his chief means of offense and defense. Suppose the antiseptic

applied to the wound is feeble or worthless, and a fatal infection ensues. Suppose the ampul carries a medicament that is not chemically correct, and a violent reaction follows its administration. Suppose that the diphtheria antitoxin is impotent and a high percentage of deaths occurs. Who, in the eyes of the world, must shoulder most of the blame? The manufacturer? No. The doctor, the one who has managed the case, is the one who has failed. And too many failures will certainly cost him his professional reputation. He cannot afford, in the least degree, to take a chance on any medicinal agent. His professional reputation is too valuable.

Common Errors in Medical Copy

Coming specifically to the writing of the medical advertisement, let us look at both sides of the question. Let us consider, on the one hand, some of the things to avoid, and, on the other hand, some of the constructive angles of writing medical copy.

The Misdirected Message

First of all, among the things to avoid is the misdirecting of your appeal. This seems like an unnecessary admonition among a group of experienced advertising men, but now and then a piece of copy comes blithely sailing in to us for THE JOURNAL A.M.A. apparently without any recognition of the fact that it is going to be read only by doctors. I well remember an advertisement which pleaded and argued through $125.00 worth of space the advantages of a certain type of nursing bottle. It was for THE JOURNAL A.M.A., read almost exclusively by doctors, yet it persisted from start to finish in talking about "your baby." It required two or three letters to the agency to make it clear that the term "your baby" was more or less of a miscarriage in a medical journal. I hesitate to express an opinion as to what that agency might write were they to prepare an advertisement on obstetrical pituitary or corpus luteum.

A second class of difficulties in copy arises over the use of downright sloppy English—words and phrases which, when considered in their actual meaning, are entirely without justification.

Big Words No Substitute for Ideas

One of the manifestations of sloppy English is the use of high sounding phrases or pseudo-scientific terminology. Now, I would not deny the advertising man the benefits of the medical dictionary. But if the dictionary is employed chiefly as a means of garnering words for the affectation of a scientific style, the result is just about

as convincing as the verbal gymnastics of Andrew Brown, president of the Fresh Air Taxicab Company of America, Incorporated. Amos and Andy are selling considerable quantities of toothpaste to the American public; they are also teaching us some valuable lessons in the use of the English language. They are showing up the fellow who "starts messin' round with big words."

Keep your copy simple. Some of the best medical writers use the simplest style. For example, a medical work called *The Handbook of Therapy* is expressed in such simple words that it has often been said that "Almost any layman could take that book and make a fair attempt at the practice of medicine." Yet, it has enjoyed a tremendous popularity. It has gone through eight editions. It has had a total sale of more than 75,000 copies. Obviously, the doctor likes simplicity.

The Lure of the Superlative

Another manifestation of careless English is the much abused superlative. I admit that the superlative is a tempting phrase. It seems so simple to the copy writer. He will simply step out in a bold, emphatic manner and say that his cascara, his arsphenamine or his soda bicarbonate is "the best" and that will settle the matter. With one fell swoop he will put all his competitors in second place. Nobody wants a second-rate product. His firm will get all the business.

Now, there may be times when a superlative statement is justified. Certain qualities can be measured in actual physical units, such as size, length, duration of time, etc. But you cannot speak of abstract qualities in superlative terms and expect an agreement. There is no one automobile that is "the best"; no one woman who is "the most charming"; no one child who is "the most wonderful." The best automobile for you is the one you bought. The most charming woman for you, the one with whom you cast your lot for life. The most wonderful child is not the brat down the street, but none other than your very own. Remember this in choosing the verbiage for your copy. To attempt to sweep the doctor off his feet with mere braggadocio is a puerile procedure. Instead of convincing, it causes doubts to arise in his mind. And when two firms break into print, each claiming their product is "the best," that is a signal to the doctor that perhaps neither advertisement is likely to be true. Make your English fit the facts in the case.

"The One and Only"

Here are a few examples of misfit English. Why say that a certain product is a "necessity for nursing mothers"? It may or may not be.

Isn't it better to say, "valuable for nursing mothers"? Why should any manufacturer claim that his is "the arsenical of choice"? The facts are it is "the arsenical of choice" for certain physicians. Periodically there bobs up the phrase, "the safe hypnotic." But if you would talk as I recently did, with the proprietor of one of the largest institutions for the treatment of the drug habit, you would be told in very vigorous language that there is *no* "safe hypnotic." In the advertising of antiseptics, we see again and again that this or that is "the ideal antiseptic." Yet, if you read up on all of the work being done by present-day authorities on antiseptics you will find that there are wide differences of opinion regarding the efficacy of Iodine, Mercurochrome, Dakin's Solution, Hexylresorcinol, Metaphen and other preparations, all of which have claim to merit, but none of which, on the basis of present-day opinion, can lay claim to being the ideal antiseptic. Even the statement that "mineral oil is the safest of all laxatives" would be at once attacked and denounced by any number of gentlemen who have had the experience of using the product rather too enthusiastically.

Know your English. Make it fit the facts. Your troubles will be fewer and your copy will be better.

Packing in the Names of Diseases

Another trouble-maker in medical copy is the device of packing the advertisement full of the names of diseases for which a product may be used. It is hard to tell just where the line should be drawn. But, remember this: The medicine of today is not the medicine of forty or fifty years ago. The vast increase in our knowledge of physiology, bacteriology and pathology has educated physicians away from the idea that this or that drug is a specific. You can take a simple, yet meritorious, and useful product such as a dusting powder and give indications for it in practically every bed-confining illness from acne to zoster. Of course, a dusting powder can make almost any bed patient feel just a little more comfortable. But, why be ridiculous? After all, a dusting powder is a dusting powder. There is certainly no excuse for anyone to attempt to build up a dusting powder system of therapeutics.

Unhitch the Trouble-makers

Now, why do these trouble-makers keep bobbing up in medical copy? I can answer that best by telling you a story. A number of years ago, I moved my family from the city to a suburban home. My youngest child was then about two years old. The open country was

a new experience to her. One evening, while out walking, I pointed across a field and said, "Look, there is a horse." The child looked and then shook her head. "No, daddy," she said, "that isn't a horse; that's a cow." "Why, yes, it is a horse," I replied, "why do you say it is a cow?" "Well," she said, "it can't be a horse because it hasn't any wagon on it." Gentleman, the cause of most of your troubles in medical copy is the mistaken idea that a medical advertisement must have hitched on to it the customary formulas and technic that we see in the general field of advertising—the sweeping superlative, the affected scientific style, the big words, the long list of therapeutic indications, etc. But, remember, a horse can still be a horse without a wagon. General advertising is one thing; professional advertising, another.

What to Put Into Copy

Now, you may say it is easy to tell what to keep out of copy. I believe it is easier to tell what one can put *into* copy. Our analysis of the doctor will tell us some things that make good medical copy.

Proofs of Dependability

First of all, we can say that one of the doctor's chief concerns in selecting drugs is the dependability of the manufacturer. By that I mean more than honesty and fair dealing. Those are qualities which are demonstrated by actions rather than by advertising. But the idea of dependability is also conveyed to the doctor by telling him about such concrete things as your manufacturing facilities, your processes, your means for distribution. If you have a plant of which you are proud; if you have specialized machinery; if you have a well-equipped laboratory; if you employ painstaking processes, make those things living and real to the doctor through your advertising. And he will then know that your claims of dependability rest upon a solid foundation. Excellent examples of this kind of advertising may be found in some of the pages recently run by Mead Johnson & Company, Frederick Stearns and Company, and Eli Lilly and Company.

Tell Where Products Are Available

Availability certainly interests the doctor. Do not forget that when he needs a drug, time is almost always a very important consideration. If you have thorough, nation-wide distribution, do not hesitate to say so. If your distribution is but partially complete, it is certainly a mistake to say "at all dealers." Exact facts about avail-

ability of the product are a service feature that should not be overlooked in copy.

Practical Facts

Practical information is also a quality that fits naturally in with the doctor's requirements. A piece of poetry or the picture of your president may be an artistic triumph, but in the last analysis, the doctor wants something that he can use. He wants material that is timely—not diphtheria antitoxin facts in July or information on infantile paralysis serum in January. A close regard for the seasonal incidence of various diseases will aid greatly in making copy of more practical value to the doctor.

The Interest in New Things

The doctor is interested in newness. He wants to know about new things. That is why he reads medical journals; why he attends conventions. Remember that, while medical literature usually paves the way for advertising of new products, it is constantly shedding new light on the old remedies. Consider the efficiency of the advertising man who would attempt to sell cod liver oil on the basis of the knowledge of 1910.

The doctor also likes complete information because, as we have said, he is critically minded, and his problems are exceedingly complex. An outstanding example of an advertisement that gave complete information was the one run some time ago by the Corn Products Refining Company and bearing the caption, "The Uses of Dextrose." It occupied eight full pages, carried no illustrations, but it gave the doctor a critical summary of practically all that was then known about the use of dextrose.

Getting the Therapeutic Claims Straight

Last, but perhaps most important of all the types of information that go into your advertising is that relating to therapeutic claims. Let me preface my remarks on this point by a story: A general practitioner in Chicago found himself completely baffled by a high blood pressure in one of his patients. No remedies or treatments he could apply brought satisfactory results in reducing the hypertension. He finally consulted one of Chicago's outstanding specialists in internal medicine. After reviewing what had been done, the specialist suggested that it might be worth while to try a certain remedy then being developed for lowering the pressure of the blood. About one month after, the general practitioner and the specialist met. The specialist's first question was as to the condition of the patient.

"Fine. Fine," replied the general practitioner. "His blood pressure has come down nicely, and his condition is now very satisfactory." "Well," said the eminent specialist, "then it appears that this new remedy is something quite promising." "No," said the general practitioner, "you see, the stuff wasn't on the market yet, so I couldn't give it to him."

Effects or Events?

Such incidents are legion. They can be found in the experience of almost every layman or physician. They are simple, homely illustrations of the fact that in measuring the effects of drugs, we are dealing with a living organism which in itself has mighty resources for spontaneous recovery. If a patient improves after taking a remedy, we do not know whether it is because of that remedy, in spite of that remedy or in total disregard of that remedy. What happens may be effects or mere events. The real problem is to determine whether there is any causative connection between the remedy and the succeeding events.

How, then, shall we arrive at the largest measure of facts regarding the therapeutic values of the drugs we wish to advertise? Here are some suggestions.

Work With Your Own Scientific Department

First of all, consult your own scientific department until you know the product almost as well as the scientific man himself. You may think that he is slow, that he is unsympathetic to the commercial department, and entirely unappreciative of the speed of modern business. But, remember, he is a bear for facts. His one great obsession is to arrive at truth. He may take some of the grandiloquence out of your copy, but it will shine all the brighter with the reflection of truth.

Get the Help of Outside Investigators

A second agency by which you may arrive more nearly at the truth regarding therapeutic claims for a product is through the aid of competent outside investigators. In no other field of human endeavor will you find such a magnificent machinery for scientific investigation, and nowhere will you find greater willingness, greater eagerness to investigate. But the investigator must be competent, and the investigation must be planned in a thoroughly scientific manner. To the advertising man who desires to cooperate in and interpret scientific investigations, I would commend the constant reading of reports on research, whether they bear directly upon the products of his firm or not. Such reading habits will inculcate in

him an appreciation of what scientific reasoning really means, and school him in the correct technic of scientific expression. For example, in a current surgical journal, you may read a report about the effect of iodine for preoperative treatment of goiter patients. The author declares that, in the experience of himself and associates, it has practically eliminated the need for preliminary ligations, and has decreased the mortality from 4.1 per cent to 0.9 per cent. But that statement is not mere opinion. It is based on actual experience with 5,081 patients. Nor is the statement dogmatic. This author, even with the records of more than 5,000 patients, does not attempt to settle the question for all the rest of the profession. He simply tells what iodine *has done* in his experience; not what it *will do.*

A Mine of Information in the Medical Journals

A third and perhaps the most practical source of information for the copy writer is in the medical journals of the day. If a man can read and use a library, he will generally find plenty of material about almost any product he will want to advertise. A mere glance in any issue of the *Quarterly Cumulative Index Medicus* shows what a tremendous volume of articles is being published by investigators in the field of medicine. For example, the *Index* shows that in 1929 there were 108 articles on the subject of dextrose; on irradiated ergosterol, 80 articles; on ergot, an old established drug, there were 58 articles.

On first thought, this abundance of literature would seem to simplify the job of writing medical copy. In reality, it makes it more difficult. If there were only one author writing on the subject of dextrose, the copy writer would have easy sailing. When two men write on dextrose, the situation changes. Then there arises the need for critical judgment. Then, one man's findings must be balanced against those of the other. But when we find 108 articles on the subject of dextrose as there were in 1929, then we begin to see how enormous is the job of writing medical copy which is effective, and which at the same time keeps its statements in line with the preponderance of medical opinion.

The Help of the Council on Pharmacy and Chemistry

I mention, therefore, a fourth and last agency for assisting in arriving at the truth regarding medicinal products. I refer to the Council on Pharmacy and Chemistry of the American Medical Association.

This body, because of its personnel and its resources, serves as a clearing house for facts in a way that perhaps no one individual or one firm could function. It is composed of seventeen men, each chosen because of outstanding accomplishments in some branch of medical science. The secretariat of the Council has at its disposal library facilities for keeping in touch with the current medical literature of the entire world. It has a system of records that extends back over a period of twenty-five years, and furnishes a complete history of every product considered by the Council during that time. In short, the Council brings into its consideration of any one product the knowledge of a group of qualified authorities, a world-wide acquaintance with medical literature, and an experience of twenty-five years in a critical study of medical preparations. Its service is at the disposal of any manufacturer desiring its aid in arriving at the truth regarding any of his products.

The Council "Acceptance Seal"

Incidentally, I should refer here to the recent development and adoption of an "Acceptance Seal" or emblem for Council-passed products. This emblem, of distinctive design, bearing the words "ACCEPTED, AMERICAN MEDICAL ASSOCIATION, COUNCIL ON PHARMACY AND CHEMISTRY" will soon be available for use in connection with the labels and advertising of products that are Council accepted. It is a simple, effective device for telling the medical profession at a glance that the manufacturer has submitted his claims to the Council, and those claims have been given official Council recognition.

I might go on and discuss at greater length what to put *in* and what to keep *out* of medical copy. But this paper lays no claim to exhaustiveness. The things I have mentioned are illustrative, and are meant to act as guides rather than as hard and fast formulas.

Be Medically Omniscient

If you will remember that you are co-partners with the physician in fighting his battle against disease; if you will remember that the doctor is critically minded, that he knows his medicine, that his professional reputation is endangered every time he uses a questionable drug preparation; if you will remember the vastness and the complexity of medical science; if you will arrange in some way or other to keep posted on the whole of medical literature, and base your copy, not merely on isolated facts, but on all the facts; if you will recognize that in no other field of advertising is it so dangerous and foolish to make dogmatic statements, then you will find that

the articulate expression of copy ideas is relatively easy. Then it is chiefly a matter of knowing how to write good English.

But the writing of medical advertising is not a job for your office boy, your stenographer, or your third assistant clerk. It is one of the most important tasks in the drug manufacturer's business. Your financial department may make a mistake in extending credit; your production manager may figure wrong; your scientific department may pursue a false hunch, but the effect of such errors is mostly self-contained. They are matters which can be adjusted and forgotten. Not so with errors in advertising. Your advertisement is your public declaration to the members of the medical profession. Whoever will may read it, and the claims you make are tried at the mighty bar of professional opinion.

RESPONSIBILITY FOR PROFESSIONAL ACCEPTANCE

Today, practically all firms recognize the value of expert scientific advice in the preparation and marketing of drug products. Unfortunately, not every manufacturer can develop overnight the staff that is adequate for this job. He then must seek outside assistance if he does not have sufficient help available within the organization. Regardless of the source of advice, one individual or office should be responsible for coordinating scientific facts and for the proper utilization of these facts when the drug is marketed.

The medical director is the individual who should be qualified for the work. The part that can be played by him can be best described simply by outlining some of his responsibilities.

It is difficult to offer a truly descriptive definition of a medical director. He should be a man or woman who is charged with guiding the policies directly related to specific medical problems. While the details that he undertakes depends on the amount of work that is done by the company and its ability to pay for professional service, the medical director should be a key figure in management. Medical problems ought to be a major responsibility, but, included in his duties, would be those concerned with, for example, new product development, promotion, and professional service. In other words, around the medical director should revolve medical questions. If he knows

the answers he would be expected to supply them. If he doesn't, he should be free to obtain outside help from competent individuals.

It does not seem possible to make the best use of this type of specially trained individual unless he is an integral part of top management and unless he assists in determining policies. Too frequently he has been considered as a casual advisor on medical problems. This viewpoint is not only wrong, but indeed shortsighted and uneconomical. After all, if management is paying for special services it might as well get as much as it can for the money spent. Certainly it would place this criterion on any other service.

The medical director, in general, should be intimately concerned with research, both laboratory and human, with promotion, with professional relations, and even with determining the possible extent of the sale of a product. He should be the guiding and restraining influence on advertising copy and should know the possibilities and limitations of his firm's products. When there is doubt, he must press for further evaluation of the agent by additional observations, thus outlining, beyond question, any limitations. Obviously, he also usually becomes the focus for medical complaints and the "answer man" for physicians, pharmacists, and others engaged in health services.

The medical director must be fully informed at all times; he should consequently have extensive files, appropriate scientific contacts, and adequate help—clinical, professional, and financial. To pursue these activities successfully he must be well trained, capable of administrative activities, and willing to undertake such work. Of course, a pleasing personality is no handicap. These points seem obvious, but occasionally one encounters a misfit, either because he is not the desk type of man, although he had been pushed into the position by his management, or because his mental outlook and training do not permit him to recognize and meet his responsibilities. Sometimes the prospects of the job arouse enthusiasm not fulfilled by ability. Strange as it may seem, moreover, occasionally management seems to overlook such factors as neat appearance,

pleasing personality, and other points that would be demanded from a salesman or other type of employee coming in touch with the public.

The responsibilities of the medical director may be grouped into several classes: (1) those to his firm; (2) those to the health professions; (3) those to the general population; (4) those to himself. Perhaps these could be regrouped according to two objectives—the prevention and treatment of disease, and personal security. It is not necessary to discuss in this book security for the employee, but it is something that must be kept in mind if those charged with the problems of professional acceptance are to be adequately trained and maintained to provide the best possible service for the manufacturer.

The work of the medical director in his relation with professional acceptance can again be divided into three broad groups —research, product and treatment evaluation, and education. Included in education is information and consultation extended to detail men, copywriters, and other individuals and departments that make up his organization. One thing is worth emphasizing, however: Under no circumstances should he attempt to diagnose and treat by mail.

Professional acceptance involves a major responsibility and activity. The task associated with it cannot be undertaken by just anyone, nor can it be indifferently treated by top management. Today, indeed, to deal with government agencies, such as the Food and Drug Administration, and voluntary organizations, such as the Council on Pharmacy and Chemistry, it is necessary to hire or retain highly trained and qualified individuals to undertake this work. With proper qualifications, training, and good understanding the job becomes relatively easier. Without these, and lacking an appreciation for the need of critical study of what constitutes professional acceptance, stumbling blocks will continue to appear with the lamentable result that professional acceptance becomes at best, if at all, merely professional tolerance.

21

Retail Price Maintenance

ISAAC W. DIGGES

FREQUENTLY available to the manufacturer of the new drug preparation—or, for that matter, a product already being marketed—is the privilege of fixing its wholesale and retail resale price. This practice goes under the designation of "fair trade." Today, forty-five States—all except Vermont, Missouri, and Texas—by statute permit manufacturers and distributors of branded goods to make valid resale price maintenance agreements. And a Federal statute—the Miller-Tydings law—implements this legislation so far as it affects products moving in interstate commerce to these jurisdictions.

The exponents of "fair trade" find various justifications for pricing by this method, legally, ethically, and economic. However, it is our sole purpose in this chapter to present a simple factual picture of the factors that make "fair-trading" a subject of serious consideration for the manufacturer or distributor of a new drug product.

Perhaps the primary factor is that the majority of drug retailers throughout the United States will be found to be enthusiastic advocates of "fair trade." In fact, for almost half a century groups of retail druggists have fought for the principles embodied in "fair trade." The reason for the popularity of the practice among retail druggists generally is not hard to find.

One of the banes of the small drugstore's existence has been the price-cutting practices indulged in by a certain type of competitive store. Sharp, and at times startling, reductions in the price of nationally-advertised brands of drugs have frequently been utilized to attract customers into their premises. One factor encouraging this action is the relatively high

"mark-up" on some drugs and cosmetics that allows a wide variation in the quoted price. Another, of course, is the fact that increased sales thus obtained, unless the sales are below cost, serve to reduce overhead; the reductions, in a sense, are charged to advertising costs.

To the average druggist, however, these advantages are neither available nor attractive. His shelves are burdened with thousands of different kinds of articles, many of which move slowly. Much of his stock, moreover, consists of products which serve the purchaser for a comparatively long period of time. Thus, a tube of toothpaste, a bottle of soda tablets, a saline laxative, or a vial of iodine may be in the consumer's medicine chest many weeks before the need again arises of replenishing it. It follows that the customer is not ordinarily as frequent a visitor to his drugstore—save possibly for non-drug products—as he is, for example, to his butcher or grocer. In consequence, the druggist finds himself with a comparatively large capital investment in an inventory of great variety, much of which turns over very slowly. Unfair price competition tends to jeopardize this investment; it presents a constant hazard to his business—one that can be dealt with only by meeting or bettering the price reductions made by his competitor. In many localities, the resulting conditions become chaotic and economically unwise. In resale price maintenance, consequently, the average druggist recognizes the opportunity not only to make a fair profit on drug items commensurate with the length of time his investment is frozen in inventory, but also gains a sense of security as to the continuing value of his stock on hand.

On the other hand, the advantages of "fair trade" to the manufacturer and distributor of the drug have been summarized by a firm, whose line has been "fair-traded" for many years, in this manner:

> First, it has permitted us to establish a definite value for our products in the minds of the consumer through national advertising and promotion;
>
> Second, price maintenance has assured a fair profit to everyone handling our line;

Finally, it has prevented chaotic market conditions and price wars which result in retailers withdrawing all promotional support; first, hiding the line under the counter, and eventually refusing to carry it at all.

Of these reasons, perhaps the most material one is that outlined last. At first glance, there appears no substantial ground for the manufacturer or distributor to fix the resale retail price of his product; his wholesale price is met, and, indeed, his sales may even be increased temporarily by the intensified advertising and price-cuts of his outlets. In practice, however, these ostensible advantages disappear. While it is true that his product at a reduced price succeeds in bringing purchasers into the store, once there, the efforts of the retailer are all too often directed at "switching" the customer from the branded articles—where his profit is naturally low or nonexistent—to another possessing a wider profit margin. Switching or substitution are widespread practices in the price-cutting stores, to the detriment of the manufacturer of the branded and favored item.

Another development has also brought home the necessity of resale price maintenance to some manufacturers. Where a branded product became the subject of price-cutting by a few chain and "cut-price" stores, every retailer in the vicinity was forced to meet the competitive price for the article, not only to dispose of his inventory but to prevent his store being castigated as a "high-priced" one. Frequently, this meant selling below cost to him. The resentment thus engendered often found outlets refusing to stock the product at all. A number of manufacturers consequently found it difficult to maintain proper distribution of their brands.

We have, in the foregoing paragraphs, submitted several of the arguments advanced in support of retail and wholesale price maintenance. Needless to say, whether to "fair-trade" or not is a decision that can be made only by the individual manufacturer or distributor. That "fair trade" is a practice capable of being abused must also be recognized. To fix the retail price too high, merely to curry favor with a group of retail druggists, is a fallacy which will be sharply brought home by diminishing

sales and reduced distribution. In the final analysis, it is the eventual consumer of the product whose reaction governs the acceptance or rejection of a product, nor should he be priced "out-of-the-market" by unconscionable retail prices, artificially supported. If nothing else, self-interest dictates that a manufacturer not set the retail price too high. Prices disproportionately high serve only to invite competitive encroachment on his market. Nor should one be unmindful that competition in trade-marked products is far more severe than in other classes of goods. In short, the manufacturer must always be cognizant of the fact that, next to quality, price is the most potent factor in building and holding distribution.

WHEN PRICE-FIXING IS AVAILABLE

Before the enactment of the "fair trade" statutes, most efforts made to control the retail resale price of commodities ran afoul of the anti-trust laws. Indeed, most of us are familiar with the attempt of Dr. Miles Medicine Company to enforce a resale price agreement two score years ago which failed on suit of the Government.

The "fair trade" laws have been devised and generally accepted as giving legality to contracts specifying the resale price of a trade-marked, or similarly identified, commodity, designating as a form of unfair competition the willful and knowing advertising or selling of such an article at less than the stated price. It should be noted, however, that this type of legislation permits only *vertical* price standardization, the manufacturer being entitled to fix the price at which the goods may be sold to others only in *his* chain of distribution.

As a matter of fact, all "fair trade" statutes are in accord with long-established legal precedent by specifically prohibiting *horizontal* price-fixing. Thus, the prevailing injunction against the establishment of prices by persons normally in competition with each other, such as groups of producers or retailers, has not been abrogated and still remains in effect. Resale price maintenance under "fair trade," it should be emphasized, bears no relation

to competition in this sense. It is an enforceable agreement made between the owner of the trade-mark or trade name and the distributors—whether wholesale or retail—of commodities bearing this brand. Moreover, under these statutes, price maintenance is permissive. All trade-mark owners need not participate in this system; only those who so desire.

Since "fair trade" is a creature of statute, it is essential that a manufacturer or distributor resorting to it comply fully with the statutory requirements. Although the laws of the various States differ in the phraseology used, as a general rule there are two basic prerequisites to be met before a manufacturer is eligible to enter into a "fair trade" agreement. First of all, the product must be identified by a trade-mark, brand, or name. When the identity of either the manufacturer or his preparation does not appear, no protection is afforded under any "fair trade" law. This becomes apparent when we note that one of the definitions of "fair trade" is that it comprises a system of protection of trade-marks, brands, and commercial names which permits the resale of merchandise, so branded, at standardized and uniform prices fixed by the manufacturer.

The second requirement is that the article must be in free and open competition with products of the same general class produced or distributed by others. Through this phrase shines the legislative safeguard in enacting these statutes. Theirs is not the purpose of permitting monopolistic price-fixing; on the contrary, competitive prices in the same category of goods are viewed as a brake on the greed of any individual manufacturer.

It should be recognized that a strict interpretation of this provision would have the effect of sharply restricting the application of "fair trade" agreements, particularly in the case of patented and secret drug formulas. Several court decisions, however, are symptomatic of a more liberal construction. Thus, in South Dakota, the Supreme Court has accorded the protection of the "fair trade" statute to a proprietary "patent medicine." California's Superior Court has also ruled that a patented nylon tooth-brush may be "fair-traded," pointing out that "brushes of other materials and produced by several manufacturers are

in fair and open competition with plaintiff's products." In the *Eli Lilly* case, North Carolina's highest court held that a drug manufactured and sold exclusively under a patent was a proper subject of "fair trade" contracts. In Maryland, moreover, a copyrighted book has been ruled to be amenable to price protection under that State's "fair trade" law.

These decisions show a liberal attitude on the part of the different State courts in determining when an article is "in free and open competition with commodities of the same general class." They seem inclined to give free rein to what appears to be the primary legislative intent of these statutes: the protection of the good-will of the producer as symbolized by his trade-mark.

This liberality of interpretation, however, is by no means universal. The Department of Justice and the Federal Trade Commission, in particular, have exerted considerable efforts to narrow the scope of "fair trade" operation. Illustrative is an order of the Federal Trade Commission issued against the Eastman Kodak Company, denying the right of "fair trade" to "Kodachrome" film and film sold in magazines on the ground that these articles are not in "free and open competition" with other film. The Commission's order was appealed and has been upheld by the Circuit Courts of Appeals for the Second Circuit. It is interesting to note, however, that several Federal district courts in another circuit have decided differently in connection with these same commodities.

In support of the attitude of the State court decisions mentioned as to what constitute "commodities of the same general class," weight should be given to the logic of John Stuart Mill who, it will be remembered, pointed out:

> As soon as we employ a name to connote attributes, the things, be they more or fewer, which happen to possess those attributes, are constituted *ipso facto* a class.

In this sense, a *general* class would consist of all those things which possess *general* attributes. Generically, definitions do not concern themselves with such minor distinctions as may differentiate one man from another, animal from animal, patented

improvements from the general art, copyrighted books from the field of literature, or a secret process from the article to which the process is applied.

The above analysis appears to have motivated the decisions of the State courts we have cited. Any other interpretation, of course, defeats the major purpose of the "fair trade" laws. For it would mean that every new concept would remove the commodity affected from the protection of these statutes; no copyrighted book, no secret process, no trade-marked article of distinctive characteristics, and no patented device could gain the advantage of this legislation.

ESTABLISHING "FAIR TRADE" PRICES

The mechanics of establishing "fair trade" prices in those States in which the practice is permissible are relatively simple. The first step, obviously, is for the manufacturer to determine the lowest price his product should bring in order to enable him to produce an article of good competitive value and at the same time make it possible for re-sellers to obtain a fair and reasonable profit. One must be mindful that "fair trading" is not a device to foist an exorbitant price upon the ultimate consumer. Rather it is a judicious effort to fix a price fair to all concerned. Abuse of this privilege may well result in a concerted attack by organized consumers against the entire system.

It is as a friend and advocate of "fair trade" that these remarks are offered. It has long been recognized that the advertised list price of many proprietary drugs are out of proportion to their manufacturing and wholesale costs. Indeed, this wide margin has served as the incentive for much "price-cutting" in the past. With the protection now afforded by "fair trade," the manufacturer has a much sounder motive in fixing a retail price of reasonable dimensions than one allowing exorbitant profits.

It should be borne in mind, moreover, that "fair trade" prices, once established, are not frozen for all times. As economic and production conditions vary the manufacturer may at any time adjust the prices set by agreement. Notice of these price changes,

of course, must be sent to all outlets with whom the manufacturer deals.

Once the resale price is fixed, it is implemented by a price contract made between the manufacturer and one or more resellers in each State having a "fair trade" statute. Except in the State of Utah, the price does not have to be registered or reported to any State or Federal agency. Nor is it necessary to have *every* re-seller execute the "fair trade" contract before he comes under the operation of the statutes. Once the manufacturer has, in good faith, entered into such an agreement with one or more wholesalers or retailers of the product in a particular State, all that is essential to bind other dealers is to place them on notice of the manufacturer's newly established "fair trade" policy. Cooperation in promulgating the "fair trade" prices may be obtained from the various State associations of retail druggists. For example, the New York State Pharmaceutical Association has issued a loose-leaf binder to hold the "fair trade" price lists of manufacturers that it regularly distributes. Furthermore, assistance in enforcing these agreements is frequently rendered by these associations.

THE "FAIR TRADE" CONTRACT

Once the two basic prerequisites have been met, the manufacturer is eligible to execute "fair trade" contracts regarding his product. A contract of this nature may, as we have already pointed out, be made with either wholesalers or retailers, or both, in the forty-five States in which they are legally sanctioned —and probably in Vermont as well. In this last-named State, although no statute exists which expressly permits resale price maintenance agreements, none condemns their execution. Since it is likely that they are allowed under the common law of the State, agreements of this kind are evidently permissible. It may also be noted that the District of Columbia does not at present sanction "fair trade" contracts.

In a brief presentation such as this, it is manifestly impossible to suggest how all "fair trade" contracts should be drawn. Each

manufacturer has his own particular marketing problems which will find recognition in the final provisions of his form of agreement. Nonetheless, if the maximum benefits of the statutes are to be secured, there are a number of basic clauses which must be inserted in every contract of this nature.

It is perhaps needless to point out that every agreement should set forth that the product to be "fair-traded" carries the trade-mark, brand, or name of the producer. Nor should it omit the declaration that the article is in fair, free, and open competition with commodities of the same general class produced or distributed by others. And, of course, the agreement should state the minimum, or established, price at which the product is to be sold.

Although it is not an essential provision, it is advisable that the contract reserve the right to the manufacturer to change the price so fixed by giving notice of the new price to the wholesaler or retailer, as the case may be. Similarly, an option should be granted to the manufacturer to add other items of his branded merchandise to his "fair trade" system on appropriate notice.

Many contracts, moreover, extend to the manufacturer the privilege of repurchasing "fair-traded" merchandise from his vendee, at cost to the purchaser, should the sale of the product be discontinued. Under such a provision, the buyer is usually required to give the manufacturer notice in writing of his intention to "close out" the goods, affording the latter an opportunity to buy them back, or not, as he decides.

All in all, the instrument itself need not be a complicated affair; indeed, it should and can be the very essence of simplicity. However, it is of the utmost importance to observe the following precautions in all contracts of this nature: (1) Their operation should be confined specifically to States in which "fair trade" is sanctioned by statute; (2) The minimum or established price should be clearly and definitively set forth in the agreement. Thus, a price which is merely "suggested" cannot support a valid contract. A typical form of "fair trade" agreement, suitable for use in the case of a drug product, reads as follows:

MANUFACTURER-WHOLESALER CONTRACT

AGREEMENT, made in the city of ..... State of ..... by and between ..... (hereinafter called the Manufacturer), and ..... (hereinafter called the Wholesaler);

WHEREAS, the Manufacturer is the producer or the distributor of various Commodities and the Wholesaler is engaged in the sale of such Commodities at wholesale in various states which have enacted fair trade acts, so-called and the Manufacturer and the Wholesaler desire to avail themselves of the provisions of such fair trade acts and of the fair trade acts of such other states as shall enact such statutes;

NOW, THEREFORE, in consideration of the premises, and the mutual benefits and obligations accruing to and assumed by the parties hereto from and by the execution and delivery of this agreement, the parties hereto agree as follows:

1. The word "Commodities" as used in this agreement is hereby defined to mean commodities which bear, or the label or container of which bears, the trade-mark, brand or name of the Manufacturer and which are in free, fair and open competition with commodities of the same general class produced or distributed by others.

The word "Products" as used in this agreement is hereby defined to mean the Commodities which are specified in Schedule A hereto attached as such schedule shall from time to time be constituted.

The word "state" as used in this agreement shall be construed so as to include in its meaning, as the context requires or permits, "territory," "the District of Columbia" and each dependency and insular possession of the United States of America in which the Sherman Anti-Trust Act, so-called, shall at the time have force and effect, and the word "states" shall be construed accordingly.

2. The Wholesaler will not (except as specifically permitted by statute), directly or indirectly advertise, offer for sale, or sell any of the Products to any buyer in any state in which at the time of such sale a fair trade act shall be in effect at less than the minimum wholesale selling price at that time stipulated therefor in such state by the Manufacturer.

3. The minimum wholesale selling prices stipulated by the Manufacturer for the Products in various states are those now or hereafter designated in Schedule A plus, in each sale, the amount of all sales and excise taxes applicable to such sale.

The Manufacturer, at any time and from time to time, by written

notice given to the Wholesaler as hereinafter provided, may (a) eliminate one or more Products from Schedule A; (b) add one or more Products to Schedule A and stipulate minimum wholesale selling prices therefor; and/or (c) change the minimum wholesale selling price of any one or more of the Products.

Each elimination from and each addition to Schedule A and each change in any minimum wholesale selling price, including each such change made pursuant to article 4 of this agreement, shall be effective at the opening of business on the date specified in the notice thereof, and such notice shall be mailed so that, in the ordinary course of the mails, it will be received by the Wholesaler before the date so specified.

4. In the event that, pursuant to any agreement similar to this one, the Manufacturer shall stipulate a minimum wholesale selling price for any of the Products in any given state which shall be different from the minimum wholesale selling price at the time stipulated for such Products in such state under this agreement, the Manufacturer will give prompt written notice of such fact to the Wholesaler and such different minimum wholesale selling price shall be effective under this agreement as provided in article 3 hereof.

5. (a) The offering or giving of any article of value in connection with the sale by the Wholesaler of any of the Products; or (b) the offering or making of any concession of any kind whatsoever (whether by the giving of coupons, trading stamps, or otherwise), in connection with any such sale, or (c) the sale or offering for sale of any of the Products by the Wholesaler in combination with any other merchandise shall, unless specifically authorized by the Manufacturer, constitute a breach by the Wholesaler of article 2 of this agreement.

6. The Manufacturer in good faith will employ all appropriate legal means, which in the circumstances shall be reasonable, to prevent, and to enforce the discontinuance of, any violation of said minimum wholesale selling price stipulations, whether the person so violating or threatening such violation is or is not a party to a fair trade contract with the Manufacturer covering the Products involved in such violation or threatened violation.

7. In addition to any other legal remedy, the parties hereto may have the remedy of injunction to prevent or to enforce the discontinuance of any violation of this agreement.

8. This agreement may be terminated by either party hereto on ten days' written notice to the other, but such termination by the Wholesaler shall not affect the rights or obligations of either of the

parties hereto under any applicable fair trade act, whether now or hereafter enacted, or by reason of any contract made pursuant to any such act.

9. Any notice given under any of the provisions of this agreement shall be well and sufficiently given by delivering the same personally to the party hereto to whom it shall be addressed or by mailing the same in a sealed postpaid envelope to such party at its address given below.

10. This agreement shall apply to sales of the Products, or any of them, only at such times as agreements of the character of this agreement shall be lawful as applied to intrastate transactions, under any statute, law or public policy now or hereafter in effect in any State, Territory, the District of Columbia or any dependency or insular possession of the United States of America in which the Sherman Anti-Trust Act, so-called, shall at the time have force and effect, in which such sale is to be made, or to which the Products in question are to be transported for sale.

11. This agreement shall become effective on the ..... day of ..... 194....

By .....
Manufacturer

.....
Street *City* *State*

.....
Wholesaler

.....
Street *City* *State*

Although the "fair trade" statutes do not impose the requirement that any definite number of contracts be entered into in a particular State before protection is accorded the manufacturer, nevertheless, it is good practice to make several agreements with vendees in each State in which it is sought to conduct business under such auspices. Once such contracts are made, other resellers are required to observe the prices so fixed merely by notice to them that the manufacturer is operating under "fair trade," advising them of the prices established in the contracts. No particular form of notice is specified by the law. However, one that has been used in connection with the contract reads:

FORM OF LETTER TO ALL WHOLESALE DISTRIBUTORS TO ACCOMPANY MANUFACTURER-WHOLESALER CONTRACT

TO OUR SELECTED WHOLESALE DISTRIBUTORS

Gentlemen:
We are enclosing herewith Manufacturer-Wholesaler Contract forms, which when properly executed will establish minimum wholesale selling prices for our products in all States wherein fair trade laws have been enacted.

We ask a duly authorized official of your company to sign both of these and return them to us, whereupon we will affix our signature and return one copy to you. In the event that you do not make any sales in States which have enacted fair trade laws, then, of course, you need not sign our contracts. We request all of our distributors who make wholesale sales of our products in states which have not enacted fair trade laws to observe the minimum wholesale selling prices stipulated in our contract.

It is our intention to restrict our distribution in states having fair trade laws to wholesalers who will sign our Manufacturer-Wholesaler Contract, and in States which do not have fair trade laws, to those who may voluntarily observe our suggested minimum wholesale selling prices.

Yours truly,

Nor is it essential that notice, to be binding, be given personally to the vendees. Ordinarily, the notice may be sent by registered mail, a return receipt being requested as a matter of record; this serves as acceptable evidence of its delivery.

ENFORCEMENT OF "FAIR TRADE" CONTRACTS

Once "fair trade" prices have been established, their enforcement is not altogether a difficult task. There is no need, for example, to maintain an espionage system to detect violators. Flagrant price-cutting will, it is obvious, soon be reported to the manufacturer by competitive dealers. These violations can usually be corrected by a letter, calling attention to the breach. A recurrence of the matter may, of course, call for more serious measures.

In the ordinary case, "fair trade" prices may be enforced by injunction. The aggrieved party—usually the manufacturer—is empowered to apply to a court of equity to restrain the price-cutter from continuing to sell below the price established by the "fair trade" contract. In addition, monetary damages are frequently recoverable by the injured party. These possibilities serve as a powerful deterrent to violations.

Moreover, stringent penalties are available against dealers continuing to under-price the article after the issuance of an injunctive order prohibiting such practices. Since this action violates the terms of a court order, punishment for contempt of court may follow. These proceedings, if successful, result in a fine or imprisonment. As we have intimated, however, resort to court action is seldom necessary.

At this point it may be observed that the manufacturer placing his product on the market under "fair trade" is neither compelled nor required to play the role of a watchdog. In other words, there is no obligation on his part to see to it that *each* violator of the contract is brought into court.

It is equally true, however, that when the manufacturer does decide to enlist the aid of the courts to enjoin an act of price-cutting, he must be in a position to prove that he has not "estopped" himself, by his own acts, from obtaining the relief he seeks. For example, he cannot, on the one hand, disregard widespread violations of the established price, or, on the other, proceed against one dealer only who may have offended. On the contrary, he is called upon to show that he has, and is, making an honest effort to prevent all price-cutting on the part of all violators whose practices have come to his attention.

To put this equitable requirement in another way, the manufacturer is not permitted to pick and choose among a group of retailers who have cut the established price, acting arbitrarily in enforcing his contract rights. To allow him to select certain violators to proceed against, leaving others free and unhampered to enjoy the results of their illegal practices not only runs counter to the tenets of a court of equity but constitutes conduct which invalidates the effectiveness of the price maintenance

agreements. In short, "fair trade" imposes a distinct obligation on the manufacturer to enforce the provisions of his contracts in an equitable fashion at the risk of losing its benefits and advantages if he does not do so.

"FAIR TRADE" AND THE ANTI-TRUST LAWS

The subject of price maintenance cannot be concluded without reference to the anti-trust laws on the Federal statute books. Indeed, the anti-trust division of the United States Department of Justice has displayed an uncommonly active interest in certain aspects of "fair trade" in the drug industry. Its views are of considerable importance in many respects and should have our attention.

As a general rule and policy, the Department of Justice condemns, with no uncertainty, any practice that serves to foster mutual restraints of competition among manufacturers, wholesalers, or retailers. Specifically, it maintains a watchful eye on *group* activities in the distribution of drug products. Thus, it has charged some groups of wholesale druggists with combining, through the medium of a trade association, to force manufacturers to give them profit margins satisfactory to themselves. Moreover, the Department has drawn a sharp line of demarcation between the acts of a manufacturer, at his option and acting alone, in fixing prices *vertically* through the wholesaler and the retailer to the consumer, and *horizontal* price-fixing agreements between manufacturers, between wholesalers, or between retailers.

To put this prohibition in other terms, the individual manufacturer may agree with his jobbers and dealers on scheduled resale prices at his own election. But should his actions be dictated to him by groups of wholesalers or retailers, possessing no proprietary interest in the trade-mark sought to be protected from price-baiting, the procedure is tantamount to a restraint of competition and hence in violation of the law.

It follows, consequently, that the organized drug dealer—whether operating at the wholesale or retail level of distribution

—should avoid group activities based on coercion, threats, duress, boycott, or intimidation whose objectives are to force the manufacturer into "fair trade" or the enlargement of his discounts. Generally speaking, difficulties in this regard will be avoided if three aspects of the "fair trade" legislation are borne in mind.

In the first place, it should be reiterated that the authority under the "fair trade" laws is coextensive with the precise language of the statutes themselves. No attempt should be made to utilize the legislative phraseology to accomplish a purpose beyond the scope and objective of these Acts. Secondly, "fair trade" should be recognized, and maintained, as a *voluntary* choice on the part of the manufacturer; his decision in this respect should not be coerced in any way. Finally, it should be emphasized that the law in regard to restraints of trade is exactly what it has always been, except as it has been modified to the extent permitted by the "fair trade" statutes. This, as we have stated, bars organized group activities directed toward price fixing and maintenance.

The antagonism of the Department of Justice against price maintenance appears to be dictated by more than legal considerations, it must be reported. However, too much weight need not be given to arguments springing from the personal views of these attorneys. As a matter of fact, the purely economic and social ramifications and aspects of "fair trade" are, generally speaking, no proper concern of the members of the Department. Nor should it be overlooked that the public policy of the United States, which, in the final analysis, is vested in the Congress, has been affirmed by that deliberative body as favoring voluntary "fair trade" agreements. The Department of Justice does not function as a policy-making agency; its task is confined to the enforcement of the Federal statutes.

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Index