New Drug Information Requirements*

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The subject of this paper is one with which I have been concerned for the past 13 years. Although this is a relatively short time, it covers half the period during which the Government has played a role in testing and introduction of new drugs.

Biological scientists, representing many specialized disciplines, are well acquainted with the scientific method and the interpretation of its results. They can and do apply strict self-discipline in fulfilling its precepts. Whether the scope of the work be narrow or broad, they speak with authority within its confines. When one transgresses the confines of actual experimental observations, however, he immediately recognizes the severe limitations of the laboratory investigations and properly proceeds to qualify his statements and opinions in terms of the data and experience developed. I suggest that the opportunity for such qualification is indeed a scientific luxury. It is a luxury which the administrator in Government can rarely enjoy.

Our Federal Food, Drug, and Cosmetic Act establishes certain provisions of law, and the administrator must abide by them. But by definition almost, I believe it may be said fairly that all biological data are incomplete as distinguished from inadequate data. There always remain variables which are unknown in any biological system. At any one time a given bio-system or series of bio-systems may inexplicably fail to respond as predicted or may respond in an adverse fashion. At best, then, we are dealing with bio-statistics in which probability must play a major role. In investigational work, as scientists, we are respectful of these tenets.

Based on the above defined incomplete biological data and recognizing all of the vagaries and variables of biological systems, the Government administrator has the tremendous responsibility of making a "yes" or "no" decision, a task often complicated by conflicting data and controversial opinions. Yet the law requires a definite decision and properly so if any semblance of order is to be beneficially maintained.

Let us turn our attention to see how this finds expression in the field of medicinal chemistry. Despite the disease-abating strides, and perhaps to some extent because of them, in the last two decades we now are faced with medical and pharmacological problems of a complexity which was not heretofore contemplated. The rapid scientific advances of the past two decades have had their effect in the pharmaceutical industry, resulting in the greatest development of new drugs ever experienced in any like period of recorded medical history. Technological applications of new scientific discoveries have placed increased responsibilities on scientists and technologists in industry and in Government to maintain the safety and effectiveness of drugs. The development of so many new drugs has placed a tremendous burden on the prescribing physician not only in keeping pace with the names, but in evaluating potent new agents which are on one hand capable of providing treatment for his patients where often none was previously available but also capable of causing a variety of side effects and occasionally a serious hazard. The increasing sophistication of the public in all phases of science, and particularly in the medical field, has attracted interest in drugs and the drug industry. There are few families indeed at any level of our society who have not in the recent past had a personal experience with one or another of these new medicines.

It is probably unnecessary to tell you that the development of a new drug in this day is a complex and extensive procedure. Possible sources of drugs are numerous. They may have natural origins such as extracts of animal tissues or of plants. Partially purified extracts may be developed as marketable drugs without isolation of active principals, or pure principals may first be isolated and marketed in this form. In the latter case chemical structure may be identified and established by synthesis. A further possible step is variation of this structure in an attempt to develop more efficacious and safer compounds or compounds which differ qualitatively in action. As examples of such developments we have but to think of hormones, plant alkaloids, and antibiotics. Reports in chemical and pharmacological journals are common in which are described the synthesis and testing of a series of derivatives of a compound known to have a certain pharmacological action. From such a series one or two compounds, on the basis of results obtained on initial screening, may be chosen for further examination and development.

The new drugs of the past twenty years for the most part are tremendously potent and hazardous, and are also effective when properly and skillfully used. In the days when drug products were relatively simple, standard methods of analysis set forth in the "U. S. Pharmacopeia" and the "National Formulary" sufficed for much of the work that we were called upon to do. Only a limited amount of animal assay and animal pharmacological study was required. Very much the contrary is true now that the com-

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position and the nature of the drugs are tremendously more complicated, and their potency and effects are significantly more involved.

We in the Food and Drug Administration, in carrying out our responsibility of evaluating the safety and effectiveness of new drugs, do not have as much a role in charting the course of new drug development as we do in trying to maintain a safe passage once the course has been laid. However, since the course of the future is often in large measure determined by the experience of the past and the exigencies of the present, it is appropriate for us at this time to review the FDA's present requirements with respect to new drug information in its approach to processing, reviewing, and evaluating sponsors statements ("Notices of Claimed Investigational Exemption for a New Drug") and new drug applications.

The basic prohibition, under the Federal Food, Drug, and Cosmetic Act, is the interstate shipment of adulterated or misbranded foods, drugs, or cosmetics. This prohibition of course applies to newly developed products as well as to old ones. It thus becomes necessary for the introducer to be certain that his products are properly controlled, conform uniformly to their label declaration, and carry proper directions for use and warnings against misuse. But there are additional requirements established with respect to new drugs. The term "new drug" means any drug which is not generally recognized as safe and effective by experts qualified by scientific training and experience to evaluate the safety and effectiveness of a drug when used under the conditions prescribed, recommended, or suggested in its labeling, or which is recognized as safe and effective as a result of investigations but has not otherwise been used for a material time or to a material extent.

The law lists among the prohibited acts, the introduction or delivery for introduction in interstate commerce of a new drug for which a new drug application is not approved. To become "approved," the application must include adequate data to show that the drug is safe and effective when used under the conditions set forth in its labeling. The Act requires a new drug application to contain: (1) full reports of investigations which have been made to show whether or not the drug is safe and effective; (2) a full list of the components of the drug; (3) the quantitative composition of the drug; (4) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of the drug; (5) required samples; (6) proposed labeling.

The significant purpose for the processing of new drug applications is contained in section 505(d) of the Act which establishes the grounds for refusing a new drug application. Essentially, the Act permits refusal of an application if it fails to contain adequate tests by all methods reasonably applicable, showing the drug to be safe; if the methods and controls are inadequate to assure the drug's integrity; if the labeling is false or misleading in any particular; if there is a lack of substantial evidence the drug will have the effect it purports or is represented to have under the conditions prescribed, recommended, or suggested in the proposed labeling. "Substantial evidence" of effectiveness means adequate and well-controlled investigations, including clinical studies, on which it can reasonably and responsibly be concluded that the drug will have the effects claimed. The kind of information required to be submitted in a new drug application is outlined under section 130.4(c) of the New Drug Regulations. In this section is found Form FD-356, the new drug application form.

Although the law prohibits interstate distribution of a new drug without an approved application, it does allow an exemption for shipping it solely for investigational use to experts qualified by scientific training and experience to issue regulations in this connection [505(i)]. The regulation requires that the label of an investigational drug bear the statement that it is limited to investigational use only. Prior to the distribution of the drug for testing in man, the sponsor of the investigation must submit to the Food and Drug Administration certain specified information as part of a "Notice of Claimed Investigational Exemption for a New Drug" (Form 1571). This includes:

(1) The name, dosage form, components, quantitative composition, and the chemical structure, if known, of the new drug substance.

(2) A description of the source and preparation of any new drug substances and the methods, facilities, and controls used for the manufacturing, processing, and packing of the new drug to establish and maintain appropriate standards of identity, strength, quality, and purity as needed for safety and to give significance to the clinical investigations made with the drug.

(3) Adequate information on preclinical testing to show that it is reasonably safe to initiate the proposed clinical studies.

(4) The labeling or other information to be furnished to investigators.

(5) The name and a summary of the training and experience of each investigator or expert.

(6) An outline of the planned investigations, which may be submitted by phases. Phases I and II cover the clinical pharmacology with administration of the drug in a closely controlled scientific environment to a limited number of patients and under professional supervision which assures a large measure of safety. Phase III covers the clinical trial in which the drug is used with a larger group of patients by different physicians following substantially the same investigational procedures.

(7) If the drug is sold, a full explanation of why sale is necessary.

Further, each investigator involved in clinical pharmacology (Form 1572) or clinical trials (Form 1573) is required to submit the following information to the sponsor of the investigation:

(1) A statement of his education, experience, and the facilities he will employ in the investigation.

(2) An outline of the plan for his investigation.

(3) Statements showing he understands the conditions governing the use of investigational drugs, including the maintenance of records, the submission of reports to the sponsor, and making his records available for Government inspection.

It should be noted that when the sponsor files with the Food and Drug Administration the notice of claimed investigational exemption for a new drug, he and the investigators are free to proceed without prior FDA approval. However, the Commissioner may terminate the exemption if he cannot conclude from the information and data submitted that it is safe to continue it or if the conditions of the investigation are not met. Their regulations also provide that:

(1) The sponsor is required to inform all investigators and FDA of findings suggesting any hazard in use of the drug and to discon-

tinue the investigation and recall outstanding stocks of the drug if the investigations adduce facts showing there is substantial doubt they may be continued safely.

(2) The sponsor is required to submit reports of the progress of the investigations at least once a year.

(3) The drug may not be supplied to investigators who repeatedly or deliberately fail to maintain or make available required records or reports.

(4) The investigation may not be unduly prolonged and the drug may not be commercially distributed or test marketed until an application is approved.

(5) Neither the sponsor nor any person acting on his behalf may disseminate any promotional material representing a drug to be safe or useful for the purposes under investigation.

The intent both of the regulations and of the law is to ensure, among other things, that the pharmaceutical manufacturer who wishes to have his product tested on man will conduct adequate preliminary studies to justify clinical testing and will make the results of these tests fully available to the expert investigator and to the Government before the drug is administered to man. The manufacturer will have to develop a scientifically sound program for the clinical tests he proposes. He will have to see to it that the new drug is turned over to qualified investigators who will test it on patients under their personal supervision or under the supervision of qualified investigators responsible to them.

A definition of who is an "expert qualified by scientific training and experience to investigate the safety of drugs" is not contained in the law or the New Drug Regulations. We believe that at least in the early phases of clinical investigation of a novel drug it refers to physicians who have experience in drug investigation and are specialists in the field applicable to the specific drug. Furthermore, they should have adequate facilities for investigation with respect to patients, clinical laboratory services, and time to give attention to such studies. This usually does not apply to the busy general practitioner. Clearly, a clinical investigator should be qualified, should maintain and make available required records and reports, and should use sound scientific judgment in testing a new drug.

With this background let us proceed to a consideration of some new drug information requirements in the handling of "Notices of Claimed Investigational Exemption for a New Drug" and new drug applications. Many of you are concerned with development of data and information which are eventually included in "Notices" and applications. I cannot cover all situations and do not have the knowledge to do so in detail, since specific requirements arise with specific drugs. I will attempt, however, to impart at least a general view of the requirements with respect to new drug animal studies, clinical studies, quality control studies, and records and reports.

It is not possible to design a single protocol of the studies that are necessary and sufficient to establish the safety and effectiveness of new drugs in general. The nature and extent of the investigations reasonably applicable are related to the nature of the article under investigation and its intended conditions of use. The Food and Drug Administration scientists cannot reasonably make an advance commitment that a specified group of studies will be sufficient to establish the safety and effectiveness of a given article, but will furnish comment on proposed plans of study before or during the course of investigations. It is frequently desirable in the course of such investigations to modify the plan of study on the basis of preliminary results obtained.

As part of the "Notice," adequate information on preclinical testing is necessary to show that it is reasonably safe to initiate the proposed clinical studies. Although the results of animal studies have limited applications to the ultimate therapeutic use, they are necessary before even cautious use on human subjects. Animal studies yield certain types of information rarely obtainable in the clinic, at least with any degree of precision, such as relationship of effective to acute toxic or lethal doses. Administration over an appreciable part of the life span of smaller rodents and for several months in larger animals at different dosage levels extends this information. Supplemented with gross and histologic studies of the tissues, information is gained on the types of toxicity resulting from overdosage.

In many instances we are dealing with a desired demonstration of safety for a small amount of a chemical which may be consumed by man for a long time. Therefore chronic toxicity studies may be required. However, before such studies are started, other data, such as acute and subacute studies, are necessary.

Consideration must also be given to special requirements for toxicity studies on newborn and immature animals which may be applicable to drugs used in pediatrics and on pregnant animals to detect possible adverse effects on the fetus. The present policy of FDA is to require fertility studies and a screening test in pregnant animals before a drug is used in any women of childbearing age. The minimum reproduction study consists of one or two test groups and one control group of 20 male and 20 female rats each, followed through two litters. (Details of the test may be obtained from the Division of Toxicological Evaluation, Food and Drug Administration, Washington, D. C. 20204.) This procedure may be expected to detect drugs which affect spermatogenesis, fertilization, or implantation, cause teratogenetic effects, or otherwise adversely affect the development of the fetus or the welfare of the newborn. It is realized that negative results in tests of this type do not necessarily indicate safety of the drug during pregnancy. Only experience will determine the applicability or productive value of tests which may be devised.

To date there has been no adequate study correlating the results of drug effects in animals with those obtained from later clinical tests on human beings. However, a booklet, "Appraisal of the Safety of Chemicals in Foods, Drug, and Cosmetics," prepared by the staff of the Division of Pharmacology, Food and Drug Administration, and published in 1959 by the Association of Food and Drug Officials of the United States, contains useful information with respect to views of the Food and Drug Administration concerning safety studies. Preclinical studies provide data which are useful guides to the first trials in man but do not allow a precise prediction of the effects in man. So testing in humans must be carried out. The clinical pharmacologist must learn whether the results obtained on animals can be applied to man. Is the drug effective? Benzyl penicillin proved to be in mice but not in man. A barbiturate which looked very promising in the laboratory was discarded after two cautious trials in the human revealed tremors induced by it.

It is difficult to predict how much clinical investigation will answer the questions of safety and effectiveness of a new drug. It is impossible to state simply how many patients must be studied. To a large extent the quality of the study means more than purely volume. The most meaningful information is derived from a well-performed clinical evaluation reporting detailed information on each individual case, such as age, sex, conditions treated, dosage, frequency, and duration of administration of the drug; results of clinical and laboratory examinations made; and a full statement of any adverse effects and therapeutic results observed. Since investigators, clinical facilities, and patient material will vary, one can hardly expect to achieve all of the needed information on a new drug from one or even two clinical studies. It is difficult at best to get an accurate picture of the clinical behavior of a drug and, recognizing that some investigators are enthusiastic about any new drug while others are hypercritical, it is obvious that a variety of studies from different clinical centers is needed for a fair evaluation. While some clinical investigations should be this detailed, complete with laboratory study, this does not mean that in addition helpful information is not derived from broader usage; in fact, this may help approximate the use of a drug as it will occur once it is marketed. As an example, we need only recall the large number of well-planned investigations undertaken with the synthetic hypoglycemic agents, tolbutamide and carbutamide. Tolbutamide has been a most useful drug, but it was only after some 8,000 well-documented cases with carbutamide that the investigations caused five deaths and the sponsor abandoned the drug.

Careful planning of the total investigation and of the individual studies are important to obtain decisive answers to all essential questions. The nature and extent of the required studies naturally depend on the drug and the purpose for which it is used. Results obtained in the course of such studies may necessitate investigations not originally conceived or may suggest emphasis on a particular aspect of the planned investigation. This is by no means a rare experience. As an example, we may consider briefly the isomers, dextro- and levo-methorphan. The racemate is an antitussive and analgesic agent. While clinical trials of the merits of dextro-methorphan as an antitussive were in progress, it was demonstrated in experimental animals that levo-methorphan accounts for the analgesic activity of the racemate and was strongly addicting. It was then demonstrated that dextro-methorphan is devoid of addiction liability. A program of clinical studies was then undertaken to demonstrate that dextro-methorphan was a safe antitussive agent while levo-methorphan and the racemate were strongly addicting analgesics.

It may not be generally appreciated that the regulations make a distinction between the type of information that must be provided to the Food and Drug Administration for the clinical pharmacology studies referred to as Phase I and Phase II, and the clinical trial, referred to as Phase III. In a Phase I study, possibly only one or two subjects may be involved. Initially small doses of the drug in question may be given, different routes of administration explored, and the subject followed closely with the appropriate pharmacologic studies. For this purpose it would not be necessary that exhaustive animal toxicities be done. For example, LD_{50} determinations and short-term subacute studies might suffice. In Phase II, studies would be extended to include the initial therapeutic trials on a limited number of patients and may require additional animal studies beyond those considered adequate for Phase I. Considerable leeway during Phase I and Phase II would be permitted in regard to the plan of investigation and such details as the route of administration and the physical form in which the drug is administered.

Phase III covers the clinical trial in which the drug is used with a larger group of patients by different physicians following substantially the same investigational procedures. Reasonable flexibility of a plan of investigation is provided for. Considerable more preliminary animal work would be done. The route of administration and the formulation would be more or less standardized.

At times it is wise to use a double-blind procedure so that the investigators and subjects will not be aware which is the drug and which is the placebo (or standard). In this connection, the Food, Drug, and Cosmetic Act requires that the labels of drugs moving in interstate commerce give certain information including the identification of the drug. A frequent suggestion is that, for double-blind studies, the firm be allowed to ship drug and placebo identified by code numbers only, the key to the latter being held by the firm. Such a procedure would, however, be in violation of the Food, Drug, and Cosmetic Act and would result in an unnecessary risk to the public. It is possible to aid double-blind studies, however, by the use of some sort of tear off or folded label and suitably coded containers. A nonparticipant of the study located at the site of the test, such as the pharmacist, could then remove and retain the tear-off portion of the labels and be responsible for keeping the key to the identity of the drug and placebo, furnishing it immediately to the physician should the necessity arise.

Experts in the field of pediatrics have pointed out infants and children may react to drugs differently from adults. Incompletely developed enzyme systems may result in impaired metabolism of drugs, or conversely, drugs may have greater effects on the incompletely developed enzymatic processes of the infant than on those of the adult. Safety of new drugs for infants and children must be shown by actual use in the various age groups.

We are aware that the manufacture of a new drug substance and the dosage form of an investigational drug is subject to change throughout the phases of clinical pharmacology and clinical trials. These changes are brought about, in part, by additional experience with the drug. Improved methods of manufacture and analysis invariably provide more comprehensive and better specifications. Controls and specifications for new drugs employed in the research stage may be different from those that will be used later in commercial production.

For a novel drug being studied in Phases I and II (clinical pharmacology), the "Notice" should contain the list of components and the proposed quantitative composition of the drug. It should identify the drug, as completely as possible, by chemical name and structural formula, if known. A description of the synthesis of any new drug substance should be given. In the absence of established specifications on a novel drug, evaluation would necessarily be based on the method of preparation. The "Notice" should disclose the methods by which the new

drug substance and finished dosage form are examined. We realize that methods employed in the early stages may be dropped later, but these methods should appear in the "Notice" when used. Later amendments may modify them. Specifications and methods to check them for exipients, diluents, etc., are required as part of the "Notice." Without information on all components, adequacy of the controls for the clinical study cannot be evaluated.

Since it is the intention of the sponsor to submit a new drug application after completion of Phase III studies, we expect, in the progression of investigational study, that the claims for exemption will be amended as appropriate to provide for more extensive methods, facilities, and controls used in manufacturing, processing, and packing of the new drug dosage form. We would expect that the sponsor would amend his "Notice" to provide for the establishment of his final dosage form, a firm listing of components, and the optimum formulation. Based on additional batches or scaled-up processes the synthesis may be modified. The raw material controls should closely resemble those that will be submitted later in a new drug application; this should also hold true for the final dosage form and the laboratory control methods.

The complex chemistry involved in the synthesis of new drugs and the information derived from newer techniques in analytical procedures indicate the need for a more detailed description of the synthesis and the specifications for the new drug substance and reliable tests for the drug as used in its investigational dosage form. These should be incorporated as part of the necessary information in a sponsor's statement. In some cases the statement in a "Notice" of the methods, facilities, and controls used for the manufacturing, processing, and packing of the drug, including the specifications and test methods for the new drug substance, is too vague and fragmentary for safety and to give significance to the clinical investigations. When the sponsor has specific information on the identity, strength, quality, and purity of the new drug, it should be submitted as part of the "Notice."

The new drug substance in a dosage form of a drug is probably not the sole determinant of its pharmacological effectiveness. The physiological response may be a function of the formulation of the dosage form as well as the new drug component. The rate at which the amount of the new drug component in the dosage form is physiologically available to the patient upon administration is an important consideration. We have encountered cases of varied clinical response between batches of the same pharmaceutical formulation. Additional study has indicated that differences in physical and chemical properties were caused, among other things, by differences in physical properties of the raw materials such as crystalline or amorphous form and particle size, conditions encountered during processing, and contact of the components in the dosage form resulting in complexing, binding, and adsorption. Therefore, early consideration of these factors during the investigational stages of the drug is necessary.

It also becomes important to establish the reproducibility of the dosage form of a drug from batch to batch if the clinical studies are not to be biased by an unknown variable. All batches must be uniform in identity, strength, and quality so that the patient receives what he is supposed to be getting. We have only to recall recent observations that there exists a considerable lack of homogeneity between tablets from the same batch to realize the importance of early work necessary to produce a uniform dosage form of the drug from batch to batch.

The investigational evidence that a drug is safe and effective in use does not necessarily establish that its deterioration products are safe and effective. Evidence establishing the safety and effectiveness of one or more batches of a new drug under investigation has no significance with respect to the safety of subsequent batches of the drug unless they can be shown to be the same as to identity, strength, quality, and purity as the batches studied. The requirement in the law and regulations that the methods, facilities, and controls employed are adequate to preserve the characteristics of a new drug necessitate study of the stability of the preparation during the investigational stage.

On occasion, drugs which have an approved new drug application are retested in double-blind studies for effectiveness. In such studies the formulation of one or more drugs under study may differ from that described in the new drug application in order to disguise the nature of the drug to resemble the placebo or another drug given in the study. In general, such changes should be described in a "Notice" or new drug application. It is well known that on occasion apparently minor modifications in the form of a drug may have a profound effect on the adsorption of the drug and therefore possibly on its safety and effectiveness. An example may serve to emphasize this point. Medroxyprogesterone acetate, a compound used investigationally in the treatment of cancer, was found in lesser quantity than the predicted amount in patients, although analysis of the tablets showed the correct amount of the drug to be present. Tests, however, showed poor absorption from the intestinal tract, the failure being due to the size of crystals used in compounding the tablets. Micropulverization of the drug resulted in a 15- to 17-fold increase in adsorption over that occurring with the batch showing relatively poor absorption.

The sponsor is required to monitor the progress of the investigations and currently evaluate the evidence relating to the safety and effectiveness of the drug as it is obtained from the investigators. Accurate progress reports of the investigations and significant findings, together with any significant changes in the informational material supplied to investigators, are required to be submitted to the Food and Drug Administration at reasonable intervals. In time the Food and Drug Administration will have received a large portion of a new drug application before the application itself if filed.

There has been significant change in the procedure for clearing a drug for commercial marketing once the clinical tests have been completed. The new drug application form (Form FD-356), mentioned earlier, furnishes a detailed outline of the requirements for the substance of an application, but we are limited by time to only a few comments concerning them. The form is available on request from FDA. The outline should be followed in assembling the data for the application. "Assembling" is used advisedly and applies to the case of the applicant who employs able pharmacologists, clinicians, pharmacists, chemists, bacteriologists, statisticians, possibly other scientists, and pro-

duction employees, and who has or contracts for the facilities essential to new drug research, development, manufacture, and control. Such an applicant will have developed substantially the same information as is required in a new drug application to satisfy himself of the safety, usefulness, integrity, and to ability of the new drug, and need only assemble it in the form of an application to be submitted to FDA. There will probably be little or no differences of opinion between the conclusion that are drawn by an able group of nongovernment scientists and by the FDA scientists who review an application developed on this basis. It should be noted that the new drug application form requires the submission of all information available to the applicant from any source which is pertinent to our evaluation of the safety and effectiveness of the drug. This as well as other information required in an application may be incorporated by reference to a previous submission, including information submitted under the investigational drug requirements.

The investigations of the safety of the drug should include adequate tests by all methods reasonably applicable. There must also be "substantial evidence" of the effectiveness of the drug. The reports should contain detailed data derived from animal and clinical studies in which the methods used and the results obtained are clearly set forth. The kind and the amount of information required will depend on several factors, such as the nature of the drug and its indication, and must be determined individually for each new drug. While the primary motive of the investigator may be the satisfaction of his own personal intellectual needs, in many instances, the investigation is undertaken for eventual submission of the results to the Food and Drug Administration as part of a Sponsor's "Notice" or a new drug application. It is therefore proper to view submission of the results as an integral part of conducting the investigation. If the interpretation must begin with the making of the observation, then the level to which interpretation must be carried depends upon the kind of submission being made. The investigator has a responsibility to digest the data, extract the findings that appear consequential, and to present these simply and clearly. Charts and graphs should be simple, clear, and adequately labeled.

We find the tabulation of data is very helpful in terms of summarizing such information as the number of patients, their ages, the duration of the treatment, the dosages used, control measures, the frequency and nature of adverse effects, the therapeutic results, method of assessment of subjects at the end of the trial, and the statistical technics employed. However, this would be in addition to the needs of our medical officers to have available for review and evaluation the investigator's case reports, the over-all conclusions of each investigator, the design of each individual investigator's experiments, and the criteria used for each investigator's evaluations. The reports from each individual investigator must be evaluated. We cannot delegate our responsibility of evaluating a new drug to a sponsor or to an applicant.

The discovery of a new drug becomes of practical significance only if it can be presented in a therapeutically active form. Therefore, formulation and quality control are important. Increasing attention has been given to these points over the course of years to assure that the product marketed meets adequate and uniform standards. With new chemical substances, there are new problems of compounding, identification of isomers, stability, and assay procedures which must be resolved before the drug is marketed. A break in the control procedures may be just as disastrous as the occurrence of unexpected toxicity.

Control methods applicable to the whole process must be worked out to maintain the strength, quality, and purity of each batch. This applies not only to the synthesis of an active ingredient but to the complete manufacture of the final product including packaging, labeling, and identification of each lot. It includes adequate identification of each component which is used and quantitative assays of active ingredients, sometimes at various stages of preparation as well as in the final product.

The application must include specimens of the proposed labeling, including a package insert for prescription drugs. Package inserts must consist of so-called full disclosure information which includes indications, effects, dosages, routes, methods, and frequency and duration of administration, and any relevant hazards, contraindications, side effects, and precautions under which practitioners licensed by law to administer the drug can use it safely and for the purposes for which it is intended.

After an application is approved it may be desirable to continue or initiate additional investigations with the drug. If such investigations are limited to use of the drug under conditions covered by the approved labeling as to indications, dosages, duration, etc., then no advance notification to the Food and Drug Administration is required. An example of such studies might be double-blind comparison of the approved dosage form of the new drug with a placebo and other active drugs to develop additional information with respect to effectiveness. Although no prior notification is required, the results of such studies should be reported to the Food and Drug Administration under the records and reports requirement for approved drugs and antibiotics. However, if the clinical investigations involve use of the drug for purposes or under conditions as to indications, dosage, or duration of use differing from the approved lableing, prior to starting clinical study, it should be covered by submission to the Food and Drug Administration of the claimed investigational exemption to the extent applicable. Data required by the sponsor's statement may be incorporated by reference to the approved new drug application. New drug information requirements for investigational antibiotic drugs are identical with those for other new drugs. The information submitted as part of an Antibiotic Form 5 or Form 6 is substantially the same information as is required in a new drug application.

All antibiotic drugs intended for human use are subject to premarketing testing by FDA to make certain that they meet standards designed to ensure their safety and effectiveness. However, the law authorizes FDA to establish exemptions so that a particular antibiotic drug, even though intended for use in humans, may be exempted from batch certification if the manufacturer can comply with the exempting regulations. Manufacturers of antibiotic drugs are required to notify us of any reports they receive of adverse reactions caused by their antibiotic drug.

New drugs used for laboratory study or animal tests only are exempted from the new drug provisions of the

Act, provided that they are labeled "not for human use." It is not necessary to submit a "Notice" for new drugs intended for *in vitro* use in the regular course of diagnosing or treating disease while they are being evaluated for usefulness since *in vitro* testing provides no hazard when used and compared with accepted methods. Before such preparations can be marketed, however, a new drug application for the article must be approved. It is necessary to submit adequate proof of effectiveness of the material since false claims of effectiveness might well deprive the patient of the correct treatment because of incorrect diagnosis. When an application for certification for a new antibiotic is submitted, it is customary for it to include information relative to diagnostic discs.

We received a number of inquiries with respect to the special status of radioactive new drugs for investigational use. Pending further consideration, these drugs are exempt from the investigational drug regulations if they are shipped in accordance with current regulations of the Atomic Energy Commission. There is no exemption from submission of new drug applications when the appropriate investigational information has been obtained.

The law coins a new phrase, the "established name," meaning the nonproprietary name by which a drug or drug substance must be designated on the label. The New Drug Regulations require that an application shall propose a nonproprietary name for use as the established name for a new drug substance if no established name exists. For substances that have been available for years, it will turn out in most instances that the "established name" is the name that is already familiar as the "common or usual name." The Secretary of HEW is authorized to designate the "established name" of any substance when this is desirable in the interest of usefulness and simplicity. As the number of drugs multiplies, the problem of finding simple nonproprietary names for them becomes more and more difficult. The USAN Council sponsored by the American Medical Association, the American Pharmaceutical Association, and the United States Pharmacopeia is dealing with the problem and has already developed a number of improved names. The Food and Drug Administration is cooperating with the Council. We hope that it will be possible for pharmacists, doctors, and the industry to handle this nomenclature problem almost entirely on a voluntary basis.

Persons holding approved new drug applications now are required to keep records of clinical experience [505(i)]. They will be required henceforth to make reports (130.13 and 130.35) as experience accumulates and advise us when they receive reports of adverse reactions, untoward reactions, contraindications, and the like, when associated with their new drugs and antibiotics. This will enable more prompt detection of the relatively infrequent cases in which a product, despite the most careful premarket testing, shows additional kinds of side effects when widely used. This will shorten the time lag between the occurrence of adverse reactions and the decision as to what corrective action is needed. These reports and records are intended to facilitate a decision as to whether the drug should be continued on the market without change, labeling changes should be required, or the product should be recalled.

This is illustrated by two drugs, isoniazid and iproniazid. Both were offered initially as anti-tubercular agents. Isonizaid has had a useful and uneventful history. However, iproniazid, after release for use as an anti-tubercular agent, showed promise in the treatment of depression and other mental conditions. Because of its effectiveness for alleviating mental depression, release of the drug for use by physicians in treating this condition resulted in widespread use. This increased use resulted in the appearance of an increased incidence of adverse effects and removal of the drug from the market.

The regulations require that the applicant promptly submit complete reports to FDA of information concerning any unexpected adverse effects associated with use of the drug, failure to exhibit its expected activity, mix-ups of the drug or its labeling with any other article, changes or deterioration in the drug, or failures to meet its specifications. Other types of information derived from clinical experience or investigations, and copies of any new labeling, including mailing pieces, and in the case of prescription drugs all advertising are required to be submitted to FDA at designated intervals. Deliberate or repeated failure to establish or maintain these records, or to make any required reports, or to permit copying of these records will constitute grounds for withdrawing approval of the new drug application to which the records apply. Products that were cleared under the safety provisions of the law, as it existed prior to October 10, 1962, had until October 10, 1964, as a grace period, but by that time, satisfactory evidence of effectiveness had to be available. If such evidence of efficacy is lacking, the law directs withdrawal of approval of the new drug application.

With respect to new drugs cleared on the basis of safety alone, new regulations were issued in final form on May 28, 1964, to require an industry-wide review of the safety and effectiveness of these drugs (130.35). By July 27, 1964, firms were required to report to FDA the approved new drugs which are still on the market and those which have been discontinued or never marketed. For those drugs discontinued, the reason for discontinuance had to be given. By September 25, 1964, firms are to report for each drug previously cleared through the new drug and antibiotic procedures and currently being marketed information with respect to safety and effectiveness of the drug under its present labeling and advertising. Applicants should propose changes in labeling and advertising as needed to assure the safety and effectiveness of drugs.

Following these initial reporting requirements, on the anniversary dates of approval of a drug, reports are required to be filled with FDA, giving any changes or additions to the information previously submitted. Applicants are required to report promptly any new information suggesting significant hazards such as mix-ups of the drug or its labeling with another drug, or unexpected side effects.

The volume of information submitted under the new drug requirements has taxed our capacity to document, store, and retrieve the available information so necessary in evaluating new drug submissions. For some time past we have established and maintained manual indexes to applications for new drugs and more recently to sponsor's submissions on investigational drugs. Such indexes have facilitated our access to some of the scientific and technical information in these files and will continue to be useful to us for answering queries on individual submissions. However, we recognize the contribution that can be made to

our program by the utilization of modern machine methods for information storage and retrieval. The paper in this symposium of Dr. Donald G. Levitt of FDA describes our accomplishments in this area, and the paper by Dr. Joseph F. Sadusk, Jr., our Medical Director, discusses the direction this program will take in the years ahead. These papers affirm our intention to develop this program in full cooperation with industry and the scientific community at large.

To meet the challenge to our society presented by developments in the field of new drugs requires the highest degree of individual, as well as collective effort, plus the cooperation and free communication on the part of all concerned with these problems—researcher, manufacturer, clinician, and government. This effort is demanded if we are to meet and conquer the new drug problems of today so that we can look forward to the even greater challenge of tomorrow, that of providing still other new drugs in the conquest of more and more of the serious diseases with which mankind is afflicted.

Drug Information Handling by the American Medical Association*

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The continuing education of the physician is one of the major programs by which the American Medical Association fulfills it prime mission, the promotion of the art and science of medicine and the betterment of the public health. That part of the educational program related to drugs, which is the responsibility of the Department of Drugs, is dedicated to providing the medical profession with timely, authoritative information on drugs and drug therapy. This mission is accomplished primarily by the publication in the *Journal of the American Medical Association* of statements on drugs, including their evaluation, adverse reactions, and nomenclature, and by the publication of the annual volume, "New and Nonofficial Drugs" (NND), which has now been replaced by a new book, "New Drugs."

Providing this service to the medical profession involves the handling of a considerable volume and variety of data on drugs. As the volume of these data has increased and as new needs have evolved, various procedures, including the use of mechanized systems, have been developed to facilitate the handling of this information. Inasmuch as the evolution and development of these procedures are continuing, this presentation should be considered as a progress report.

The procedures I shall discuss are the result of the efforts of several members of the Department of Drugs and I should like to give credit to those responsible for this work, namely, Dr. Joseph Jerome, Director of the Nomenclature Section, Dr. Norman De Nosaquo and Dr. Betty Jo Tricou, Director and Assistant Director, respectively, of the Adverse Reactions Section, and Dr. Philip Seitner, Assistant Director of the Literature Documentation Section. I also wish to acknowledge the assistance of Dr. Eugene Conrad and Mrs. Helene Weston in the preparation of this material.

The drug information accumulated in the files of the Department of Drugs is obtained from several sources. These consist primarily of (1) manufacturers, who submit data on new drugs, most of which are unpublished and thus are confidential and must be handled as such; (2) physicians or hospitals, who submit individual case reports of adverse reactions to drugs; and (3) the published literature. Some of the information originates within our Department, including the previously mentioned drug evaluations and nonproprietary names selected under the drug nomenclature program.

DRUG NOMENCLATURE PROGRAM

It is of the utmost importance that a potential drug not become known by an inappropriate name, or, even worse, by several names, since this makes it extremely difficult to correlate information from various sources and may create an almost hopeless problem of recognition for the practicing physician. To help solve this drug nomenclature problem, the AMA Council on Drugs has, for many years, operated a program in which it negotiated with manufacturers in the selection and adoption of appropriate nonproprietary (generic) names for new drugs.

This work is now carried on by the USAN Council, an organization composed of representatives of the AMA, USP, and NF, and staffed by the AMA. The USAN Council also collaborates with other national and international nomenclature agencies (*e.g.*, the World Health

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