Assuring the Safety of New Drugs

By RALPH G. SMITH, M.D.

Before the Federal Food, Drug, and Cosmetic Act was passed in 1938, new drugs could be introduced into interstate commerce without approval from any Federal agency or without consultation with any Federal agency. The distributor had no responsibility under Federal law for the safety of the new product. The marketing of drugs was subject to the provisions of the Food and Drugs Act of 1906, which dealt with adulteration and misbranding of drugs only after a drug was in the channels of distribution. The 1906 act did not deal directly with safety of drugs.

Although many of the drugs on the market in 1938 were satisfactory, further control was needed. With the advancement of pharmaceutical chemistry and the expansion of pharmacological research and screening procedures, particularly by industry, many new products were becoming available for drug use.

Most of the new products were synthetic compounds, but a few were purified active agents of old galenical drugs or derivatives of these agents. Many had specific pharmacological actions and were, accordingly, of interest from the therapeutic standpoint. In addition to useful therapeutic actions, however, some of the new products possessed potentialities for harmful effects. As with all new compounds, the nature of these effects and the margin of safety could be revealed only by appropriate study. Some control, additional to the judgment of the distributor, on the safety of the drug seemed to be in the public interest.

Accordingly, early drafts of the Federal Food, Drug, and Cosmetic Act included a provision that a drug was misbranded if it was unsafe for the use suggested in its labeling. By a coincidence, the well-known elixir of sulfanilamide disaster, which occurred while the bill was under consideration, convinced the Congress of the necessity for new drug provisions in the law. As a result of a new toxic vehicle or solvent in the sulfanilamide product, more than 100 deaths occurred within a very short time and before adequate warnings or removal of the drug from the market was possible.

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For Effective Application

The new drug section of the 1938 act prohibits the distribution in interstate commerce of a new drug until an application for it is effective. In order for the application to become effective, adequate evidence that the drug is safe when used according to the labeling furnished for it must be included in the application.

Applications for new drugs are received and reviewed by the New Drug Branch of the Division of Medicine, Food and Drug Administration. The review procedure calls for the assistance of other FDA technical divisions whenever indicated. The advice of original investigators or of other organizations or of experts outside the FDA may be sought in specific instances.

Since products which are not new drugs may still be introduced into interstate commerce without any legal formalities or even notification to the Food and Drug Administration, it is of obvious importance to decide whether a drug is new. In many instances the answer is apparent, but in certain cases some definite criterion is necessary for a decision.

A definition of a new drug is included in the 1938 act. In simple terms, a new drug is a drug which is not generally recognized, by experts qualified to evaluate the safety of drugs, as safe when used as directed in its labeling.

A yardstick is even more necessary to determine when a product ceases to have the status of a new drug. This point is also covered by definition in the act. Even though sufficient evidence may be available from investigative studies to show that a drug is safe for use, the drug continues to be considered as a new drug until it has been used to a material extent or for a material time under the conditions set forth in its labeling.

Continuance of a product in new drug status for a considerable period of time is significant in two ways. It means that the product must not only be indicated as safe by investigative studies but that it must stand the test of use under ordinary marketing conditions before it loses its new drug status and is freed from the restrictions which the status entails. It also means that any company wishing to market the drug must also obtain an effective new drug application even though the drug is already being distributed by the company holding the original effective application. Each additional application must include adequate evidence of the drug's safety.

The definition of a new drug is further interpreted by regulation. Food and drug regulations point out that a product may be considered new not only when it contains a new active ingredient but also when it includes a new excipient, coating, menstruum, carrier, or other component. A new combination of two or more old drugs or a change in the usual proportions of the ingredients in an old combination may cause the product to be considered a new drug. A new use, a new dosage schedule, or a new route of administration for a commonly recognized drug may also result in a new drug within the meaning of the definition.

In many instances little difficulty arises in deciding that a drug is new, but there are also numerous cases in which a decision can be reached only by careful consideration of all available facts. It must be determined whether the changes from recognized formulations or therapeutic procedures are sufficiently significant to raise a question of safety. An honest difference of opinion on the new drug status of a product occasionally arises between the manufacturer and the Food and Drug Administration. The difference may be resolved in either direction on consultation. Generally, however, the advice of the Food and Drug Administration is accepted although the Federal courts have the jurisdiction for deciding the matter.

Although the new drug section of the 1938 act is applicable to most new drugs, there are certain exemptions. Drugs which were distributed under essentially the same labeling prior to the effective date of the act (June 25, 1938) are excluded by definition even though they may not be generally recognized as safe. Vaccines, serums, toxins, antitoxins, and most blood products which are licensed under the Biologics Control Law enforced by the Public Health Service are exempt by regulation from the new drug procedure. Likewise, the five antibiotics, penicillin, streptomycin, aureomycin, chloramphenicol, and bacitracin, and derivatives of those antibiotics that are subject to certification by the Food and Drug Administration are exempt by law from the new drug section of the act.

For Safe Use of a Drug

The application should contain detailed reports of well-planned animal and clinical experiments. Data of the following type are important: the age, sex, and pathological condition of the subject; the dose of the drug used; the frequency and duration of administration; the results of clinical and laboratory examinations; the nature and incidence of adverse effects; and the therapeutic results.

Animal studies are usually considered necessary, particularly if the product contains an ingredient new to therapeutics. These studies demonstrate the nature of the pharmacological action of the drugs and also the type of effect

obtained by overdosage. Acute toxicity experiments yield a measure of the therapeutic index or safety margin. Subacute and chronic experiments with hematological examinations and histopathological studies give additional information in this connection. The clinical investigator may be expected to demand reports of such studies before he uses the drug on patients.

The type of investigation, both animal and clinical, should be determined by the proposed use of the drug with respect to method and duration of administration. A drug which is recommended for the treatment of chronic conditions such as arthritis, epilepsy, or parkinsonism will require animal toxicity studies of prolonged duration. Shorter toxicity studies would suffice for a drug such as a general anesthetic for use in a single administration. Likewise, a chemotherapeutic agent indicated for the treatment of an acute infection would be used only for a few days to a week or so and, consequently, would not require prolonged animal toxicity studies. Drugs for topical application, such as ointments, lotions, and topical anesthetics and antiseptics, should include studies on their potentiality to produce primary irritation and sensitization. Information on the degree of absorption from skin or mucous membranes may also be indicated when there is a question of systemic toxicity.

The application must also include a full list of the components which go into the preparation of the drug even if they do not appear in the final product. Their disclosure is of interest from the standpoint of their possible retention as impurities in the finished preparation. A complete quantitative statement of the composition of the drug is an obvious requirement. A description of the manufacturing methods and control procedures used in producing the new drug is required to provide the assurance that a preparation of definite specifications with respect to identity, strength, quality, and purity will be produced.

A sample of the drug may be required with the application, and completed market packages are required as they become available. Finally, copies of the proposed labeling must be furnished as part of the application since the safety of the drug must be evaluated on the basis of all the conditions under which it is recommended for use.

If the New Drug Branch is satisfied that the drug will be safe when used as proposed, the application is allowed to become effective, which means that permission is granted for distribution of the new drug in interstate commerce.

Marketing New Drugs

Since a drug retains its new drug status for some time after initial distribution, its use under actual marketing conditions is a further test of safety and usually a more severe test than the carefully supervised investigative studies. The general distribution of a drug which appears safe on the basis of investigative studies may be followed by reports of effects of an unexpected nature or of a higher incidence of side effects than occurred in preliminary use. Provision is made in the law to suspend an effective application under these conditions if the hazards of use are considered sufficiently serious. Applications have been suspended for this reason.

Much experience has been gained in the new drug section in the 18 years since the act was passed. As of January 31, 1956, applications for new drugs numbered 10,350, and 7,365 became effective. These figures include applications for veterinary medicaments, which account for approximately 18 percent of the applications submitted since July 1, 1954.

The 3,000 applications which did not become effective fall largely into three classes. Approximately 1,800 were incomplete. Some 500 were withdrawn, usually as a result of objections based on inadequate showing of safety. About 600 were not considered to be new drugs and, accordingly, did not require an effective application for marketing. Action is still pending on 100 applications.

The fact that 7,365 applications became effective does not mean that 7,365 new chemical compounds were introduced as therapeutic agents during the 18-year period.

Numerous firms may submit an application for the same drug. Separate applications may be submitted for various dosage forms of the same drug, such as oral preparations and injections. Or, the new drug in combination with a variety of old drugs may account for a num-

ber of applications. Although each application does not represent an entirely new chemical substance, it does represent a distinct effort by both the manufacturer and the Food and Drug Administration to assure that the consumer can use the product with safety.

The distributor, in addition to following the marketing experience of the new drug, frequently has occasion to change the provisions of his effective application. He may find it advisable to modify certain procedures in the manufacturing process, to make changes in the formulation, or to revise the labeling. A revision of the labeling may involve the inclusion of a warning statement or an additional indication for use of the drug, or it may provide for the product to be distributed under the label of another company.

Changes in the effective application may be made by submitting supplements, which are processed in the same manner as the original application. This procedure is in effect as long as the product remains a new drug. In view of the large number of effective applications on file, it is not surprising that the current number of supplementary applications and related correspondence exceeds 4,500 pieces a year.

It is probable that the safety of the new drug would be achieved in most instances without governmental control. The control procedure, however, is justified if it prevents even rare instances of injury by the distribution of drugs. The necessity of additional safeguards was felt in 1938 when the new drug section of the act was introduced. Since that time, the necessity has become still more imperative because of an even more rapid increase in the production of new products with a potentiality for drug use.

The Calculated Risk

The New Drug Branch has seen the quality of new drug applications improve during the past few years. A concept of adequate investigation of a new drug has been gradually developed by the Food and Drug Administration and by the pharmaceutical companies so that today new drugs are being investigated more thoroughly than ever before. Greater precautions are being taken by the adoption of stricter manufacturing control procedures to assure the marketing of products of specified potency and adequate purity. The new drug procedure has been instrumental in promoting these achievements.

Such safeguards should justify the physician's reliance on the declared potency and purity of the product he administers or prescribes and should strengthen the patient's trust in the safety of the remedy. In spite of this, certain facts should be kept in mind.

Safety is a relative term. Probably no two drugs are safe to the same degree. The wide variation in individual tolerance to drugs is recognized. Consequently, a wide margin between the effective dose and the toxic dose is essential if the drug is to be safe for the vast majority of potential consumers. The wide margin of safety is particularly necessary for remedies which are not life saving or which are used for conditions amenable to treatment by other methods or drugs that are relatively safe. In contrast, applications may be allowed to become effective for drugs that are known to be dangerous and for which the safety margin is critical. Granting of these applications is considered to be justified only when the drugs are useful as a life-saving or life-prolonging measure in conditions for which there is no safer efficacious remedy.

In the use of drugs which involve a calculated risk, their potentialities for harm are decreased if the physician recognizes that the potentialities exist and takes all possible precautions against adverse occurrences. Usually, care is taken in the labeling of a drug to outline optimal dosage ranges from the standpoint of both efficacy and safety and to include necessary warnings, precautions, and contraindications for its use. Careful labeling can serve its purpose only if it is read. With the introduction of so many new drugs, the physician can become familiar with only a few. Those which he selects, however, should be studied with particular care by taking advantage of all information imparted in the labeling instructions and in the published literature. The physician can contribute significantly to the safety of a new drug by reporting to the Food and Drug Administration, or by publication, any adverse reactions he observes in his practice.