NEW DRUGS AND THE COSMETIC CHEMIST

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I SINCERELY appreciate this opportunity to have the privilege of taking part in your program. Many of you are interested in new drug application procedures as they pertain to your field, both from the theoretical and practical standpoints. It will be my purpose to present in a general way the introduction of new drugs under the legal requirements of the Federal Food, Drug and Cosmetic Act. I hope that this discussion may be helpful.

Today, as scientific knowledge advances, we find increasing use of quantities of synthetic materials developed in research laboratories. They are being employed for a wide range of purposes, extending from improved product appearance to responsive biological activity. These have included bacteriostats, hormones, vitamins, antiperspirants and even substances claimed to change the texture of the skin.

It has become common practice to incorporate these materials in cosmetic-type preparations (dentifrices, deodorants, shampoos, skin creams, soaps, etc.) and to make therapeutic claims in the labeling for them. It is important, therefore, that the cosmetic chemist recognize that the incorporation of some components in his formulation or the use of therapeutic claims may cause an article regarded as a cosmetic to be a drug under the Federal Food, Drug and Cosmetic Act.

Whether or not a product falls within the category of a drug or a cosmetic depends not only upon its composition but also upon its labeling. A cosmetic, as defined in the Act, is an article (except soap) "intended to be rubbed, poured, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance." The definition of the term drug includes "articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man or other animals; and articles (other than food) intended to affect the structure or any function of the body of man or other animals." It is evident that labeling with therapeutic or prophylactic claims makes a cosmetic also a drug. For example,

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an article which is an antiperspirant is a drug because it affects a structure or function of the body relating to perspiration.

If the cosmetic-type article meets the definition of a new drug it is subject to the new drug procedure, in spite of the fact that no such requirement exists for a new cosmetic. The Federal Food, Drug and Cosmetic Act prohibits the shipment in interstate commerce of any new drug until an application is effective for it. This gives the distributor of a cosmetic, when it is a new drug, a responsibility to acquire an effective new drug application before he markets the article.

The purpose of this requirement of law is to insure that a new drug is adequately tested for safety before marketing. It is not sufficient for the distributor of a new drug to satisfy himself that it is safe, although this is an obvious first step. It is equally necessary under the law to satisfy the Food and Drug Administration that the new drug is safe.

The term "new drug," as defined in the Act, may be paraphrased as any drug whose composition is such that it is not generally recognized, by experts qualified by training and experience to evaluate safety of drugs, as safe for use as suggested in the labeling. The definition also includes a drug which has gained recognition of its safety as a result of studies but which has not otherwise been used for a material time or to a material extent under the conditions suggested in its labeling.

Under this definition safety may be recognized to the extent that one firm has an effective new drug application for a drug but, until it has been used to a material extent and for a material time, it is still a new drug, and other firms wishing to manufacture and distribute it must also obtain an effective new drug application.

Now that we have considered the why and when to submit a new drug application, we may explore more fully the purpose and substance of an application. The Act provides that an application shall contain (1) full reports of investigations that have been made to show whether the drug is safe for use; (2) a full list of the articles used as components of the drug; (3) a full statement of the 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 of the drug and its components; and (6) specimens of the proposed labeling for the drug.

The significant purpose for the processing of new drug applications is contained in section 505(d) of the Act, which provides that an application may be refused, after giving the applicant notice and opportunity for a hearing, if it is found (1) that the submitted reports of investigations do not include adequate tests by all methods reasonably applicable to show whether the drug is safe for use; or (2) the tests show that the drug is unsafe or fail to show that it is safe; or (3) the methods, facilities and con-

trols used for the manufacture, processing and packing of the drug are inadequate to preserve its identity, strength, quality and purity; or (4) there is insufficient information to determine whether the drug is safe for use under the conditions prescribed, recommended or suggested in the proposed labeling.

This authority to refuse an application also gives the Food and Drug Administration the responsibility to refuse any application until it has been adequately demonstrated that the drug is safe according to the criteria outlined above.

Based upon our experience with cosmetic firms entering the new drug field, we believe that many pitfalls encountered are those which can be attributed to lack of background with respect to new drug application requirements. Therefore a few of the more common obstacles to obtaining an effective new drug application should be covered.

Let us consider more specifically the contents of an application for a new drug. A new drug application form is available on request from the Food and Drug Administration. It furnishes a detailed outline which should be followed in assembling the data for the application, which must be submitted in duplicate.

The investigations of the safety of the drug should include adequate tests by all methods reasonably applicable. 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. This usually means pharmacologic studies in animals and subsequent clinical investigations. The kind and the amount of information required will depend on several factors, such as the nature of the drug and its indications, and must be determined individually for each new drug.

Cosmetic-type drugs may be employed daily or several times daily and during the greater portion of the individual's lifetime, that is, by the young, by the old and even by individuals in varying conditions of health. Although the risk of adverse effects is justified to seek the benefits of a life-saving drug, no significant risks should be tolerated from the administration of a product for essentially cosmetic purposes.

A dogmatic statement cannot be made of the requirements with respect to animal toxicity studies since such will vary with the drug and the nature of its use. If the intended use includes prolonged or continuous administration, then chronic experiments of from six months to a year or more are probably indicated. A useful guide in this connection is a booklet, "Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics," prepared by the staff of our Division of Pharmacology and published in 1959 by the Association of Food and Drug Officials of the United States. Of particular interest in connection with cosmetic-type preparations intended for external application is the chapter on "Dermal Toxicity."

Perhaps it is appropriate to make a few points in connection with clinical studies. Before undertaking the investigation of a new drug, prepare a program for it. Do not send the product to a number of investigators haphazardly and wait hopefully for what you can get. After six months or a year, you will examine the reports and begin to realize that most of the questions have not been answered. If you have not had experience in planning a study, get help. Consult a competent investigator. Food and Drug Administration scientists cannot reasonably make an advance commitment that a specified group of studies will be sufficient to establish the safety of a given article but will furnish comment on proposed plans of study before or during the course of investigations.

It is difficult to predict how much clinical investigation will answer the question of safety 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.

Choose investigators who are experts in the field appropriate for the drug A dermatologist is usually best trained to evaluate a preparation for application to the skin. For such products you might also include an allergist.

In a review of the clinical reports in applications we are often confronted with the necessity of making difficult decisions on their adequacy to demonstrate the safety of the product. In most instances this could be avoided by an understanding of the requirements. The deficiency may be one of inadequate reporting.

The second part of a new drug application requires a complete listing of the components of the drug. This includes not only the ingredients of the final product but all substances used in the synthesis or other method of preparation of any new drug substance. This may alert us to the possibility of contamination of the final product with such components. It may suggest the necessity of control procedures or specifications to insure their absence from the final product or their presence only in a limited concentration. Omissions in this connection result in additional correspondence and loss of time.

The full statement of the composition of the drug should offer no difficulty and is usually presented in a satisfactory manner. Occasionally

some detail is omitted, such as the quantitative declaration of a perfume, which you may consider of no importance but which the law requires. In addition to the formula for the dosage form, a representative batch formula is required. This serves as a check on the quantitative composition and should disclose overages which are used in the manufacturing procedure.

I will not attempt to discuss in detail all the requirements in Part Four of the new drug application, which deals with manufacturing procedures and controls. The new drug application form contains a detailed outline which is largely self-explanatory. Such procedures and controls are necessary in establishing the safety of a drug. They offer assurance that the product marketed will meet adequate and uniform standards. There are certain omissions and misunderstanding of our requirements which frequently occur. These merit some attention.

The chemistry involved in the synthesis of new drugs, the use of outside manufacturers and laboratories in the preparation of a drug dosage form, the checking of specifications of raw materials, information derived from assay procedures and product stability studies are necessary information in a new drug application. Omissions or inadequacies in these areas become the causes of delay in the handling of an application.

When the specifications and controls of a new drug are inadequate in themselves to determine its identity, strength, quality and purity, the methods used in synthesis, extraction, isolation and purification must be described in detail. The method of preparation may be one of the most important points in establishing the identity of the product. Less detail is usually required in a description of the synthesis of a compound of known structure which has clearly defined specifications.

Frequently the applicant does not perform all of the manufacturing procedures himself. Some operations may be done by another firm. When such is the case, a signed description of all procedures conducted by the second firm should be submitted to the Administration, either directly or through the applicant, to be included in the application. Similarly, descriptions of control procedures performed by a consulting laboratory for an applicant should be prepared and signed by that laboratory. We believe it is desirable for the applicant to check independently compliance of an article manufactured for him with its specifications. When this is the case, it should be described in the application.

Raw material control is an essential part of an over-all control program that is capable of maintaining the integrity of the product. In the Division of New Drugs we adopt the view that adequate control must include defined standards for each raw material used in a drug and the use of appropriate methods to insure compliance with the standards. Standards and methods adequate to determine the identity, strength, quality and purity of each raw material, and therefore its safety, are as important for any raw material, whether an active or inert substance.

The manufacturer is, of course, responsible for the integrity of his finished product. Despite this, some manufacturers wish to rely to a lesser or greater extent on their suppliers of the raw materials going into the finished product. Sometimes the supplier may take short cuts, too. We believe that adequate control includes some rechecking of the supplier's representations in the laboratory of the applicant or an independent laboratory of his choice. It is unwise to submit a new drug application that fails to show exactly who performs the laboratory tests insuring that a raw material meets the standards it professes. The Division of New Drugs may hold the application until it receives such information.

The description of raw material or other control elaborated in a new drug application is a representation that these controls will be used for every batch as long as the article is a new drug. If the applicant fails to employ the standards and methods he describes in his application, it is subject to the suspension provisions of the Act. We are concerned with the indications that some manufacturers fail to observe the commitments they made in an application. We recommend conscientious observance of the standards the manufacturer writes into his new drug application, for though they are initially self-imposed, after the new drug application becomes effective, they become a legal obligation.

Laboratory controls may be used during various stages of the manufacturing process and are certainly required for the finished product as well as for the raw materials. It is necessary that control over the finished product be exercised to establish that the active ingredient (or ingredients) will be present in the finished dosage form within a reasonable range of the amount declared in its labeling. This means that the new drug application should contain limits of acceptance based upon the assays of the active components. In many instances, however, the applicant fails to give the standards or limits of acceptance for each batch. Without such a commitment in the application the whole procedure is relatively meaningless from our standpoint.

The assays used to check the finished product should be described in the application in sufficient detail to permit duplication in our laboratories. The assays insofar as possible should be specific, or, if not specific for the component, an adequate identification test should be provided. The assays should be capable of yielding reasonably reproducible results, and data to this effect should be a part of the application.

Of course, specifications other than control of the active component in the finished product should be established. These will depend upon the type product involved.

In connection with assays and Part Five of a new drug application, the New Drug Regulations require that specific samples be submitted with a new drug application. These regulations require, as part of each new

drug application, samples of the dosage forms the applicant proposes to market representative of the drug employed in clinical studies, of the drug proposed for initial marketing, and of commercial scale production, together with samples of the new drug substances used in producing the batches of the drug represented by the foregoing samples, and such reference standards and blanks as may be required to perform the assay procedures described in the application.

The new drug sample regulations were designed for the purpose of checking the adequacy of the proposed methods in a new drug application to determine whether or not these methods to be employed are adequate to preserve the identity, strength, quality, and purity of the article to be marketed, and to verify specifications, especially for new drug substances.

Our experience to date with the drug sample regulations has brought out some common faults which arise to cause difficulty in complying with these regulations. We have received insufficient and inadequately identified samples. In some instances, applicants fail to submit their results on the batches represented by their samples. As to the methods submitted by the applicant for the laboratory test procedures of the samples, many are not given in sufficient detail. We can evaluate the adequacy of proposed drug controls only when an applicant submits adequately described methods and unambiguous laboratory reports. We would recommend that you submit methods that can be employed routinely by our laboratories to assay your product without the necessity of having the blanks involved in a particular batch.

A demonstration of the stability of a proposed preparation should be submitted as a part of a new drug application. The potency of a drug is most important at the time it is consumed. This suggests that prolonged stability may be even more important for an over-the-counter drug that may be used intermittently over a long time until exhausted than in the case of a prescribed drug entirely consumed as directed during a short period of illness.

There are a number of significant factors affecting the stability that should be considered in designing studies of the shelf life of a formulation but which are not always given the full consideration that they deserve. For example, temperature, pH, particle size, moisture, air oxidation, diluents, preservatives, containers, closures, light and the presence of certain trace metals, are some of the important factors.

It is most important in this day of new and different containers and closures for packaging drugs that the samples for stability study be taken from material stored as it will be in the market package.

Once the stability of a formulation of a drug in a specific market container has been established, it does not follow that a change in formulation or

container, no matter how minor, will not change the stability of the preparation. Changes in the container, closure, excipients, flavor and manufacturing and processing operations may affect the stability adversely, requiring additional studies of stability. It should be emphasized that almost any changes in process or composition require evaluation as to their effect on the stability of the product.

In interpreting the results of stability studies many firms have found to their disadvantage that the carrying over of stability data from one formulation to another is not acceptable. In general, the results of any stability study are applicable only to the formulation under the test conditions imposed, such as temperature, diluents, container, moisture, pH, closures, etc., employed on a particular article.

The chemical assay methods on which stability studies are based should be sufficiently specific to differentiate between the unaltered drug and its possible degradation products. A method that does not differentiate the original product from the degradation products is of no value in reaching a conclusion that the preparation is stable.

Too often we are expected to evaluate the stability of a product on the basis of data derived from a single batch. In addition, we are continually being asked by members of firms about how long their firm should run—or be required to run—stability studies of a preparation for acceptance in a new drug application. They seem to ignore the fact that we must be as guided as they by what the data indicate.

A preparation may be stable, apparently, in the hands of one pharmaceutical firm under the conditions of his own manufacture. The preparation of the same composition in another's hands, using different raw materials, different equipment, different containers, and variation in technique, may not be stable. Frequently, we find that an applicant, when his formulation is the same as that of another firm, relies entirely on the other firm's stability studies. He finds to his disadvantage that studies of the stability of his formulation are an essential part of his own new drug application.

I do not propose to discuss in detail all the requirements in Part Six of the new drug application which deals with labeling. A drug must be safe for use as labeled, so that evaluation of labeling is another vital step in the consideration of the safety of a new drug. The information derived from the animal and clinical studies provides knowledge regarding the indications, dosage, contraindications, precautions and side effects of a new drug.

Generally the labeling of cosmetic-type drug preparations will be similar to the pattern of labeling employed on other drugs, with perhaps a few unique characteristics. If the drug is to be sold over-the-counter, that is, without prescription, the package should include among other things adequate directions for use in self-medication and adequate warnings. The

list of drug warning statements published in the Federal Register of March 25, 1960, which is available from the Food and Drug Administration on request, may be helpful. Generally a new drug application for an over-the-counter drug may not be made effective unless it bears the substance of the recommended warnings in that list, when applicable to the product.

If the preparation is a prescription drug, the labeling on or within the package should include full information for its professional use as well as the prescription legend. The label of a prescription drug should bear a quantitative statement of its composition.

It is not necessary to undertake the expense of preparing proposed labeling in final printed form for submission with a new drug application. Typewritten or other draft copies of labeling are acceptable for conditional consideration of an application. It may be noted in this connection that the preparation of a large supply of expensively labeled containers in advance of clearance of a new drug application may lead to a total loss of that investment. Unsatisfactory labeling will not be cleared on the grounds that there is a substantial investment in it.

Another area which may be of interest to you and which became a part of the New Drug Regulations last year deals with establishment inspections. These regulations explicitly recognize that the marketing of a new drug may be delayed or prevented until inspectors of this Administration have been furnished an adequate opportunity to verify the adequacy of manufacturing, processing and packing methods, facilities, and controls, and records pertaining to them. These regulations also recognize that in most cases an adequate inspection can be completed during the time other aspects of an application are undergoing study.

We strongly recommend that you inspect the general controls of the plant to assure that they are in accord with those set forth in an application. We believe that general controls by a firm are as important to the uniform production of a new drug as those described in the new drug application for that particular article. They are, in essence, inseparable.

When an applicant obtains an effective new drug application he can revise his application to reflect changes and improvements in his product. This can be done by supplementing his application. The applicant should submit full information regarding the proposed change to the Division of New Drugs for our review and appropriate action.

There is an important point I would like to emphasize in connection with supplements. Cosmetic and drug manufacturers as well as the Food and Drug Administration know that occasionally adverse effects are found in the course of extensive distribution of a product under marketing conditions, although they were not encountered during the more limited investigational use. Further, marketing experience may yield significant informa-

tion with respect to the incidence of adverse effects found but not accurately assessed as to incidence during the investigational period.

Over the years responsible manufacturers have promptly submitted such information to this Administration on a wholly voluntary basis. In some cases this had led to labeling changes with respect to conditions of use, such as dosage, indications, precautions, and the disclosure of adverse effects. In other cases it has been necessary to remove the drug from the market.

We think the prompt reporting of such adverse information with respect to a drug is essential. We are very much concerned with evidence that in some cases it is not being done. We have encountered from time to time information with respect to untoward reactions with new drugs in reports in the literature or through correspondence with physicians. We have followed up these leads only to learn in some cases that these reactions, and even additional cases, were known to the manufacturer but were never submitted as part of his new drug application. We view the failure to submit such information as a serious violation of the intent and the purpose of the entire new drug application procedure. If information going to the very essence of the safety question is not made available to users of the product through informative labeling or is not used to remove the drug from the market, the essential purpose for the existence of the new drug provision of the Act is completely defeated.

A supplement is not an entity in itself but only a part of the new drug application which it incorporates. The failure to disclose any vital information available to the applicant, such as an adverse reaction, an unstable lot, or difficulty with an assay, is indeed, in our opinion, sufficient grounds for an application to be suspended on the basis that it contains an untrue statement of a material fact.

I hope I have clarified the requirements in the field of new drugs by this brief description of our activities in handling new drug applications. Many of the areas discussed are open to a diversity of opinions. I would remind you that we welcome your opinions in this new drug area and recognize that an exchange of ideas is the healthiest atmosphere for all of us.

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