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MANUFACTURING AND CONTROLS SUBMISSIONS TO IND's AND NDA's FOR ORAL CONTROLLED RELEASE DRUG PRODUCTS

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Abstract. The regulatory responsibilities of the Food and Drug Administration, in regard to manufacturing and controls, for oral controlled release drug products are reviewed. The requirements for IND and NDA submissions are outlined, with emphasis on quality control and documentation. The importance of submitting adequate scientific and technical data on which a reviewing chemist can make a meaningful review is discussed. Submission of the data in a format that not only documents the scientific data but also presents it in a clear and cogent manner is discussed. The discussions will include manufacturing, packaging and stability documentation for both clinical supplies and the commercial product.

Seventy seven years ago the Congress of the United States passed the first federal law to provide protection to consumers

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from dangerous, adulterated and misbranded food and drug products. On June 30, 1906 President Theodore Roosevelt signed this legislation into law.

In 1938, the current Act, the Federal Food, Drug and Cosmetic Act, was enacted being sparked by the Elixir of Sulfanilamide tragedy. This act required, among other things, the preclearance of new drugs on the basis of safety.

The next great movement in drug regulation came on October 10, 1962, when the Kefauver-Harris Amendments were passed. For the first time drug manufacturers were required to prove to FDA the effectiveness as well as the safety of new drugs before marketing. These amendments also required the submission of a Notice of Claimed Investigational Exemption for a New Drug (IND).

Since we will be discussing controlled release drug products I would like to bring to your attention that in 1959 a regulation was finalized which dealt with controlled release products. This regulation (200.31) is titled "Timed release dosage forms". It states that any such dosage form that contains per dosage unit a quantity of active ingredient(s) which is not generally recognized as safe for adminstration as a single dose under the conditions suggested in its labeling, is regarded as a new drug. This regulation is still in our regulations and deals only with safety. Please note this regulation was published before the

enactment of the 1962 Drug Amendment which requires a showing of efficacy. Thus, we now consider new controlled-release products that enter the market for the first time, to be new drugs that need pre market clearance before marketing, even though the drug substance in a conventional dosage form is not considered a new drug.

When a sponsor, be it a pharmaceutical firm, individual or institution, submits an IND, he must wait 30 days before initiating such trials so as to permit a safety review to ensure that there are no undue risks to the subjects. Under certain extenuating circumstances the 30-day delay requirement may be waived by the FDA.

As you are aware the investigation progresses through three phases; Phase I, Clinical Pharmacology, which is the initial introduction of a drug in man, Phase II, Clinical investigation, which includes early small controlled clinical trials designed to demonstrate effectiveness and relative safety, and Phase III, Clinical Trials, which are the expanded controlled and uncontrolled trials. All drugs that are classified as "new drugs" do not necessarily have to go through all three phases.

As INDs are submitted to the Agency, the reviewing division will evaluate and monitor the information submitted. If deficiencies exist, the sponsor will be notified. If deficiencies and/or results are of such a nature as to present a serious safety

problem, the investigation will be limited or discontinued until the deficiencies are corrected; or the IND withdrawn/terminated. In contrast, in an NDA, when adequate data to demonstrate safety and effectiveness are not submitted, a not approvable letter is sent to the applicant.

The manufacturing and controls requirements of the IND are found in Parts 1 through 5 of Form FDA 1571.

In submitting manufacturing and controls data, they should be clear, well organized, cogent and fully documented so that the reviewing chemist can make a meaningful review within a reasonable period of time.

The amount and type of data submitted in each phase depends upon such factors as the uniqueness of the drug, type of dosage form, method of manufacture, stability, and duration of study. For example, if the new drug substance is a new molecular entity we would normally expect more detailed information on the synthesis and stability than a new drug substance that has been used for many years, with many publications, and an adequate public standard, such as in the USP.

Adequate stability data should be generated to assure that the dosage form(s) used in the studies has the identity, strength, quality, and purity that it purports to have at the time of use.

If placebos are used they should mimic the drug product not only in appearance but also in taste, odor, etc. at the time of manufacture and at the time of use.

As the studies of the investigational drug progress, and as the sponsor continues to gain experience, both in the clinic and the laboratory, the IND must be amended to include new protocols, progress reports, new and additional tests, and stability data, so that at the time the new drug application is submitted adequate data are available to fully assess the safety and effectiveness of the new drug under the conditions of its intended use. If the information submitted in an IND needs further clarification, additional data or indicates a problem, a letter will be sent requesting clarification, additional data, or expressing concern. We expect a response in a reasonable time. If the conditions are such, it may warrant a discontinuance of the studies or termination of the IND.

When the new drug application (NDA) is submitted it should contain full and adequate information in a format as designated in Form FDA 356H. The manufacturing and controls requirements are found in parts 5 through 9. The information should include adequate scientific and technical data which has been generated during the investigational stages. In preparing and collating submissions, it may be helpful to place yourself in the position of the reviewer at FDA. The reviewer evaluates the submissions

and makes comments and recommendations, basically, on the information presented in the NDA. If the information is complete, well analyzed and organized, including background information, the review will be expedited, which in turn speeds up the approval process. If there are voids, uncertainties and/or deficiencies, the applicant will be requested to clarify and/or submit additional information, thereby possibly delaying the final review or be a basis for a not approvable letter.

In reviewing new drug applications it must be understood that the reviewer has not been part of the research and development team at the pharmaceutical firm but is one who must evaluate the adequacy of the information on the basis of what has been submitted. He must determine that the drug product proposed for marketing is the same or similar to the one that has undergone clinical trials or, in certain cases, the drug product has been shown by bioequivalency studies to be "equivalent" to a drug product that has undergone clinical trials and/or has been legally marketed. The reviewer must be assured that the manufacturing and controls procedures are such that future batches of the drug product will be the same, within certain limits, as that approved in the NDA. These concerns involve synthetic organic chemistry, specifications, test methods, manufacturing technology, in-process and final release controls, packaging, and stability. In this presentation I will discuss some of the areas involved in the manufacturing and controls sections of the NDA.

The specifications and tests for the new drug substance must be adequate to assure its identity, strength, quality and purity. If the drug substance is recognized in an official compendium it should be so stated. Additional specifications and tests may be needed for the particular dosage form. For example, crystal size and crystal form may need to be strictly defined. Moisture content may also be critical. Similarly inactive ingredients may need to be controlled by additional specifications beyond that provided in a public standard.

In regard to the drug product, the quantitative composition of the dosage form should be stated in terms of quantities of all the active and inert ingredients per unit dose, e.g., per tablet, per gram, or per milliliter. It is also required that the batch formula should include the names and amounts of any components utilized in manufacture but do not appear in the finished product. In addition, any predetermined or calculated excesses of ingredients over label declarations should be designated as such and the percent excess clearly indicated. Proposed variations in quantities of ingredients should be reasonable and realistic.

The description of the manufacturing process for the final dosage form should be given in detail. The final dosage form is usually not a chemically pure substance entity, but must be a highly reproducible, stable composition with constant physical and chemical properties. Controlled release dosage forms usually present a greater challenge in this area.

The information to be submitted for these operations should be coherent and well organized in order to permit a meaningful review and verification. Each step should be clearly and precisely described and should include the amounts, the actual operating conditions and equipment to be used together with the controls utilized, appropriate details of the container treatment prior to use, method of sampling, labeling procedure and the types of labels to be used.

Chemical analysis of a dosage form is one of the parameters by which quality of formulation can be accurately measured. Therefore, the development of an efficient and sensitive method is most important. As in the case of a good formulation, the physico-chemical properties of a drug substance play an important part in the development of an acceptable method. The analytical methods(s) should provide:

a. unequivocal identification of the active ingredient(s) in the dosage form

b. specific quantitation of the active ingredient(s),

c. proof that excipients and degradation products, if formed, do not interfere in the assay of both the freshly prepared dosage form (s) and throughout the expiration dating period.

In order to ascertain whether the analytical method(s) meets the stated objectives, the information should include:

a. method of sampling

b. number of unit doses required per assay

c. preparation of sample

d. identification of the active ingredient(s)

e. specific analytical reaction

f. detailed method of quantitation, including graphs, spectra, and calculations

g. accuracy, precision, specificity and sensitivity data

h. number of assays recommended

The reviewing chemist, in addition to reviewing the data submitted in the application, has the responsibility of having the regulatory analytical methods validated in FDA laboratories. Instructions on the type of data needed with the samples are described under Part 9 in the NDA. It is important to submit raw data. This not only includes calculations but also pertinent chromatograms, spectra, graphs, etc.

In the current Form FDA 356H there is a requirement that samples be submitted with the NDA. More recently, we announced in the Federal Register of October 19, 1982, pertaining to the NDA rewrite, that samples need not be submitted at the time of submission of the the application. When the reviewer has finished the review of the submission and finds the information adequate to have the FDA laboratories validate the regulatory methods, the reviewer will contact the applicant and request that samples be sent to the particular laboratories that will do the validating along with copies of pertinent analytical sections of the NDA. Reserve samples will be sent to the National Center for Drugs and Biologics at the same time. This procedure is in effect now.

The product specifications reflect the quality of the intended product and the degree of precision with which it can be repeatedly produced. Rigid specification thus imply the confidence in the manufacturing process and associated testing methods. The specifications should be established on the experience gained in the investigational and developmental stages, on the analytical methods utilized and on the association or correlation with in-vivo data.

The elapsed time between the preparation of the drug product and its ultimate use depends on many factors. Thus, the most carefully produced formulation can be no better than the quality of the container in which it is held. Whether or not a drug is safe, contains the correct dose and is therapeutically effective

all depend to a significant extent upon the suitability of its packaging. The information on the packaging must be complete. Information on the composition, method of manufacture and controls must be included. If the container is glass and meets compendial standards it may be sufficient to state the type and the controls utilized.

To assure its safety and effectiveness, a pharmaceutical product must retain its identity, strength, quality, and purity throughout the expiration dating period. Assurance that the drug product in its container will be adequately stable for the stated expiration period must come from an accumulation of data on the drug. These data involve chemical, physical, microbiological, therapeutic and toxicological considerations. Information from initial and subsequent tests performed on drug substance(s), the various dosage forms, and containers provide the basic data upon which the stability profile is constructed.

Stability studies should be submitted in a manner that will include full details and make them conducive to easy review. They should be cumulative with all conditions, lot numbers, dates, methods, etc., clearly indicated.

Stability studies should be monitored by test methods which are capable of distinguishing the intact drug form its degradition products. The experimental evidence to support this capability,

as well as the accuracy and precision of the method(s) must be included in the application. Degradation products should be qualitatively and quantitatively identified and the mechanism(s) elucidated, if known.

When the final marketing container has been selected, it should be used in the stability studies exactly as proposed for marketing. For example, screw caps should have the same torque as that intended for the market package and if a liquid product is involved, containers should be utilized both in the upright position as well as on the side or upside down where the liquid is in contact with the closure.

Accelerated studies combined with basic stability information (including chemical kinetic data) on the new drug substance, dosage forms, and containers are useful and acceptable to support expiration dates.

In an internal study carried out on 92 not approvable letters during 1977-78, it was shown that the greatest number of deficiencies in the manufacturing and controls sections occured with analytical procedures. The second in number were in stability studies while the third highest involved containers and closures.

This study indicates that there is a need for improvement in the quality of submissions if we are to expedite the review and

approval process. For example, the majority of deficiencies in the analytical information was that the procedures were not clearly described or were described inadequately. A smaller number were deficient because the procedures were inadequate for their intended purpose. In order to assist the NDA applicants in this regard, FDA is drafting guidelines in the various manufacturing and controls areas so that there will be a better understanding of what is expected in INDs and NDAs.

The Food and Drug Administration's role in assuring drug quality is one that was established by Congress. Both the pharmaceutical industry and the Food and Drug Administration have their particular responsiblility of which we must be cognizant. We recognize that many of the great advances in the development of drugs, whether they be new molecular entities or new dosage forms, certainly would not have been possible without the research and development conducted or funded by the pharmaceutical industry. The ultimate goal of both the pharmaceutical industry and FDA is, of course, to have drugs of highest quality available to the American public of which you and I are members.

The great advances in controlled release dosage forms and the research that is going on is exciting and establishes a new era. Hopefully, in addition to new molecular entities, we can develop dosage forms, and delivery systems, that will help to cure and/or prevent illnesses without challenging the whole body structure by

targeting to specific regions utilizing smaller doses, fewer doses, and more uniform release to the body.

As you are aware older drugs that have had little use previously have been rejuvenated because of these newer dosage forms.

Let us expend every effort in our chosen profession to develop, produce and maintain the high quality of drugs. This tremendous effort can only be accomplished by the full effort of everyone of us.