CENTER FOR DRUG EVALUATION AND RESEARCH

Guidance for Industry

The FDA published Good Guidance Practices in February 1997. This guidance was developed and issued prior to that date.

Additional copies are available from:
Office of Training and Communications
Division of Communications Management
Drug Information Branch, HFD-210
5600 Fishers Lane
Rockville, MD 20857

(Tel) 301-827-4573
(Internet) http://www.fda.gov/cder/guidance/index.htm

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

August 4, 1993

Dear Sir or Madam:

The purpose of this letter from the Office of Generic Drugs (OGD) is to provide you with a variety of important information including details about labeling, scale-up, packaging, minor/major amendment criteria, and bioequivalence requirements.

1. ACCEPTABILITY OF DRAFT LABELING TO SUPPORT A TENTATIVE APPROVAL

Generally, OGD requires final printed labeling before it approves an Abbreviated New Drug Application (ANDA) or Abbreviated Antibiotic Application (AADA). An applicant cannot market a tentatively approved product until a full approval is granted, which may occur days, months, or even years after tentative approval was granted. Between the time of tentative and final approval, a change in the insert labeling of the listed drug may occur. If that happens, the applicant must revise labeling, which can be a costly and burdensome effort, before full approval is awarded. Therefore, OGD will accept the labeling plan described below.

Final printed insert labeling is not required for tentative approval of an application if it is granted with more than 90 days remaining from the date when full approval can be considered. Final "printers proof" labeling, which should be generally correct in content, but may contain minor inaccuracies, and which shall reflect an accurate presentation of print size, prominence, readability, etc., will be acceptable. Approximately 90 days before full approval can be granted, the applicant will be expected to learn if the insert labeling remains accurate or requires revision. In either case, the applicant will be expected to provide final printed insert copy with an updated amendment for review before final approval is granted.

Final printed insert labeling will be required for tentative approval of the application if it is awarded within 90 days of the date when full approval can be considered.

Labeling pieces other than the professional insert must be "final printed" before tentative approval of the application is awarded, regardless of the expected time to full approval.

2. DIRECT COMMUNICATIONS FROM THE LABELING REVIEW STAFF TO APPLICANTS

For some time, the Office's Labeling Review Staff has corresponded directly with applicants on labeling deficiencies

and recommendations under certain circumstances. Such communications are generally conveyed either by a telephone call or letter, as appropriate. Examples of this communication include the following:

A. When labeling is part of a minor amendment, and OGD requests final printed copy or a revised labeling piece;

B. When all labeling deficiencies have been addressed and final printed labeling has been submitted, and OGD requests a revision because either there is some previously undetected incorrect information, or new labeling by the innovator makes the current generic labeling unacceptable; or

C. When labeling is part of a major amendment that is at the third review or later, and OGD requests the firm to submit a "draft" rather than final copy to revise some labeling piece. OGD is approving more applications after only two reviews. Therefore, effective the date of this letter, OGD will communicate this type of labeling request after the second review to decrease the likelihood that an application will have met all approval requirements except those associated with labeling.

The labeling telephone call or letter for the above examples will request a labeling-only amendment to be sent in response. This represents a change from the usual requirement that all deficiencies, including chemistry and labeling, be responded to in one amendment. OGD believes that the Labeling Review Staff will be able to review the new material during the same cycle as other Office reviews, thereby improving the efficiency of the approval process.

3. BATCH SCALE TERMINOLOGY IN POLICY AND PROCEDURE GUIDE 22-90

Based on comments received in OGD the following clarification is provided for words used for Batch Description, such as "intended," "desired," "full-scale," and "maximum" production batch sizes.

These terms all refer to the proposed maximum-size production batch that the applicant might manufacture, generally after approval of an application. Therefore, the applicant is required to provide a blank record for the proposed maximum-size production batch for each strength of the drug product. When such authorization to scale-up is sought by the applicant, Policy and Procedure Guide 22-90, section 4.A., should be used for determination of number of units that must be manufactured to meet the application requirements for the test batch (bioequivalence/ stability studies).

Thus, prior to approval of an application, the proposed maximum-size production batch determines the size of the test batch (at least 10% or 100,000 finished dosage-units, whichever is greater). After the approval of the application, Guide 22-90, section F, allows scale-up of the test batch to the authorized maximum-size production batch in the application. However, if scale-up BEYOND the "maximum-approved batch size" in the application is needed, the applicant must follow Guide 22-90, section G.

The above requirement to manufacture "10% or 100,000 units, whichever is greater" should be used consistently during communications with the Office rather than "scale-up factor of 10X" for the reason that the latter terminology is not necessarily valid. For example, if the applicant proposes to manufacture 500,000 units as a maximum-size production batch, the minimum test batch for an ANDA will be 100,000 and not 50,000 units. Conversely, the scale-up factor, to be determined from this test batch to coincide with the proposed maximum-size production batch, will be only 5X and not 10X when the application is approved. In this circumstance, the scale-up factor of 10X is not valid.

4. MINIMUM PACKAGING REQUIREMENTS FOR THE TEST BATCH (BIOEQUIVALENCE/STABILITY)

Under item 7 of the November 8, 1991, OGD letter to regulated industry, it was clearly stated that the bioequivalence or test batch should be packaged entirely if manufactured after January 1, 1992. However, because there have been some queries from applicants, the following additional clarification is provided for packaging Tablets and Capsules:

A. The test (bioequivalence/stability) batch must be completely packaged. Policy and Procedure Guide 22-90, Section 4.A., defines minimum batch size requirements, and Section 4.B. defines the conditions under which manufacturing (including packaging) must take place. The containers proposed for marketing must be used for packaging the test batch.

B. Any bulk packaging performed must be in addition to the minimum packaging quantity requirements described above.

C. The Office will request additional justification for those applications currently under review that describe partial packaging of the test batch manufactured after January 1, 1992. However, effective the date of this letter, the Office will issue a Refuse to File letter for an abbreviated application that fails to provide data supporting complete packaging of the test batch.

D. The Office will accept a "packaging protocol" for evaluation, in which less than the total test batch is packaged, provided that batch is for a full-scale production batch (e.g., more than one million units) to be used for bioequivalence/stability studies, if filed before actual manufacture of such a batch.

E. These considerations also apply to bioequivalence or test batches submitted in supplements.

5. PARENTERAL SCALE-UP REQUIREMENTS

Primary stability data must be generated for each ANDA and AADA parenteral drug product on at least one batch which has been packaged in the final container. The homogeneous bulk solution or powder shall be defined as the "exhibit bulk." The yield from the "exhibit bulk" must be at least ten percent of the proposed maximum-size commercial batch for which authorization is sought. All batches must be prepared under conditions which meet the applicable provisions of Policy and Procedure Guide 22-90, sections 4.B. to 4.F. The ability to package the solution (or powder) on a high speed filling line, while maintaining sterility, stopper integrity and content uniformity, is critical.

The entire "exhibit bulk" must be packaged in all cases on the intended production line/room. Within a single application, only similar multiple size containers, as described in Guide 20-90, may be used for the packaging of bulk solutions and powders. A minimum yield of ten percent of the "exhibit bulk" must be used for each container size. The finished dosage form yield will determine the production batch size and any scale up factors.

6. COMMON GRANULATIONS

Policy and Procedure Guide 22-90, Section 4.C., permits applicants to use one "batch" of the pre-compression mixture (common granulations) to manufacture 100,000 units of tablets or capsules for each strength of the drug product. However, here the word "batch" should be interpreted as an in-process material because, according to 21 CFR 210.3(b)(9), a pre-compression mixture is an "in-process material" and not a "batch," as it is produced for and used in the preparation of the drug product. Therefore, common granulations should not be confused with the batch size of the drug product.

Also, the applicants are requested to follow the examples cited below in using common granulations for manufacture of multiple-strength drug products:

A. If 1 mg, 2 mg, and 5 mg strength tablets having a total

weight of 50 mg, 100 mg, and 250 mg, respectively, are to be manufactured for bio/stability studies, 40 kg of the common granulations (5 kg, 10 kg, and 25 kg) will be needed to manufacture 100,000 tablets of each strength. The maximum-size production batch to be proposed for each strength of the drug product should be such that the common granulations produce no more than one million units of any strength while manufacturing either a single strength or a combination of multiple-strength products. If the maximum quantity used for production of the common granulations is 40 kg, it could be used to manufacture either the 1 mg, 2 mg, or 5 mg strength tablets alone because none of the batches would exceed one million tablets.

B. Similarly, if 400 kg of the common granulations is to be used, then a maximum of 50 kg, 100 kg, and 250 kg of the material can be used to manufacture the 1 mg, 2 mg, and 5 mg tablets respectively, as those quantities will give a theoretical yield of one million units in each case. The total 400 kg of granulation could not be used to manufacture only one strength tablet because the batches produced would be either 8 million, 4 million, or 1.6 million of the 1 mg, 2 mg, and 5 mg strength tablets, respectively.

The above examples follow Policy and Procedure Guide 22-90. However, applicants may propose protocols that deviate from the above example, if they submit them and receive comments on them before the test (bioequivalence/stability) batch is manufactured.

7. APPLICATION FORM 356h

Please list on the abbreviated application form 356h all Drug Master Files (DMF's) cited in the application. This information will ensure that all pertinent DMF's are provided.

8. APPLICATIONS THAT CONTAIN MICROBIOLOGICAL DATA

Policy and Procedure Guide 4-89 currently under revision outlines various review responsibilities of OGD staff microbiologists and review chemists. To facilitate processing applications that contain microbiological data, applicants are requested to clearly designate in the cover letter that the submission contains "Sterility Assurance" data.

9. MAJOR AND MINOR AMENDMENT CRITERIA FOR ABBREVIATED APPLICATIONS REFERENCING A DEFICIENT DRUG MASTER FILE

Policy and Procedure Guide 38-93 describes the criteria for the classification of major and minor amendments. In its

Appendix A, examples of major and minor chemistry deficiencies are provided. Item 3 of that Appendix states that failure to provide a letter of authorization to reference a Type II or III Drug Master File (DMF) cited in the application is a major deficiency. It will continue as a major deficiency if the applicant fails to submit appropriate letter(s) of authorization from the DMF holder(s).

However, effective the date of this letter, all chemistry, manufacturing, and controls deficiencies related to DMF's will be considered as minor deficiencies when determining the criteria for classification of the ANDA amendments. In the response, the applicant must include a statement from the DMF holder that all issues communicated to the DMF holder by the Agency have been addressed. Otherwise, the ANDA amendment will be considered incomplete, and OGD will issue a Not Approvable letter for that reason. If a minor ANDA amendment is reviewed and the DMF revision is found deficient, another Not Approvable letter will be issued requesting a minor amendment response, rather than the current practice of telephone notification. These changes do not affect the current procedures for review, documentation, or processing of the DMF's.

10. DISSOLUTION REQUIREMENTS FOR IMMEDIATE-RELEASE DRUG PRODUCTS

OGD's Division of Bioequivalence imposes dissolution testing requirements on most immediate-release drug products, except those in a solubilized dosage form and certain others. The general policy of the Division is that generic drug products should meet a scientifically sound dissolution standard when appropriate.

Drugs which have a USP XXII dissolution requirement should meet the USP requirement. In addition, dissolution test data comparing the test versus reference product are considered part of the bioequivalence requirement for many generic drug products. Therefore, applicants are required to conduct comparative dissolution testing using the official USP dissolution methods, release tolerances ("Q" values), and applicable USP dissolution acceptance tables. Applicants are also required to generate dissolution profiles of the test and reference products by sampling at 10 or 15 minute time intervals until the final test time is reached. This will allow a better comparison of the dissolution release characteristics of the test and reference products. Also, it will permit better correlation with the *in vivo* data, for those drugs for which an *in vivo* bioequivalence study requirement has been established.

In addition to requiring the firm to meet the USP requirement,

the agency, for scientific purposes, may require the firm to provide dissolution testing data using methods other than those in the USP, especially when an alternative method has previously been approved in the firm's abbreviated application.

For those drug products for which a USP dissolution requirement is unavailable, the Division of Bioequivalence will continue its policy of recommending appropriate dissolution testing requirements, based on sound regulatory and scientific considerations. As necessary, the Division will advise and work with firms to develop appropriate dissolution standards.

11. BIOEQUIVALENCE PROTOCOLS THAT HAVE BEEN PREVIOUSLY REVIEWED

When submitting an ANDA that includes a bioequivalence study, please include the protocol with comments that had been reviewed and commented upon by the bioequivalence reviewer, if such protocol had been previously submitted to the Division of Bioequivalence for comment and if such comments had been received. This version will serve as a reference source for the reviewer.

12. BIOEQUIVALENCE INVESTIGATIONAL NEW DRUG APPLICATIONS

On October 13, 1992, the Office issued Policy and Procedure Guide 36-92 regarding Bioequivalence Investigational New Drug Applications (Bio-IND's). The following information addresses questions frequently asked since the Guide issued:

A. A Bio-IND is not necessary for a comparative pharmacodynamic study unless it meets the requirements described in Guide 36-92.

B. The Office will not accept a Bio-IND unless it meets the requirements described in Guide 36-92.

C. Reporting requirements for Bio-IND's are described in 21 CFR sections 312.32, 312.33, and 320.31.

D. An applicant should withdraw the Bio-IND upon completion of the bioequivalence study and the submission of the ANDA.

E. A bioavailability/bioequivalence study conducted outside the United States must follow the provisions of Guide 36-92.

13. REVIEW BY INDUSTRY OF ITS INVENTORY

OGD restates the request it made in the November 8, 1991,

letter to industry, in which firms were encouraged to review their inventory of approved and unapproved applications. The review should be done two to four times a year. If there is no interest in continuing marketing of approved applications or in pursuing approval of unapproved applications, please withdraw the application. This action will reduce preparation time for the firm plus reviewer time and maintenance expense for OGD.

14. MAILING ADDRESS AND NEW TELEPHONE NUMBERS FOR THE OFFICE OF GENERIC DRUGS

A. The Office receives many calls from industry to obtain the address listed below.

(1) Submissions and other correspondence intended to be part of an abbreviated application, whether sent by the U. S. Mail, a courier service or by a parcel service should be addressed as follows:

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

(2) Correspondence **not** associated with an abbreviated application should have the above address, and include the name of the person to whom the correspondence is directed.

B. The Office has new telephone numbers. Simply replace the numbers 295-8xxx with 594-0xxx and proceed. For example, the number 295-8340 has been changed to 594-0340.

The Office of Generic Drugs appreciates your consideration of the issues raised in this letter. Your attention to these matters will assist us in our efforts to improve the generic drugs review and approval process.

Sincerely yours,

D. L. Sparn

Douglas L. Sparn
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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