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



NOV 8 1991

Food and Drug Administration
Rockville MD 20857

Dear Sir or Madam:

I am writing to you to request your cooperation in helping us improve the efficiency and effectiveness of the generic drug review program. The following commentaries reflect areas to which we intend to pay additional attention and ones in which your cooperation would be most helpful:

1. COMPLETENESS OF SUBMISSIONS

Carl Peck, M.D., Director of the Center for Drug Evaluation and Research, wrote a letter to the industry on June 1, 1990, indicating that the Office of Generic Drugs (OGD) would only accept complete applications for filing. The letter described several examples of data that would be required for an application to be considered complete. At about that time, OGD began to conduct a pre-filing screening review to determine whether submitted applications contained the required information. Applications that were grossly deficient on their face (i.e., that were missing complete sections of the required information) were rejected for filing. This policy benefits sponsors of generic drug applications in two ways: 1) by ensuring that scarce OGD resources are not wasted on applications that do not meet minimal acceptance standards; and 2) by notifying sponsors within a matter of days of certain basic deficiencies rather than after an application has waited for several months in the review queue.

We recently identified some additional deficiencies that, if identified and corrected during the pre-filing screening review process, could save subsequent review time.

Accordingly, please note that effective immediately, applications will not be accepted for filing if they contain any of the following deficiencies, in addition to those items identified in Dr. Peck's June 1, 1990, letter:

- a. Failure to provide an English translation for any portion of the application that is not in English;
- b. Failure to provide signed, dated letters of authorization, referencing specifically the particular ANDA and sponsor, from the holder of each Drug Master File for each source of bulk drug substance, and for each contract manufacturing

facility for which information is not included in the ANDA;

- c. Failure to provide a letter of authorization for a United States agent to act on behalf of a foreign ANDA or AADA sponsor if applicable;
- d. Failure to provide a Master Production Batch record for at least the largest size batch intended for production (note that under revised Policy and Procedure Guide 22-90, September 13, 1990, for solid oral dosage forms, approval cannot be given for more than a ten-fold scale-up from the batch used to conduct the bioequivalence test);
- e. Failure to provide an environmental assessment under 21 C.F.R. § 25.31 or a request pursuant to 21 C.F.R. § 25.23 which establishes that the application falls within the provisions for a categorical exclusion in 21 C.F.R. § 25.24 and is accompanied by a certification of compliance with Federal, state and local environmental laws;
- f. Failure to provide: 1) a list of all of the active and inactive ingredients used in the finished drug product; 2) for each ingredient, the proposed source or sources of the ingredient; and 3) for each source of each active and inactive ingredient, a Certificate of Analysis from the manufacturer of each ingredient;
- g. Failure to provide completed batch records for the batch or batches used in stability studies and bioequivalence tests and Certificates of Analysis (tests and specifications on the finished product) for each batch;
- h. Failure to provide a certification of compliance with Current Good Manufacturing Practices (CGMP) requirements.

2. IDENTIFICATION OF MINOR AMENDMENTS

Minor amendments to ANDA's/AADA's are the highest priority in our reviewers' work queues. However, frequently firms fail to identify such amendments when they submit them to our Office and thus the amendment is not expedited.

The Office of Generic Drugs now informs you in each Not Approvable letter whether the amendment required in response will be treated as major or minor. If we

inform you it will be considered a minor amendment, you should clearly include that information in your submission. We suggest that the words "MINOR AMENDMENT" appear in bold print in the header information of your cover letter.

3. EARLY NOTIFICATION OF INTENT TO WITHDRAW APPLICATIONS

We have experienced a number of instances in which firms have allowed ANDA's and AADA's to go through multiple Office reviews only to then withdraw them from the review process. While there may be economic or other reasons that necessitate such withdrawal actions, the reviews that have been done on them are essentially a waste of scarce reviewer resources. Consequently, the Office of Generic Drugs would appreciate as soon as possible your consideration of all applications currently pending in the Office to determine if any of them should be withdrawn. Conducting such an assessment on at least a quarterly basis is also encouraged.

4. IDENTIFICATION OF CORRECT MANUFACTURING SITE ADDRESSES

We occasionally find that the addresses listed in applications for one or more new drug substance or drug product manufacturing sites or testing facilities are incorrect. Incorrect addresses slow down preapproval inspections since the FDA field investigator must track down the correct location of the sites to be inspected. Please ensure you include specific and accurate addresses.

5. DMF REFERENCES

Many applications contain DMF references that far exceed the number that could be reasonably expected to be used in the manufacture of a product. Review of these DMF's is wasteful of Office resources and impedes the review process. Firms are encouraged to reference only those DMF's that represent material that is likely to be used in the manufacturing process. Similarly, if a DMF is referenced in the ANDA, it should be listed in the appropriate place on the Form FDA 356h.

6. SUPPLEMENTS

a. IDENTIFICATION OF IDENTICAL OR COMPARABLE SUPPLEMENTS

To the extent possible, when you submit a supplement, it would be helpful if you would indicate whether you intend to submit identical or comparable supplements

that affect multiple approved ANDA's/AADA's. Cross-referencing which applications are affected by the supplements is also needed.

When we have this information we will make every attempt to have a single reviewer complete the review of all of the related supplements. If we are not notified in the manner described above, the reviews may be done by different reviewers at different times.

b. SUPPLEMENTS FOR CHANGES PLACED INTO EFFECT AND TO CORRECT A PROBLEM

The Office continues to receive supplements for changes that have been placed into effect but that do not fall under any of the three conditions for changes that may be made before FDA approval (new specifications or tests, certain labeling changes, and different new drug substance manufacturing facilities) as delineated by 21 CFR § 314.70(c). In addition, the changes under the first condition must fall into the category of an improvement - an added test or specification. The Office believes that the implementation of new specifications and tests because a product has gone out of compliance does not meet the intent of § 314.70(c). The Office should be notified of the problem before a solution is implemented so that it may determine whether the proposed solution will solve the problem.

c. ANNUAL REPORT VERSUS SUPPLEMENT CHANGES

Many changes reported to the Office in annual reports are not among those permitted under 21 CFR § 314.70(d). Please be sure only those items that properly come under § 314.70(d) are included in annual reports. When appropriate, the Office has informed firms that the information provided in an annual report should be submitted as a supplement. The Office warns against placing any product into interstate commerce that is based on an unapproved change incorrectly placed in an annual report and will refer these instances to the Office of Compliance in CDER.

Sometimes changes which should be submitted in annual reports are submitted instead as supplements. Changes submitted in supplements that could be placed in annual reports overload already strained resources. An example of such changes are those updating tests and specifications to those in the current USP.

The Divisions of Chemistry in the Office of Generic Drugs recognize that clarity is sometimes lacking

regarding whether a change should be submitted in an annual report or filed as a supplement and encourage firms to contact the Divisions to obtain the necessary information.

d. CLARITY OF SUPPLEMENTS

Supplements containing revisions in manufacturing, controls and other changes should identify specific changes. Comparative information and data should be included when applicable.

7. COMPLETION OF TABLETING AND PACKAGING

Based on the opinion that it is wasteful, some generic pharmaceutical manufacturers do not fully tablet or encapsulate and package all material from the test or bioequivalence batch. The Office believes that a test batch should be fully representative of a production batch, which requires tableting the entire granulation and packaging the entire batch. Tableting only the initial portion of a granulation obscures evaluation of events that may occur in its latter part, e.g., powder fines segregation and tableting problems. Packaging only some of the tablets precludes selection of samples for the stability studies based on appropriate statistical methods. Furthermore, FDA field inspectors have commented that incomplete tableting or encapsulation and packaging makes it difficult to track reconciliation during inspections of test batch records. Based on these observations, effective January 1, 1992, all of a bioequivalence or test batch should be tableted or encapsulated and the resulting material should be packaged.

8. STABILITY

Some of the most frequently cited deficiencies in applications relate to stability testing of finished drug products. These deficiencies are due in part to the evolution of FDA's requirements for accelerated stability testing, to the lack of specificity in existing guidance on the temperature at which "controlled room temperature" studies are to be conducted, and to the failure of some applicants to provide all of the data necessary to support proposed expiration dating. In addition, applicants have failed to honor commitments made in applications regarding long-term stability studies and have extended expiration dates for their products on the basis of inadequate data. The following discussion attempts to clarify the

Office of Generic Drugs' position on these stability issues.

a. ACCELERATED STABILITY TESTING

In February 1987, the FDA' Center for Drugs and Biologics issued a *Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics*. This guideline is still the only available source of official agency policy regarding the conduct of stability studies to support the proposed tentative expiration dating period. As the Guideline states, an applicant may rely upon the Guideline in submitting documentation on stability or may follow a different approach. If a different approach is chosen, an applicant is advised to discuss the approach with the FDA in advance to prevent the use of resources to prepare a submission that may later be determined to be unacceptable.

The Guideline states that stress (accelerated) testing will be accepted for the grant of a tentative expiration dating period, provided adequate information concerning the stability of the drug substance has been submitted.¹ As the Guideline states, "The recommended stress conditions are:

- 40°C, or as appropriate for a particular drug product;
- 75 percent relative humidity (where appropriate)."²

Stability is to be analyzed initially and at 1, 2 and 3 months.

The 1987 Guideline replaced recommended stress conditions from a 1985 guidance issued to generic firms by the Division of Generic Drugs. The 1985 guidance recommended 37°C and 75% relative humidity. The FDA has, however, continued to accept data from studies conducted at 37°C but has informed firms that we will not do so indefinitely. Consequently, effective January 1, 1992, any new stability studies initiated should be conducted at 40°C unless a different approach has been discussed with the FDA in advance to prevent the conduct

¹ Guideline, p. 43.

² *Id.*

of studies that may later be determined to be unacceptable.

b. "CONTROLLED ROOM TEMPERATURE"

An applicant requesting a tentative expiration dating period based upon accelerated stability data must provide in its ANDA a protocol for the conduct of long-term stability studies using the first three commercial production lots of the product. The studies must be conducted on samples of the product contained in the market package and stored at the temperature stated on the label.³ The Guideline states, "The actual storage temperatures (numerical) used during stability studies should be specified."⁴

One of the most frequently encountered problems has been the conduct of long-term stability studies for products whose labels bear the phrase "store at controlled room temperature." The existing FDA Guideline does not specify the temperature at which "controlled room temperature" studies must be conducted. In the absence of a specific agency policy, applicants have referred to the United States Pharmacopeia which defines "controlled room temperature" as between 15° and 30°C⁵ and have submitted studies at different temperatures within this range.

The USP defines "controlled room temperature" not to specify the temperature at which stability tests are to be conducted but rather to explain to practitioners the conditions under which products are to be stored if the monograph or label specifies "controlled room temperature."⁶

FDA considers the temperature at which stability studies should be conducted as significant because the rate of a chemical reaction is temperature dependent. Therefore, the temperature chosen for stability testing can be crucial to a valid demonstration of the stability of the drug product.

³ *Id.* at 9-10.

⁴ *Id.* at 12.

⁵ *The United States Pharmacopeia, Twenty Second Revision, (Easton, PA: 1989) at 9.*

⁶ *Id.* See also, 1688-89, 1703-04.

OGD standard operating procedure is, and for some time has been, to accept studies conducted at temperatures between 15° and 30° C but to recommend that studies be conducted at the higher end of this temperature range (between 25° and 30° C). Applicants have complained, however, that what they must do is unclear because the date when such a requirement will take effect has not been specified. Accordingly, any "controlled room temperature" stability studies begun after January 1, 1992 must be conducted between 25° and 30° C unless a different approach has been discussed with OGD staff before the studies are begun. To prevent any misunderstandings, it would be advisable to obtain in writing OGD approval to conduct the studies at a lower temperature.

You should be aware, however, that the FDA is in the process of revising its Guideline on stability studies for both NDA's and ANDA's. The Guideline should specify the temperature at which future studies should be conducted. Historically, the Guidelines have provided sufficient lead time for applicants to implement changes in the recommendations. In its input to the Guideline, OGD is recommending that studies be conducted between 25° and 30° C but the ultimate outcome may be an even tighter range.

c. FAILURE OF APPLICANTS TO PROVIDE ALL NECESSARY DATA

Many of the stability deficiencies found in not approvable letters are associated with an applicant's failure to provide data for all of the stability stations specified in the stability testing protocol. For example, data at the three and nine month stations will be provided and data at the six month station will be omitted. Another frequently occurring deficiency is the failure to specify the actual temperatures at which the stability studies were conducted. Because temperature is a crucial parameter in the study, it must be specified so that the adequacy of the data can be evaluated. Some of our recent inspections have shown that some firms have not been controlling stability station temperature well enough to keep the temperature within the range specified in the stability reports.

Another deficiency frequently noted is that the containers used in stability testing do not appear to be the same as the proposed market containers described

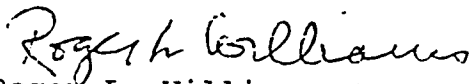
elsewhere in the application.⁷ Enough information must be provided to allow the staff to assure itself that the containers are the same.

d. FAILURE OF APPLICANTS TO ADHERE TO STABILITY COMMITMENTS

Some firms are not honoring their stability commitments to submit long-term room temperature data on the first three production lots and at least one lot yearly thereafter. This material is to be supplied in annual reports. Furthermore, the extension of an expiration date requires actual real-time room temperature data on three production batches out to the proposed extended expiration date. This data must also be supplied in the next annual report after the test period closes. The Office has reviewed annual reports and written letters to firms who have failed to submit the required information. The Office will also involve FDA Compliance and Field staff to assure compliance with these stability requirements.

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,



Roger L. Williams, M.D.
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file: GDINDUSTRY-F

⁷ Guideline, at 10.