PHARMACEUTICAL SCIENCES

RESTATEMENT OF THE OFFICE OF GENERIC DRUGS' "FIRST-IN, FIRST-REVIEWED" POLICY AND MODIFICATION OF THE EXCEPTIONS TO THE POLICY REGARDING MINOR AMENDMENTS

CONTENTS

PURPOSE

- The purpose of this Guide is to clarify the Office of Generic Drugs' (OGD) "first-in, first-reviewed" policy, and to modify the exceptions to the policy regarding minor amendments. This Guide replaces Policy and Procedure Guides #16-90 and #21-90 and related memoranda dated July 11, 1991, March 16, 1992, and May 14, 1992.

BACKGROUND

- In 1990, to assure fair and even-handed treatment of generic drug applicants, the former Division of Generic Drugs issued Policy and Procedure Guides #16-90 and #21-90 that described the "first-in, first-reviewed" policy. The policy established the order in which chemists review original abbreviated new drug applications (ANDA's), abbreviated antibiotic applications (AADA's), and supplemental applications (supplements) and established the review priorities for major and minor amendments to these applications. The procedures for handling major and minor amendments subsequently were modified in a memorandum from the Director, OGD, dated July 11, 1991. Examples of major and minor amendment deficiencies were provided to staff on March 16, 1992, and the policy for handling minor amendments was further revised on May 14, 1992.

- OGD has now determined that a comprehensive restatement of the "first-in, first-reviewed" policy should be issued to consolidate the various statements of this important policy into one Policy and Procedure Guide and to simplify the policy in certain respects.

- The "first-in, first reviewed" policy establishes the priority for chemistry reviews only.

POLICY

- **Restatement of the "First-in, First-Reviewed" Policy**

  Review of original ANDA's and AADA's and supplements to these applications will be initiated and pursued by individual chemistry reviewers, to the extent possible, in the order in which they are received in the Office, except as stated below.

- Exceptions to the "first-in, first-reviewed" policy exist for minor amendments. This Guide describes these exceptions.

- **Review Queue Priorities Generally**

  1. Original applications and major amendments. Original applications and major amendments to original applications will remain in the branch queue for assignment to the next available chemist based on the rules of random assignment. In general, these assignments are made on a first-in, first-reviewed basis and initiate the actual review of the application. For specific details of random assignment, see the memorandum dated May 21, 1992, from OGD's Chief, Management Staff, to Chemistry Division Directors and Team Leaders.

  2. Minor amendments. A minor amendment to an unapproved ANDA/AADA will be the highest priority on each reviewer's ANDA/AADA work queue. If multiple minor amendments are in the queue, they should be reviewed according to days pending, i.e., the longest pending should be reviewed first.

  3. Supplements. The review priority for supplements will be based on the date the supplement is accepted for filing. Minor amendments to supplements will be high priority. The high priority status of supplements granted expedited review is discussed in CDER MAPP 5240.1 (formerly OGD Policy and Procedure Guide #18-90).

- **Identification of Major and Minor Amendments**

  1. If OGD identifies deficiencies in an ANDA/AADA, it normally will issue a Not Approvable Letter (but see Identification of Major and Minor Amendments, Section 2 about minor amendments, telephone calls, and meetings). The letter will identify the deficiencies and tell the applicant if the resulting amendment will be considered a "major" or "minor" amendment.

     a. An amendment may be classified as minor when an experienced review chemist can reasonably be expected to take less than one hour to complete the review (excluding time required to retrieve the application and to prepare the chemistry review

documentation and action letter). All other amendments are considered major amendments.

(1) Examples of major and minor chemistry deficiencies are included in Attachment A.

(2) Even if a particularly fast or knowledgeable reviewer might be able to review the amendment in less than one hour, if this is not the norm, then the amendment should be classified as major.

(3) If the application contains even one major deficiency, the amendment must be classified as a major amendment.

(4) If an application contains more than one minor deficiency and the response to these deficiencies would take more than one hour to review, then the response should be classified as a major amendment.

(5) If there are no chemistry deficiencies and no major deficiencies in the other disciplines, the application will be placed on the "approval matrix." This matrix is used by OGD management to track the status of applications nearing approval as they move through the final administrative stages of the review.

(6) Supervisors should monitor closely the preparation of letters communicating minor deficiencies to ensure that the designations are correct and the letters are issued without undue delay. Team Leaders and Division Directors are responsible for ensuring Office-wide consistency in these designations.

b. The presence of labeling deficiencies will not influence the determination, that is, the amendment category will be determined by chemistry issues alone.

(1) Although the existence of labeling deficiencies may not be considered in determining whether to designate an amendment as major or minor, any labeling deficiencies identified before the letter is prepared will be included in the Not Approvable Letter.

(2) If the labeling review has not been completed, and upon checking with the labeling reviewer, it cannot be completed promptly, the Not Approvable Letter should indicate that the labeling deficiencies will be

communicated separately.

c. Once an amendment has been classified as major and an action letter has been issued, it may **not** be transformed into a minor amendment unless an error has been made by OGD.

(1) If a firm receives a Not Approvable Letter requesting a major amendment, it may not attempt to address the deficiencies noted in the Not Approvable Letter in a piece-meal fashion. That is, it may not transform the remaining deficiencies into a minor amendment. For example, an applicant may not withdraw a supplier of the new drug substance having problems with Current Good Manufacturing Practice (CGMP) requirements and then declare that the response to the remaining deficiencies is a minor amendment.

(2) If, however, a firm can show that OGD erred in identifying deficiencies (e.g., stability data and certificates of analysis noted as missing are, in fact, present) and OGD finds the remaining deficiencies will take less than one hour to review, it will reclassify the amendment from major to minor.

(3) OGD will reject a firm's simple claim that an amendment should take less than an hour to review unless the firm provides evidence of an OGD error in the preceding review.

d. A firm must respond to all of the deficiencies that gave rise to the minor amendment. A partial response will be identified as incomplete and returned to the firm without review.

e. A minor amendment that provides information beyond the scope of identified deficiencies ordinarily will be treated as a major amendment. For example, if in addition to responding to deficiencies identified in a Not Approvable Letter the amendment proposes a change in manufacturing site, the amendment must be considered a major amendment. Unsolicited changes to conform to a recent change in the USP will not be treated as major changes.

f. The applicant must **plainly mark** on the envelope and the cover letter transmitting the submission that the response is a **MINOR AMENDMENT** to an Agency request through a Not Approvable Letter, telephone notification, or meeting. **A minor amendment not properly identified as such may not be reviewed as a**

minor amendment.

2. After the first communication of minor chemistry deficiencies in a Not Approvable Letter, subsequent identification of chemistry deficiencies should be by telephone or in a meeting for requirements about the documentation of telephone calls and meetings).

   a. A supervisor or a Consumer Safety Officer (CSO) must monitor any telephone conversation and attend any meeting. A summary of the conversation or meeting must be prepared, signed by both the review chemist and the CSO or supervisor, and filed with the abbreviated application.

   b. The branch CSO is responsible for ensuring that the firm submits a timely response to the telephone call or meeting.

   c. The applicant's response to a telephone call or meeting conveying minor deficiencies must be submitted to OGD in writing and must completely resolve the deficiencies. With prior concurrence of the chemistry reviewer, the applicant may send a facsimile copy of that final resolution, but the original hard copy must be received by OGD before final action will be taken on the amendment.

   d. If the applicant's response does not completely resolve the deficiencies, a second telephone call may be made. If after two telephone cycles an applicant has not completely resolved the remaining deficiencies, the chemistry reviewer should consult with the Team Leader and the Division Director and reassess the situation. A Not Approvable Letter designated as either a major or minor amendment may then be issued if the Team Leader and the Division Director concur.

- **Reviewer's Implementation of Policy**

  1. **Generally**, once the review of an original ANDA, AADA, supplement, or amendment begins, it should be pursued to completion to the extent possible before the reviewer moves to the next assignment. If review is interrupted to await a document (such as a Drug Master File), the reviewer should immediately return to the incomplete review when the document becomes available.

     a. If a minor amendment arrives while a chemist is reviewing a new ANDA, AADA, or a major amendment, the reviewer should set the application aside and immediately review the minor amendment.

b. Failure to adhere to the "first-in, first-reviewed" policy or to the policy regarding review priority of amendments should be noted in the chemist's review and reported to the Team Leader who also should document the incident and discuss it with the Division Director.

c. The review of multiple supplements from a firm for the same ANDA is addressed by Office policy communicated by memorandum. The reviewer should consult with the Team Leader for the latest policy.

d. Multiple supplements from a firm for the same change to different ANDA's may be treated as having the same pending date even if they were submitted at different times. The coordination of the reviews of all the supplements will be done by a Supervisory CSO of the Program Support Staff. Exceptions to the "first-in, first reviewed" policy for such supplements must be documented.

e. OGD will stop review of the chemistry portion of an application if important not readily remedied bioequivalence problems are identified at any stage of the review of a bioequivalence submission. A Not Approvable Letter will be issued to the applicant explaining the nature of the deficiencies.

2. Major and Minor Amendments

a. When preparing a Not Approvable Letter, the review chemist will make the initial determination of whether the resulting amendment should be categorized as major or minor. The supervisor must concur before a Not Approvable Letter requesting a minor amendment is issued.

b. Before issuing a Not Approvable Letter designating an amendment as minor, the chemist must determine if there is an outstanding bioequivalence review or microbiology consult. If there is, the Not Approvable Letter should note that the timing of the issuance of the next action letter may be affected if the outstanding bioequivalence review or microbiology consult is not received in a timely manner. Further, the letter should state that if there is an uncorrectable bioequivalence deficiency or major microbiology deficiency once the bioequivalence/microbiology reviews are concluded, the subsequent Not Approvable Letter will request a major amendment in response.

(1) When there is an outstanding bioequivalence review, the chemist must notify the Division of Bioequivalence and

request to receive the results of that review within 60 days.

(2) If there is an outstanding microbiology consult, the chemist should work through the CSO Microbiology Coordinator, who will request that the Division of Medical Imaging, Surgical, and Dental Drug Products place a higher priority on that consult.

c. OGD will now make every attempt to issue an action letter (either an Approval Letter or a Not Approvable Letter) **within 60 days** of the date a **minor** amendment to an unapproved ANDA/AADA is received for filing (i.e., the date stamped by the document room), except that the timing is likely to be longer for applications awaiting an outstanding microbiology consult, bioequivalence review, or compliance clearance.

d. Minor amendments to supplements are to be processed as expeditiously as possible, but will not be subject to this 60-day time frame.

EFFECTIVE DATE

This guide is effective upon date of publication.

Attachment A

EXAMPLES OF MAJOR AND MINOR CHEMISTRY DEFICIENCIES

Major Deficiencies

1. If the application is deficient in that the test batch is not representative of the proposed production batch and the applicant must make a new batch and submit three months accelerated stability data and, in some cases, dissolution test data.

2. If the application is so poor that only a global review can be conducted and a broad rather than specific deficiencies are identified (e.g., no master batch record, no validation data for non-compendial test methods, totally inadequate stability data, batch records submitted were incomplete).

3. If no letter of authorization to review a Type II or III Drug Master File referenced in the application was provided.

4. If the applicant chooses to submit for approval an actual procedure for reworking a batch but does not provide adequate data to justify the procedure.

Minor Deficiencies

1. Small clarifications of inconsistent statements in the application are required and it is likely that the clarifications will not result in further questions.

2. The reviewer is asking that a specific change be made, e.g., to add a particular test, monitor the temperature in stability studies, add limits for acceptance or other specifications based on already submitted test results, or make a minor manufacturing revision such as slightly longer or shorter tableting runs.

3. Administrative deficiencies such as illegible pages, typographical errors, failure to certify compliance with CGMP's, failure to make the certification of compliance with state and local environmental regulations.

4. A Certificate of Analysis or certification of compliance with compendial specifications is missing from a DMF.

5. Only post-approval commitments are requested, e.g., in the future, state the source of the active ingredient on stability data reports, or provide a batch record and dissolution data for the first post-approval production batch.

6. Stability data accrued to date is requested (if the data already submitted support approval).

7. The applicant intends to submit supplementary applications for approval to rework batches and

has failed to provide a commitment to this effect.

8. The applicant needs to submit comparability data showing that a proposed alternative analytical method is comparable to the compendial method.

9. The application is for an additional strength of a product from the same firm and the deficiencies have been identified and responded to in the companion applications.