Major, Minor, FAX & Telephone Amendments

Final Guideline
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Reviewed: IAGIM Science Committee

'...a minor amendment status saves a lot of review & queue time...

APPROVED GUIDELINE

Major, Minor, FAX, and Telephone Amendments to Original Abbreviated New Drug Applications

I. INTRODUCTION

This guidance is intended to document the Office of Generic Drugs (OGD) policy regarding the determination of major, minor, FAX, and telephone amendments to original abbreviated new drug applications (ANDAs)[2].

This policy has been in use by OGD for many years. Generally, the considerations used to categorize amendments requested by OGD are determined by the nature of the chemistry, manufacturing, and controls (CMC), microbiology, labeling, and/or bioequivalence deficiencies.

II. POLICY

A. How does the Office Of Generic Drugs classify amendments?

OGD classifies requested amendments to abbreviated new drug applications (ANDAs) as MAJOR, MINOR, FAX, or TELEPHONE.

Major amendments have the same review priority as original, unreviewed ANDAs and are reviewed consistent with OGD's first in-first reviewed procedure.

Minor amendments have a higher review priority than major amendments because they often mean an application is close to approval and should, therefore, be given priority.

Major and Minor amendments are mailed in to FDA 'stopping the review clock'

The issuance of both major and minor amendments stops the review clock while the applicant addresses the deficiencies noted by OGD, but FAX and telephone amendments do not stop the clock unless the applicant does not respond within the anticipated time.

Therefore, FAX and telephone amendments represent the reviewer's highest priority work assignments.

Review by ; E Letai, Jan Kay BSc. Contact: info@iagim.org

B. When is an Amendment Classified as MAJOR?

MAJOR AMENDMENTS.

In general, OGD classifies an amendment as *major* if ***any*** of the following criteria apply at the time of the determination:

1. An experienced chemistry reviewer cannot reasonably be expected to review the requested information in less than one hour (excluding time needed to retrieve the application and to prepare the review documentation and action letter).
2. An experienced microbiology reviewer cannot reasonably be expected to review the requested microbiological/sterility assurance data in less than one working day (excluding time needed to retrieve the application and to prepare the review documentation and action letter).
3. The amendment will provide data to address major bioequivalence (BE) deficiencies (e.g., there is a need to conduct one or more bioequivalence studies and resubmit data).
4. Information in addition to that requested by OGD is being submitted in response to a request for a minor, FAX, or telephone amendment (e.g., additional and/or new strengths or manufacturing facilities for the drug substance or drug product), and the review will require more than one hour to complete.

MAJOR AMENDMENTS

Examples that may be determined to be **major** amendments include, but are not limited to:

- The submission is of such overall poor quality that only a general review can be conducted and only broad, rather than product-specific deficiencies can be identified.
- No letter of authorization (LOA) is provided to permit the review of the applicable drug master file (DMF) for the drug substance, or a drug release-controlling component of a therapeutic system.
- The ANDA contains little or no validation data for appropriate analytical methods (e.g., chromatography).
- The stability data submitted are inadequate to justify the proposed expiration dating and the stability studies must be repeated.
- The test batch is determined not to be representative of the proposed production batch, necessitating the manufacture of a new test batch.
- The applicant submits a procedure for reworking a batch in the absence of adequate data to justify the proposed procedure.
- The bioequivalence study is unacceptable (e.g., a new or additional study is needed, such as an in vitro BE study for nasal sprays), even if chemistry deficiencies may be designated as minor or FAX in nature.

MAJOR AMENDMENTS LIST
The Chemistry deficiency takes more than **one** HOUR to review
The Microbiology deficiency takes more than a **DAY** to review.
A bioequivalence fault, failure or additional testing and data is required.
Significant bioequivalence deficiencies
Poor quality CMC data that exceeds the hour limit for data review.
Any missing Letter of Authorization (LOA)
Poor, missing or incomplete Analytical Validation.
Incomplete or inconclusive Stability Data
When the commercial batch is not essentially similar to the pivotal (bio) batch
When a rework procedure does not have all the analytical and physical testing to shown no significant specification change.
If the deficiency requires more than **30** days to correct
A minor chemistry review plus a major bioequivalence fault upgrades the **minor** chemistry **to a major** review.

C. WHEN IS AN AMENDMENT CLASSIFIED AS MINOR?

MINOR AMENDMENTS.

OGD categorizes an amendment as *minor* when none of the above major criteria apply (see table), and **ALL** of the following criteria that are relevant apply at the time of the determination:

Major amendment's review priorities are the same as the original, unreviewed ANDA

1. **A**n experienced chemistry reviewer can reasonably be expected to review the CMC data in less than one hour (excluding time required to retrieve the application and to prepare the review documentation and response).
2. **A**n experienced microbiology reviewer can reasonably be expected to review the requested microbiological / sterility assurance information in less than **one working day** (excluding time needed to retrieve the application and to prepare the review documentation and action letter).
3. **I**t is expected that the applicant will need more than 30 days to respond with a complete amendment.
4. **N**o significant bioequivalence deficiencies (e.g., a need to conduct a new bioequivalence study or in vitro BE testing for nasal sprays) have been identified at the time the minor amendment determination is made. Less significant bioequivalence deficiencies (e.g., dissolution data) may have been identified.
5. **T**he remaining factors precluding approval are generally considered to be outside the immediate control of the applicant (e.g., DMF deficiencies).

MINOR AMENDMENTS

Examples that would result in a minor amendment determination **include**, but are not limited to:

Data are requested to support compendial testing requirements, including endotoxin or preservative effectiveness testing.

There are presently unresolved current good manufacturing practices (cGMP) issues that have been identified by the Office of Compliance affecting one or more of the facilities listed in the application (e.g., withhold recommendations), even if all other review aspects of the ANDA are considered sufficient.

There are labeling deficiencies that have not been adequately addressed in a timely manner for an application that is otherwise sufficient for approval, excluding an acceptable establishment evaluation request from the Office of Compliance.

MINOR AMENDMENTS LIST
No deficiency from **MAJOR LIST**.
The Chemistry deficiency takes LESS than **one** HOUR to review
The Microbiology deficiency takes LESS than a **DAY** to review.
If the deficiency requires LESS than **30** days to correct
There is no bioequivalence fault, failure or additional testing and data is required.
No significant bioequivalence deficiencies exist.
All Letters of Authorization (**LOA**) are included in file. (Actives excipients container-closure systems)
A drug master File deficiency from a Active Ingredient or container-closure supplier
Incomplete MONOGRAPH testing - i.e. data required from a USP compendial test
cGMP deficiencies from a preapproval inspection PAI
A poorly addressed labelling deficiency
A poorly addressed FAX amendment that is upgraded to a minor amendment
Any FAX amendment request exceeding **30** days is converted to a minor amendment.

D. When is an Amendment Classified as a FAX AMENDMENT?

OGD classifies an amendment as a *FAX* amendment when the above minor criteria, except section II.C.3 (i.e. more than 30 days), apply and ***all*** of the following criteria that are relevant apply at the time of the determination:

[1]. **A**ll deficiencies are judged to be within the immediate control of the applicant.

[2]. **A**ll relevant DMFs have been found acceptable.

[3]. **O**GD expects that the applicant will be able to provide a complete response to all deficiencies within **30 calendar** days from the request date.

An inadequate Fax amendment may be upgraded to a minor amendment

Examples of FAX amendment determinations include, but are not limited to:-

- **D**eficiencies that are primarily administrative or clerical revisions, such as:-
- **I**nconsistent statements in the ANDA need to be clarified, but it is unlikely that the clarifications will result in further questions.
- **OGD** has requested a specific change that will not result in additional data submission (e.g., to add a particular test, to monitor the temperature in stability studies, to add limits for acceptance or other specifications based on already submitted test results, or to make minor manufacturing revisions).

The FDA's Review Clock Does not Stop for **Fax/ Tel** Amendments

- **T**he amendment involves resubmission of illegible pages or correction of typographical errors.
- **C**ommitments are needed to provide certain items postapproval (e.g., postapproval statements on the source of the active ingredient on stability data reports, or provision of a batch record and dissolution data for the first postapproval production batch).

A Fax amendment must meet minor amendment plus 3 key additional requirements

- **C**ommitment is needed to submit a supplemental application for approval. The applicant is asked to provide additional stability data accrued during the review process.

FAX AMENDMENTS LIST
All criteria from **Minor List** apply PLUS **É**
All deficiencies can be immediately corrected by applicant
The file contains NO DMF deficiencies
All criteria from MINOR LIST apply.
Any deficiency will take LESS than **30** days to correct
If the deficiency is a clerical or administrative error.
An inconsistent statement that needs to be rectified.
An administration specification change (or minor document change) requested by the agency.
Submitting a readable copy of an illegible or poor original page.
A future post-approval commitment requested by the agency on stability, active or dissolution testing.
A requirement to submit stability or other data that accrued during the review process

E. WHEN is an Amendment Classified as a TELEPHONE AMENDMENT?[4]

An amendment is classified as a *telephone* amendment if it follows a *minor* or FAX amendment and the new amendment meets the following criteria:

1. It primarily addresses an administrative or minor technical issue, and
2. OGD believes the applicant can provide a complete and satisfactory response within **10 calendar days** of the call, and
3. The deficiencies are similar to those described for a FAX amendment.

Examples of telephone amendments include, but are not limited to:

- Clarification of data already submitted
- Request for a post-approval commitment

A Telephone amendment may follow a minor or a fax amendment.

To expedite the review, telephone amendments may also be requested during the final office level administrative review of an ANDA, immediately prior to tentative or final approval.

III. REVIEW CONSIDERATIONS

A. What are the Time Frames for Handling Amendments?

OGD attempts to review **major** amendments within **180 days** and to review **minor** amendment within **60 days**. However, not all minor amendments can be reviewed within 60 days (e.g., if consults from outside of OGD are needed).

Since the review clock is ***not*** stopped for FAX or telephone deficiency requests, FAX and telephone amendments will be placed in the highest review priority level.

B. WHEN is an Amendment Redesignated?

Deficiencies that are not satisfactorily addressed by the applicant after the review of the FAX amendment will be communicated back to the applicant as a minor amendment or a telephone amendment, based on the criteria in section II.

A inadequate fax amendment may be pushed up (redesignated) to a minor category.

There could be situations in the review of an ANDA that result in the redesignation of an amendment and consequently the status of the ANDA.

For example, the chemistry review and the microbiology review of an ANDA may be completed in different time frames.

If the chemistry review is completed first and the appropriate criteria are met, OGD will issue a request for a minor amendment response to the deficiencies.

If the microbiology review subsequently reveals major deficiencies, these will be communicated to the applicant as a request for a major amendment response. This action will also change the chemistry response to a major amendment.

In some cases the results of a bioequivalence or labeling review will result in the re-designation of an amendment.

For example, if an ANDA is in **minor** status for chemistry and it is subsequently determined that an invivo bioequivalence study fails, a re-designation to **major** will occur.

Examples that could result in amendment re-designation include:

* A FAX amendment request that has not been responded to within **30 days** will be converted into a minor amendment request.
* A chemistry or microbiology telephone amendment request that has not been responded to within **10 days** of OGD's request will be redesignated as a minor amendment.

In general, OGD will not consider a request to reclassify an amendment because certain deficiencies are eliminated by an applicant's withdrawal of a portion of the application.

C. What is the process for classifying an amendment?

Reviewers will conduct their review according to OGD policies. The reviewer makes the initial recommendation to the team leader regarding classification of the amendment to be requested.

The team leader will conduct the secondary review and concur with the amendment classification, if appropriate. Division directors (or deputies) will complete any necessary tertiary reviews.

If an applicant requests reclassification of an amendment, the director or deputy will review that request. Applicants are expected to respond to all requests for amendments in a timely manner and ensure that two hard copies are submitted of any material communicated to OGD by facsimile or telephone.

Labeling reviewers will transmit labeling deficiencies directly to the applicant via facsimile in the absence of any CMC, microbiology, or bioequivalence deficiencies, or in the event the labeling review is completed after the remaining deficiencies have been communicated to the applicant.

Unless otherwise specified, labeling deficiencies will be issued by facsimile.