ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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ANDA Submissions – Amendments to Abbreviated New Drug Applications Under GDUFA Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to explain to applicants how the review goals established as part of the Generic Drug User Fee Amendments Reauthorization of 2017 (GDUFA II) apply to amendments to either abbreviated new drug applications (ANDAs) or prior approval supplements (PASs) submitted to the Food and Drug Administration under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)).[2] This guidance describes amendment classifications and categories and explains how amendment submissions may affect an application's review goal dates. The guidance also describes how FDA should review amendments submitted to ANDAs and PASs received prior to October 1, 2017, which is the GDUFA II review goals effective date.

When final, this guidance will replace the December 2001 guidance for industry *Major, Minor, and Telephone Amendments to Abbreviated New Drug Applications* (2001 amendments guidance).[3,4] This draft guidance supersedes the July 2014 draft guidance for industry *ANDA Submissions – Amendments and Easily Correctable Deficiencies Under GDUFA*.

[1] This guidance has been prepared by the Office of Generic Drugs in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] Although not directly within the scope of this guidance, we remind applicants of the patent certification requirements applicable to ANDA amendments in 21 CFR 314.96(d)(1). See also 81 FR 69580, 69591-96, and 69636-39 (October 6, 2016).

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[4] The 2001 amendments guidance contains the relevant definitions as considered during the GDUFA II negotiations; those definitions will be maintained in appendix B of this guidance because the 2001 amendments guidance will be withdrawn and replaced by this guidance once it is finalized.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

GDUFA II was signed into law on August 18, 2017,[5] to facilitate timely access to quality, affordable generic medicines. Under the GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (GDUFA II Commitment Letter or GDUFA II Goals)[6] that accompanied the legislation, FDA agreed to certain review goals and procedures for amendments under review as of or received on or after the GDUFA II effective date.[7]

The GDUFA II Commitment Letter reflects significant changes in the classification of and review goals for amendments to ANDAs and PASs under the Generic Drug User Fee Amendments of 2012 (GDUFA I). Under GDUFA I, amendments were classified into a complex Tier system based on the following factors:

- Whether the amendment was solicited (i.e., submitted in response to a complete response letter (CRL)) or unsolicited (i.e., submitted on the applicant's own initiative)
- Whether the amendment was *major* or *minor* (as defined in the guidance for industry *ANDA Submissions – Amendments and Easily Correctable Deficiencies Under GDUFA*)
- The number of amendments submitted to the ANDA or PAS
- Whether an inspection was necessary to support the information contained in the amendment

GDUFA II simplified the amendment review goals and no longer subjects them to a Tier system; however, GDUFA II review goals are still dependent on several factors, as described in section ___ of this guidance. In general, GDUFA II amendments will be designated as either *standard* or *priority*, be classified as either *major* or *minor*, and receive a goal date based on the factors discussed in this guidance, including whether a preapproval inspection is needed.

FDA considers each and every submission to an application to be an amendment. These submissions will be classified based on the content submitted and issued a goal date consistent

[5] FDA Reauthorization Act of 2017 (Public Law 115-52 Title III).

[6] The GDUFA II Commitment Letter is available at http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf.

[7] The application of GDUFA II goals to amendments with a Target Action Date or GDUFA I goal date is discussed in section IV of this guidance.

with that classification.[8] The types of amendments and review goals described in this guidance only apply to submissions that have been received for review (i.e., review goals do not apply to submissions pending filing review).

III. CATEGORIES OF GDUFA AMENDMENTS

As stated in the GDFUA II Commitment Letter, *major* and *minor amendments* are defined in the 2001 amendments guidance.[9] The sections below provide general descriptions of the types of deficiencies that would classify an applicant's response to these deficiencies as a major or minor amendment,[10] as provided for in that guidance. In addition, FDA has developed a non-exhaustive list of examples of major deficiencies, which is available in appendix A[11]

A. Major Amendments

Examples of actions that, if requested or taken in response to deficiencies, would result in major amendments include:

- Manufacturing a new batch of drug product for any reason (e.g., a composition change or reformulation, a change in the source of a drug substance, a change in the manufacturing site, the need for a new bioequivalence (BE) study, a new in vitro study for a specific product, a change in a major manufacturing process, a new strength of the product, unacceptable impurities or impurity levels, unacceptable excipients found during review, failed stability data, or a change in the container-closure system (other than solid oral dosage forms))

- Performing a new BE study whether or not related to the manufacture of a new batch of the drug product

- Developing new analytical methods and providing full validation data

[8] Information Requests (IRs) and Discipline Review Letters (DRLs) neither stop the review clock nor add to the GDUFA II goal. GDUFA II Commitment Letter at 11. Accordingly, a response to an IR or DRL generally will not be classified as a major or minor amendment and will not receive a goal date. If a response to an IR or DRL contains information not requested by FDA, or if FDA determines that the information provided requires a more thorough review, FDA will classify the submission as an amendment with a corresponding goal date. See section V of this guidance. Similarly, amendments that are administrative in nature and do not require a scientific review (i.e., *administrative amendments*) will generally not affect the goal date. See section III.C of this guidance.

[9] See GDUFA II Commitment Letter at 26. See also supra note 4.

[10] Note that descriptions of *major* and *minor* in this guidance apply only to the classification of major and minor amendments and are distinguishable from major or minor issues that FDA staff may identify as filing deficiencies during filing review.

[11] An appendix containing examples of minor deficiencies is not included in this guidance because, in general, deficiencies not classified as major will be classified as minor deficiencies.

FDA has the discretion to consider the responses to additional deficiencies not included in either this list or appendix A as major amendments as long as the "major amendment" classification receives FDA division-level concurrence. This classification does not reflect the time it takes an applicant to respond to the complete response letter (CRL) but is based on an assessment by FDA that substantive review of the application cannot be performed without an extensive review because of the content of the information or data provided.

B. Minor Amendments

Minor amendments are those not classified as major or are a response to a deficiency that could be adequately resolved through an information request (IR) or discipline review letter (DRL). Minor amendments often consist of responses to deficiencies that are more easily addressed than those in a major amendment and typically require less extensive review by FDA. Examples of minor amendments include responses to:

- Minor deficiencies in the drug master file (DMF)
- Incomplete dissolution data
- Labeling deficiencies that have not been adequately addressed in response to an information request[12]

C. Unsolicited Amendments

An *unsolicited amendment* is an amendment with information not requested by FDA, except for those amendments considered routine or administrative and that do not require scientific review.[13]

IV. REVIEW GOALS

The GDUFA II Commitment Letter identifies the review goals for amendments submitted to ANDAs and PASs.[14] These review goals are based in part on whether the ANDA or PAS is subject to standard review or priority review and whether the amendment is classified as major or minor. Further, the review goals consider whether the priority submission requires a

[12] The 2001 amendments guidance included minor problems regarding good manufacturing practices as an example of a minor deficiency. FDA's current thinking is that, in general, any good manufacturing practice or facility deficiency is, in fact, a major deficiency. See appendix A of this guidance.

[13] GDUFA II Commitment Letter at 28.

[14] The review goals identified in this guidance apply to amendments to original ANDAs or PASs that are submitted either on or after October 1, 2017, or per the GDUFA I bridging scheme described in section IV.C.

preapproval inspection, and if so, whether the applicant submitted a timely, complete, and accurate pre-submission facility correspondence (PFC).[15]

A. Amendments to ANDAs

1. Major Amendments

a. ANDA amendments subject to standard review

FDA will review and act on[16] 90 percent of standard major ANDA amendments within 8 months of the amendment submission date[17] if FDA does not require a preapproval inspection.[18] FDA will review and act on 90 percent of standard major ANDA amendments within 10 months of the amendment submission date if FDA requires a preapproval inspection.[19]

Example: On November 27, 2017, an applicant submits an amendment in response to a CRL that identified major deficiencies in its ANDA. FDA determines that the amendment is subject to a standard review. The amendment contains information on a new facility that requires a preapproval inspection. FDA classifies the amendment as a major amendment requiring a preapproval inspection and sets a 10-month review goal. Therefore, the review goal for this amendment is September 26, 2018.

Example: On July 24, 2019, an applicant submits an amendment in response to a Risk Evaluation and Mitigation Strategy (REMS) modification request. FDA determines that the amendment is subject to a standard review. FDA classifies the amendment as a major amendment that does not require a preapproval inspection and sets an 8-month review goal. Therefore, the review goal for this amendment is March 23, 2020.

b. ANDA amendments subject to priority review[20]

[15] See the draft guidance for industry *ANDAs: Pre-Submission Facility Correspondence Associated with Priority Submissions* (PFC Guidance). When final, this guidance will represent FDA's current thinking on this topic.

[16] To *act on* an application means FDA will issue a CRL, an approval letter, a tentative approval letter, or a refuse-to-receive letter.

[17] The *submission date* is the date the amendment arrives in the appropriate FDA electronic portal. See the guidance for industry *Providing Regulatory Submissions in Electronic Format – Receipt Dates*.

[18] GDUFA II Commitment Letter at 4.

[19] Id.

[20] As described in this section and in section IV.B.b below, the GDUFA II Commitment Letter provides a timeline for the submission of PFCs (i.e., 2 months prior to the amendments submission). The FDA Reauthorization Act of 2017 at section 801 requires submission of PFCs no later than 60 days prior to the submission of the original ANDA. To ensure that PFCs for amendments are submitted consistent with PFCs to original submissions, FDA has inserted the timing required in the FDA Reauthorization Act. For the most current thinking on the submission of PFCs, see the PFC guidance, supra note 15.

FDA will review and act on 90 percent of priority major ANDA amendments within 6 months of the amendment submission date if preapproval inspection is not required.[21] FDA will also review and act on 90 percent of priority major ANDA amendments within 8 months of the amendment submission date if (1) preapproval inspection is required and (2) the applicant submits a complete and accurate PFC that remains unchanged at the time of the amendment submission no later than 60 days prior to the amendment submission date.[22] Finally, FDA will review and act on 90 percent of priority major ANDA amendments within 10 months of the amendment submission date if (1) preapproval inspection is required and (2) the applicant fails to submit a PFC no later than 60 days prior to the amendment submission date, the PFC is incomplete or inaccurate, or the facility information changes between the submission of the PFC and the submission of the amendment.[23]

> *Example*: On September 20, 2018, an applicant submits an amendment in response to a CRL that identified major deficiencies in its ANDA. FDA determines that the amendment is subject to a priority review. The applicant submitted a complete and accurate PFC on July 19, 2018. The applicant subsequently added a new facility and placed information about the new facility in its September 20, 2018, submission. FDA classifies the amendment as a major amendment requiring a preapproval inspection and sets a 10-month review goal. Therefore, the review goal for this amendment is July 19, 2019.

2. Minor Amendments

FDA will review and act on 90 percent of standard and priority minor ANDA amendments within 3 months of the amendment submission date.[24]

> *Example*: On March 8, 2019, an applicant submits an amendment in response to a CRL that identified minor deficiencies in its ANDA. FDA determines that the amendment is subject to a priority review. FDA classifies the amendment as a minor amendment and sets a 3-month review goal. The review goal for this amendment is June 7, 2019.

Table 1: Summary of Performance Goals to Major and Minor Amendments to ANDAs

Submission Type	Performance Goal
Standard major amendment to an ANDA	90% reviewed within 8 months of the submission date if preapproval inspection is not required
	90% reviewed within 10 months of the submission date if preapproval inspection is required

[21] GDUFA II Commitment Letter at 4.

[22] Id. at 4-5.

[23] Id. at 5.

[24] Id.

Priority major amendment to an ANDA	90% reviewed within 6 months of the submission date if preapproval inspection is not required
	90% reviewed within 8 months of the submission date if: (1) A preapproval inspection is required; (2) The applicant submits a complete and accurate PFC no later than 60 days prior to the amendment submission date; and (3) The PFC remains unchanged at the time of the amendment submission
	90% reviewed within 10 months of the submission date if: (1) A preapproval inspection is required and (2) The applicant fails to submit a complete and accurate PFC no later than 60 days prior to the amendment submission date or (3) Information in a complete and accurate submitted PFC changes
Standard or priority minor amendment to an ANDA	90% reviewed within 3 months of the submission date

3. Unsolicited Amendments

FDA will generally review and act on an unsolicited ANDA amendment submitted during the review cycle by the later of either (1) the goal date for the original submission or solicited amendment being amended or (2) the goal date assigned under the review goals for standard and priority review ANDAs.[25] FDA will generally review and act on unsolicited ANDA amendments submitted between review cycles by the later of (1) the goal date for the subsequent solicited amendments or (2) the goal date assigned under the review goals for standard or priority ANDAs.[26,27]

> *Example*: On August 1, 2018, an applicant submits an ANDA, which contains a request for a priority designation, 60 days after the submission of a complete and accurate PFC. FDA determines that the application is subject to a priority review and sets an 8-month review goal. The review goal for this ANDA is March 31, 2019.
>
> On October 15, 2018, the applicant submits an amendment containing a change in manufacturing site. FDA determines that the amendment is subject to a priority review, but the applicant did not submit a PFC. FDA classifies the amendment as a major amendment requiring a preapproval inspection and sets a 10-month review goal, which extends the review goal of this ANDA. The review goal for this ANDA and amendment is August 14, 2019.

[25] Id. at 8.

[26] Id.

[27] See section V.B for a discussion on FDA's practice of deferred review of unsolicited amendments.

Example: On August 5, 2019, an applicant submits an ANDA. FDA determines that the application is subject to a standard review and sets a 10-month review goal. The review goal for this ANDA is June 4, 2020.

On February 4, 2020, the applicant submits an amendment containing a REMS modification. FDA classifies the amendment as a minor amendment and sets a 3-month review goal. The review goal for this amendment is subsumed into the review of the ANDA. Accordingly, the review goal for this ANDA and amendment remains June 4, 2020.

B. Amendments to PASs

1. Major Amendments

a. PAS amendments subject to standard review

FDA will review and act on 90 percent of standard major PAS amendments within 6 months of the amendment submission date if preapproval inspection is not required.[28] FDA will review and act on 90 percent of standard major PAS amendments within 10 months of the amendment submission date if preapproval inspection is required.[29]

Example: On March 3, 2020, an applicant submits an amendment in response to a CRL to a PAS for a new strength that identified the need for a new BE study. FDA determines that the amendment is subject to a standard review. FDA classifies the amendment as a major amendment that does not require a preapproval inspection and sets a 6-month review goal. The review goal for this amendment is September 2, 2020.

b. PAS amendments subject to priority review

FDA will review and act on 90 percent of priority major PAS amendments within 4 months of the amendment submission date if preapproval inspection is not required.[30] FDA will review and act on 90 percent of priority major PAS amendments within 8 months of the amendment submission date if (1) preapproval inspection is required and (2) the applicant submits a PFC no later than 60 days prior to the PAS submission date and the PFC is found to be complete and accurate and remains unchanged at the time of PAS submission.[31] FDA will review and act on 90 percent of priority major PAS amendments within 10 months of the amendment submission date if (1) preapproval inspection is required and (2) the applicant does not submit a PFC no later

[28] GDUFA II Commitment Letter at 6.

[29] Id.

[30] Id.

[31] Id. at 7.

than 60 days prior to amendment submission or the facility information contained in the PFC changes prior to the PAS submission date or is found to be incomplete or inaccurate.[32]

> *Example*: On March 26, 2020, an applicant submits an amendment in response to a CRL that identified minor deficiencies in a PAS. The amendment adds a new facility. FDA determines that the amendment is subject to a priority review. The applicant submitted a complete and accurate PFC 60 days prior to submission of the amendment. FDA classifies the amendment as a major amendment requiring a preapproval inspection and sets an 8-month review goal. The review goal for this amendment is November 25, 2020.

2. Minor Amendments

FDA will review and act on 90 percent of standard and priority minor PAS amendments within 3 months of the amendment submission date.[33]

> *Example*: On May 1, 2020, an applicant submits an amendment in response to a CRL that identified minor deficiencies in a PAS. FDA classifies the amendment as a minor amendment and sets a 3-month review goal. The review goal for this amendment is July 31, 2020.
>
> On June 10, 2020, the applicant submits an unsolicited amendment. FDA classifies the unsolicited amendment as a minor amendment and sets a 3-month review goal, extending the review goal for the current review. The review goal for both amendments is September 9, 2020.

Table 2: Summary of Performance Goals to Major and Minor Amendments to PASs

Submission Type	Performance Goal
Standard major amendment to a PAS	90% reviewed within 6 months of the submission date if preapproval inspection is not required
	90% reviewed within 10 months of the submission date if preapproval inspection is required
Priority major amendment to a PAS	90% reviewed within 4 months of the submission date if preapproval inspection is not required
	90% reviewed within 8 months of the submission date if: (1) A preapproval inspection is required; (2) The applicant submits a complete and accurate PFC no later than 60 days prior to the amendment submission date; and (3) The PFC remains unchanged at the time of amendment submission
	90% reviewed within 10 months of the submission date if: (1) A preapproval inspection is required and (2) The applicant fails to submit a complete and accurate PFC no later

[32] Id.

[33] Id.

	than 60 days prior to the date of the amendment submission or (3) Information in a complete and accurate submitted PFC changes
Standard or priority minor amendment to a PAS	90% reviewed within 3 months of the submission date

3. Unsolicited Amendments

Like unsolicited amendments to ANDAs, FDA will generally review and act on unsolicited PAS amendments submitted during the review cycle by the later of (1) the goal date for the original submission/solicited amendment, or (2) the goal date assigned in accordance with the above goals for standard and priority review PASs. FDA will generally review and act on unsolicited PAS amendments submitted between review cycles by the later of (1) the goal date for the subsequent solicited amendments, or (2) the goal date assigned in accordance with the above goals for standard or priority PASs.[34]

Example: On November 26, 2019, an applicant submits an unsolicited amendment for a new formulation. The amendment is submitted after FDA issued a CRL that identified minor deficiencies in a PAS, but the amendment does not respond to that CRL.

On January 15, 2020, the applicant submits an amendment in response to the CRL. FDA classifies (1) the amendment in response to the CRL as a minor amendment with a 3-month review goal and (2) the unsolicited amendment as a major amendment requiring a preapproval inspection with a 10-month review goal. Because the longest goal date (i.e., the 10-month goal) applies, the review goal for both amendments is November 14, 2020.

C. Amendments to ANDAs and PASs Submitted Prior To and During GDUFA I

As described in Section II above, any amendment submitted to an ANDA or a PAS under GDUFA I was subject to classification under the Tier system with varying review goals. The GDUFA II Commitment Letter includes the following provisions for amendments to applications with GDUFA I goals and for amendments to applications that did not receive GDUFA I goal dates (i.e., ANDAs and PASs submitted prior to the start of cohort year 3 of GDUFA I (i.e., October 1, 2014)):[35]

- FDA will continue to review amendments to ANDAs and PASs submitted prior to October 1, 2017, that have been assigned a GDUFA I review goal date and will act on those submissions by the GDUFA I goal date.

[34] See section V.B for a discussion on FDA's practice of deferred review of unsolicited amendments.

[35] See GDUFA II Commitment Letter at 9-10.

- FDA will review and act on 90 percent of ANDA amendments with Target Action Dates (TADs)[36] by the goal date. For these submissions, FDA will convert the TAD to a GDUFA II goal date.[37]

- FDA will review and act on 90 percent of amendments pending with FDA as of October 1, 2017, that were not subject to GDUFA I goal dates and either (a) were not previously assigned TADs (i.e., the submission did not have a GDUFA I goal date or a TAD) or (b) were previously assigned TADs that came due prior to October 1, 2017, but remain under review as of October 1, 2017 (i.e., FDA did not take action by the TAD and the submission remains under review with FDA), by GDUFA II amendment goal dates that FDA will assign on October 1, 2017.[38]

V. APPLICATION OF REVIEW GOALS

A. Changes to Classifications or Review Goals

All initial amendment classifications and any changes to those classifications will be made at FDA's discretion. A CRL will advise the applicant whether the applicant's response to the CRL will be classified as a major or minor amendment. However, FDA may change its classification of the CRL response or its initial classification of an unsolicited amendment based on the content of the amendment (e.g., if the amendment proposes a new strength in the response to the CRL, including any information not identified by the applicant in the cover letter of the CRL response). The decision to change an amendment's classification will be made by the regulatory project manager and the ANDA review team, in consultation with the appropriate FDA division director.

If FDA determines that a preapproval inspection is required for any facility referenced in the ANDA during the review of an unsolicited or solicited minor amendment, FDA will classify the submission as a major amendment and set a review goal of 10 months from the submission date.

> *Example*: On November 13, 2017, an applicant submits an amendment in response to a CRL that identified minor deficiencies in an ANDA. FDA determines that the amendment is subject to standard review. The amendment includes a new a facility that requires a preapproval inspection. FDA classifies the amendment as a major amendment requiring a preapproval inspection and sets a 10-month review goal. The review goal for this amendment is September 12, 2018.

[36] Under GDUFA I, a TAD represents FDA's aspirational deadline for action on either a pre-GDUFA I Year 3 original ANDA or a CRL amendment or equivalent IR to an original ANDA.

[37] See GDUFA II Commitment Letter at Attachment A.

[38] For any goal date assigned by FDA on October 1, 2017, the goal will not be later than July 31, 2018. GDUFA II Commitment Letter at 10.

Example: On August 24, 2018, an applicant submits an amendment in response to a CRL that identified minor deficiencies in an ANDA. The amendment contains information on a new strength. FDA determines that the amendment is subject to a standard review and that no preapproval inspection is required. FDA classifies the amendment as a major amendment and sets an 8-month goal. The review goal for this amendment is April 23, 2019.

If an applicant does not submit a response to an IR or DRL within the time frame requested by FDA, FDA may reissue the IR or DRL as a deficiency in a CRL on completion of the current review cycle. If an applicant submits its response to an IR or DRL within the requested time frame, but the response contains information requiring a more extensive review than is typically required for such deficiencies (e.g., the applicant provides more information than anticipated by FDA when the deficiency was issued), the amendment will be classified as a minor or major amendment and the goal date will be adjusted accordingly from the submission date.

Example: During the technical review of a standard ANDA, FDA determines that an applicant failed to identify all facilities in the Form FDA 356h. FDA issues an IR to the applicant asking it to update the FDA Form 356h. On November 19, 2018, the applicant submits a timely response to the IR and provides an updated FDA Form 356h. FDA determines that the newly identified facility requires a preapproval inspection. FDA changes the classification of the IR response to a standard major amendment requiring a preapproval inspection and sets a goal date of 10 months from the submission date. The review goal this amendment is September 18, 2019.

Notification of a change in classification will be provided to the applicant after FDA determines that this change is appropriate.

B. Deferred Amendments

FDA has historically exercised, and continues to exercise, discretion in determining whether to accept or defer an unsolicited amendment submitted during the review cycle. FDA will generally accept an unsolicited amendment submitted during the review cycle and adjust the goal date for the application. However, FDA may defer review of the unsolicited amendment if the discipline reviews are close to completion and either (1) the submitted amendment contains a significant amount of new information to be reviewed or (2) the amendment is submitted after the relevant reviews have been completed and while an IR, DRL, or CRL is being prepared because, the submission of an amendment at these times causes inefficiencies in FDA's review. This discretion to review or defer such amendments enables FDA to timely review all GDUFA submissions. The review goal for unsolicited amendments is discussed in sections IV.A.3 and IV.B.3 of this guidance.

Example: FDA is reviewing an original ANDA with a goal date of November 13, 2018. On October 15, 2018, the applicant submits an unsolicited amendment containing a new source for the active pharmaceutical ingredient. The product quality review is complete, and FDA identified minor deficiencies for inclusion in a CRL. FDA determines that it

will defer review of the unsolicited amendment until the applicant submits a response to the CRL.

FDA issues the CRL on November 1, 2018. The applicant submits its response to the CRL on December 30, 2018. FDA classifies the amendment in response to the CRL as a minor amendment with a 3-month review goal and classifies the unsolicited amendment as a major amendment requiring a preapproval inspection with a 10-month review goal. Because the longest goal date applies (i.e., the 10-month goal), the review goal for both amendments is October 29, 2019.

C. Amendments Submitted Before and After October 1, 2017

In certain situations, an applicant may submit a new amendment to an existing amendment (i.e., the applicant amends a previously submitted amendment that is under FDA review). In these instances, submitting the additional amendment may extend the goal date. If an applicant submits an amendment on or after October 1, 2017, to an amendment under review that is subject to a TAD or GDUFA I review goal, FDA will review both amendments by either the TAD or GDUFA I review goal or the GDUFA II review goal, whichever is longer, to facilitate review and ultimately decrease the number of review cycles.

Example: On June 8, 2017, an applicant submits an amendment in response to a CRL that identified major deficiencies in an ANDA. FDA determines that the amendment is subject to a standard review. FDA classifies the amendment as a major amendment requiring a preapproval inspection and sets a 10-month review goal. The review goal this amendment is April 7, 2018.

On February 16, 2018, the applicant submits an unsolicited amendment. FDA determines that the unsolicited amendment is subject to standard review. FDA classifies the amendment as a minor amendment and sets a 3-month review goal, which extends the current review goal. The review goal for both amendments is extended to May 15, 2018.

D. Amendments Submitted to Tentatively Approved Applications

As described in sections IV.A.3 and IV.B.3 of this guidance, unsolicited amendments submitted off-cycle are generally not reviewed and are not assigned a goal date until the applicant submits a solicited amendment. FDA will, however, review unsolicited amendments to ANDAs that have received tentative approval (TA), as described below.

1. Requests for Final Approval

A request for final approval with no new data, information, or other changes to the ANDA generally requires 90 days for FDA review. Accordingly, these requests for final approval should be submitted no later than 90 days prior to the date on which an applicant seeks final approval (i.e., a 90-day goal date will be set upon FDA's receipt of the request). It is therefore incumbent on the applicant to plan the request for final approval to coincide as close as possible to the earliest lawful approval date. If a request for final approval is submitted fewer than 90

days to the earliest lawful approval date, FDA may not approve the ANDA by the earliest lawful approval date because of inadequate review time.

A request for final approval with substantive changes to an ANDA, changes in the status of the manufacturing and/or testing facilities' compliance with current good manufacturing practices , or the addition of new facilities will be classified as a major or minor amendment based on the content in the submission and will be assigned the appropriate review goal date. The submission of multiple amendments prior to final approval may also delay the issuance of the final approval letter.

> *Example*: On November 4, 2019, an applicant submits a request for full approval to a tentatively approved ANDA. The request contains information about a new manufacturing site. FDA determines that the amendment is subject to a standard review and that the new manufacturing site requires a preapproval inspection. FDA classifies the request for full approval as a major amendment requiring preapproval inspection and sets a 10-month review goal. The review goal for this amendment is September 3, 2020.

2. Amendments Other Than Requests for Final Approval

If an applicant submits multiple amendments between the TA and when the applicant requests final approval, these amendments will be classified as unsolicited but may not be reviewed on submission. For example, FDA may delay review of an amendment to a tentatively approved ANDA for which the earliest lawful final approval date is not for several years (e.g., an ANDA with paragraph III certifications to patents that will not expire for 5 years).

FDA will not delay review of ANDA amendments submitted under the President's Emergency Plan for Aids Relief (PEPFAR) that have received TA because PEPFAR products are eligible for purchase with PEPFAR funds in developing countries. For amendments that FDA will review upon submission, including amendments to ANDAs for PEPFAR products, FDA will set a goal date consistent with the criteria outlined in section IV of this guidance.

> *Example*: On October 5, 2017, an applicant submits an unsolicited amendment to a tentatively approved ANDA for a PEPFAR product. The amendment contains information on a new container-closure system. FDA classifies the amendment as a minor amendment and sets a 3-month review goal. The review goal for this amendment is January 4, 2018.

E. Amendments Submitted in Response to Changes in the DMF

Changes made to a DMF referenced in an ANDA that may impact the safety, efficacy, quality, or substitutability of the drug product (e.g., new facilities added by the DMF holder that need to be addressed by the applicant in an amendment to the ANDA) may be considered unsolicited amendments to the ANDA and therefore may extend existing review goals or create new review goals.

VI. SUBMISSION AND RECEIPT OF AMENDMENTS

Any amendment submitted to FDA should identify on the first page that it is an amendment. To facilitate processing, FDA recommends that the applicant provide the following information on the first page of the submission, as appropriate:

- A statement indicating whether the amendment is unsolicited or in response to a review from FDA
- The discipline from which the IR/DRL was issued or the disciplines from which the CRL was issued
- The amendment classification (major or minor) as identified by FDA in a CRL
- If unsolicited, the amendment classification proposed by the applicant
- A statement indicating that the application should be classified as priority (including a justification for that classification)
- A statement indicating that the applicant is requesting priority review for the amendment (including a justification for that request)
- A statement indicating if and when a PFC was submitted in preparation for the amendment
- A statement indicating if the amendment is addressing a change in the DMF
- A statement indicating whether the amendment contains any manufacturing or facilities changes (e.g., new facilities or changes that are of the type identified on the FDA Form 356h, including changes in responsibilities for facilities already listed in the ANDA)

The regulatory project manager will issue the applicant an acknowledgment letter to confirm submission of the amendment. Most acknowledgment letters will be issued before the technical review of that amendment begins.[39] The acknowledgment letter will not state whether a preapproval inspection is required but will instead state two possible goal dates: the goal date with an inspection and the goal date without.

[39] If a previous amendment was subject to priority review, but a subsequent amendment is subject to standard review, FDA will notify the applicant of this change in classification within 14 days of receipt of the solicited amendment. GDUFA II Commitment Letter at 12.

VII. REQUESTS FOR RECONSIDERATION OF MAJOR AMENDMENT CLASSIFICATION STATUS

Applicants may request reclassification of their major amendment status via a teleconference with FDA. FDA will schedule and conduct the teleconference and decide 90 percent of such reclassification requests within 30 calendar days of the date of FDA's receipt of the request for a teleconference.[40] This goal applies only if an applicant accepts the first scheduled teleconference date offered by FDA.[41] Requests for reclassification should be submitted to the ANDA, with a copy to the appropriate signatory authority and to ANDAReconsideration@fda.hhs.gov.

Following resolution of a request for reconsideration, an applicant may pursue formal dispute resolution above the division level following the guidance for industry *Formal Dispute Resolution: Appeals Above the Division Level*.

[40] See GDUFA II Commitment Letter at 12-13.

[41] Id.

APPENDIX A: MAJOR DEFICIENCIES

This appendix contains a non-exhaustive list of examples of deficiencies that the Food and Drug Administration (FDA) may consider major. During either the course of submission review or the inspection of any facility referenced in a submission, data integrity issues related to any discipline(s) below may be found. If FDA, through further investigation or follow up, determines that the data supporting the submission is unreliable, FDA may consider the issue a major deficiency.

A. Pharmaceutical Quality Deficiencies

1. Drug Master File (DMF)

    a. Inadequate selection or justification of starting materials

    b. Toxicological studies are needed to qualify an unqualified impurity

    c. Reference to a secondary DMF which has not been reviewed, is currently inadequate, or requires submission of a technical dossier from a third party supplier with significant additional manufacturing information

    d. Failure to provide adequate analytical methods or method validation which would require significant new method development

    e. Insufficient physical or chemical characterization data to demonstrate structure, form, or drug substance sameness (especially for complex active pharmaceutical ingredients (APIs)) in the DMF

    f. Major change in drug substance manufacturing process with inadequate supporting data

    g. Requirement to manufacture a new API batch

2. Drug Product

    a. Toxicological studies are needed to qualify an unqualified impurity)

    b. Need new API source

    c. Post-filing addition of new API source

    d. A new strength of the finished dosage form added post filing

    e. Need new manufacturing site for finished dosage form

    f. Unacceptable physical properties for drug product

g. Need full-term stability data to establish expiration dating (failing accelerated, intermediate stability data)

h. Need new packaging system for product performance (current system is not delivering the proper dose (e.g., a device is needed for product performance))

i. Failure to provide analytical methods or method validation

j. Need substantial revision to proposed analytical methods (proposed method is not stability-indicating or is not discriminating enough to address product quality)

k. Need to identify or include critical quality attributes (CQAs) or methods for controlling them (e.g., CQAs related to nasogastric (NG) tube administration, abuse deterrence properties, as indicated in the reference listed drugs (RLD) labeling)

l. Failure to provide environmental assessment for plant-derived products, when needed

m. Insufficient data to demonstrate drug substance sameness (especially for complex drug products)

n. Insufficient data to support use-related risk analysis and any human factors studies associated with the proposed product

o. Insufficient data to support drug/device compatibility and sustainability for the proposed product

p. Need for safety assessment of extractables and leachables, inadequate assessment of extractables and leachables, or submission of that assessment in an unsolicited amendment

3. Process

a. Major change in drug product manufacturing process (e.g., change from wet to dry granulation)

b. Change in specification that would require changes to the manufacturing process

c. Significant differences between the manufacturing process proposed for commercial batches and exhibit batches

d. Size of exhibit batches is fewer than the minimum requirement, unless justified

e. Change in or lack of information about the form of the drug substance during drug product manufacturing, which could adversely affect CQAs of the drug product

f. Product quality adversely affected by interaction of API and excipients during manufacturing

g. Product quality adversely affected by inadequately scaling up manufacturing process (e.g., process parameters)

h. Commercial manufacture at risk by scaling up any unit operation >10 times

i. Requirement to manufacture a new batch (e.g., stability failure)

j. Significant differences between process descriptions, in-process controls, or scale-up information in Module 2 and Module 3

4. Microbiology

a. For terminally sterilized products, failure to provide sterilization validation data to support the terminal sterilization of the drug product

b. For aseptically filled products, failure to provide validation data to support the sterilization of the equipment or components utilized in production of the drug product

c. For aseptically filled products, failure to provide sterilization validation for the method proposed for sterilizing the drug solution (either drug substance or drug product) prior to aseptic filling (e.g., sterilizing filtration bacterial retention validation results)

d. For aseptically filled products, failure to provide media fill process simulation data supporting the use of the appropriate filling line/machine

e. For multi-dose products, failure to provide antimicrobial effectiveness test results

f. Failure to provide depyrogenation validation data for the container-closure system, when appropriate

g. Absence of finished product release or stability specifications, or excessively high specification acceptance criteria with no adequate justification (e.g., high bacterial endotoxins limit)

h. Failure to provide suitability studies, when appropriate, for finished product release/stability testing methods (e.g., bacterial endotoxins testing, sterility testing, or container closure integrity testing)

i. Need for safety assessment of extractables and leachables, inadequate assessment of extractables and leachables or submission of the assessment in a unsolicited amendment

5. Biopharmaceutics

a. Proposed in vitro release (e.g., dissolution) method or related analytical method, including development report and validation, is inadequate or lacking (i.e., new method is required)

b. Data supporting the proposed in vitro release acceptance criteria (e.g., in vitro in vivo correlation (IVIVC), data or in silico physiologically based pharmacokinetics (PBPK) modeling is inadequate)

c. Failure to include an in vivo study (e.g., bioequivalence, IVIVC, vasoconstrictor assay) when it is required for a post-approval change[42]

6. Facilities

a. All deficiencies issued from this discipline will be classified as major

B. Bioequivalence Deficiencies

1. Bioequivalence (BE)

a. Inadequate in vivo studies (pharmacokinetic (PK), pharmacodynamic (PD), or clinical) or in vitro BE studies (e.g., failed study, in vitro NG tube and gastronomy tube (G tube) testing, in vitro nasal/inhalation product testing, sampling times did not capture C_{max}, study outliers, wrong RLD used, metabolite data not supportive, T_{max}/T_{lag} issues, other PK or statistical issues) requiring submission of new studies

b. Inadequate physicochemical data for ophthalmic products, oral solutions, or injections, as needed

c. Deficiencies related to device comparability for nasal/inhalation products

d. Insufficient validation data

e. Reintegration of chromatograms (including manual reintegration)

[42] See guidances for industry *SUPAC-MR: Modified Release Solid Oral Dosage Forms; Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation*, and *Immediate Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation*.

f. Reanalysis of samples (e.g., due to contract/clinical research organization (CRO) issue, site issue, or analytical issue)

g. Insufficient justification for protocol deviations, such as inclusion or exclusion of subjects

h. Submission contains an in vivo study with serious adverse event, death, or different safety profile between the test product and RLD

i. Inadequate in vitro alcohol dose dumping dissolution testing or in vitro half tablet dissolution testing

j. Inadequate in vitro dissolution testing due to aged or expired batches

k. Information needed to address the impact of significant Office of Study Integrity Surveillance inspectional or review findings

l. Inadequate formulation (e.g., due to safety, capsule size, in vitro alcohol dose dumping)

m. Deficiencies related to excipients above inactive ingredient limit

n. Deficiencies related to sugar alcohol content in a drug product formulation (e.g., sugar alcohol content differs significantly from RLD)

o. Inadequate due to consult-related deficiencies including, but not limited to: insufficient data submitted to address safety issues (e.g., insufficient pharmacology/toxicology data to support the safety of the formulation); insufficient safety data to address tablet size, or a change in device/container closure; and insufficient information to address changes related to PK studies

p. Deficiencies related to changes in FDA's guidances for industry (e.g., new statistical analysis, new study design)

q. Inadequate information provided to support that the alternate method (e.g., deviation from recommendations in FDA's guidances for industry) is acceptable for demonstrating BE between products

2. Clinical Review

a. Failure to show statistical non-inferiority of the proposed product to the reference product in the skin irritation, sensitization, and adhesion study with regard to irritation potential or adhesive performance

b. Failure to show statistical non-inferiority of the proposed product's vehicle patch to the positive control (e.g., sodium lauryl sulfate) in the skin irritation and sensitization study with regard to irritation potentials

c. Failure to demonstrate BE of the test and reference products in the clinical BE endpoint study

d. Unacceptable clinical endpoint BE study due to incorrect endpoint selection, inappropriate dosing regimen selection, inappropriate treatment duration, or study population

e. Failure to demonstrate superiority of the test and reference products over placebo in the clinical endpoint BE study

f. Inadequate information provided to ensure the safety of the proposed formulation in clinical use

g. Inadequate information provided to support that the efficacy and safety of the proposed formulation would not differ from that of the reference product

h. The surrogate endpoint (or measurement scale/questionnaire) is not generally recognized as a validated measure for the indication

i. Unacceptable study data due to a concern about study conduct or data integrity

3. Pharmacology/Toxicology

a. Inadequate safety justification to ensure the proposed formulation's composition and specifications would have a similar safety profile as the RLD

i. Justification may include, but is not limited to nonclinical studies supporting the safety of the proposed drug substance or drug product (e.g., safety justification for an unqualified impurity or proposed excipient level, genetic toxicology data (*in silico*, in vitro, in vivo), general toxicology data, safety justification for residual solvents or product and process-related extractables and leachables)

4. Clinical Consultation

a. Inadequate information provided to ensure the safety of the proposed product in normal clinical use would not differ from that of the RLD

b. Inadequate information provided to support that the safety of the proposed formulation would not differ from that of the RLD

c. Inadequate information to support the safety of the inactive ingredients in the labeled population (e.g., safety in pediatric population)

d. Unknown safety of the inactive ingredients because it has not been used in other drug products with similar conditions of use

e. Inadequate information to ensure the side effects from the proposed inactive ingredient will not exacerbate the adverse events already reported for the RLD (e.g., polyethylene glycol (PEG) exacerbating diarrhea)

f. Potential safety risk due to capsule/tablet size or appearance or potential for change in a patient's use pattern compared to the RLD

g. Device or container-closure design issues may affect safety or efficacy

h. PK profile (e.g., T_{max}) is different from RLD and may affect safety or efficacy

5. Statistical

a. Failure to collect in the study the data required for necessary analyses

b. Unacceptable study data due to significant discrepancies between datasets or presence of spurious data

c. Lack of pre-specification of the analysis methods and statistical models to be used in the protocol and the statistical analysis plan

d. Failure for study to meet its objective using either the FDA-recommended method or a pre-specified, justified alternative method

e. Failure to resolve through information requests a major issue affecting the analysis results or the ability of the FDA reviewer to perform the analyses

C. Risk Evaluation and Mitigation Strategies (REMS) Deficiencies

1. REMS with ETASU

a. Abbreviated new drug application (ANDA) does not include a required REMS submission

b. REMS submission included in the ANDA has not been updated to reflect approved modifications to the REMS after ANDA submission

c. REMS submission does not contain elements as required by the REMS for the RLD or is missing information

d. There is no established single shared system REMS finalized for the drug product and/or FDA has not waived the single shared system requirement

D. Labeling Deficiencies

2. Labeling

a. Proposed labeling differs from the last approved labeling for the RLD, outside the scope of differences allowed under 21 CFR 314.94(a)(8)(iv)

b. Proprietary name request was denied and a new name was submitted for consideration

APPENDIX B: GUIDANCE FOR INDUSTRY, *MAJOR MINOR, AND TELEPHONE AMENDMENTS TO ABBREVIATED NEW DRUG APPLICATIONS*, REV. 2 (DEC. 2001)[43]

I. INTRODUCTION

This guidance is intended to document the Office of Generic Drugs' (OGD's) policy regarding the determination of major, minor, and telephone amendments to original *and supplemental* abbreviated new drug applications (ANDAs).[44] The guidance was originally entitled *Major, Minor, FAX, and Telephone Amendments to Original Abbreviated New Drug Applications* (revised May 2000). This guidance is a revision of the May 2000 guidance. Revision 2 of the guidance (1) deletes the FAX amendment designation, which was found to be unnecessary, (2) now applies to supplemental applications as well, and (3) changes the criteria for determining the type of amendment. The changes in criteria should result in more amendments being categorized as *minor* and fewer as *major*. A minor amendment request (generally reviewed within 30 to 60 days) has a higher priority than a major amendment. Since the review of a minor amendment takes place sooner than a major amendment after the original review, there is not a long break in the review process for a minor amendment. The response to a major amendment request, however, goes into the 180-day queue. This process causes a greater time lapse from when the original review was done and results in reviewers having to refamiliarize themselves with the application. It is expected that the new policy will help in moving applications through the approval process more quickly than under the previous policy. Thus the total time for approval of ANDAs will be reduced.

II. POLICY

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

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.

OGD classifies amendment requests to ANDAs as major, minor, or telephone. Major amendments have the same review priority as original, unreviewed ANDAs and are

[43] The GDUFA II Commitment Letter specifically references December 2001 guidance for industry *Major, Minor and Telephone Amendments to Abbreviated New Drug Applications* as a source for agreed definitions of major and minor amendments. See GDUFA II Commitment Letter at 26. When this draft guidance is finalized, that 2001 amendments guidance will be withdrawn. To assure continued agreement with respect to the definitions, FDA is making that guidance an appendix to this one. Please note that certain statements in the 2001 guidance no longer apply (e.g., the reference to the "180-day queue"), and this appendix should be consulted only with respect to the definitions of major and minor amendment.

[44] This includes revision and clarification of the policy stated in Policy and Procedure Guide (PPG) 38-93, "Restatement of the Office of Generic Drugs' 'First-In, First-Reviewed' Policy and Modification of the Exceptions to the Policy Regarding Minor Amendments," relating to original ANDAs and the policy stated in the guidance to industry *Major, Minor, FAX and Telephone Amendments to Original Abbreviated New Drug Applications*.

reviewed in accordance with OGD's first in-first reviewed procedure. Minor amendments have a higher priority than major amendments because they often mean an application is close to approval and should, therefore, be given priority. The issuance of major or minor amendment requests stops the review clock while the applicant addresses the deficiencies noted by OGD, but telephone amendment requests do not stop the clock unless the applicant does not respond within the specified time. Telephone amendments represent the reviewer's highest priority work assignments. Minor amendments are reviewed when the reviewer completes his or her current assignment.

B. When is an amendment classified as *major*?

Responses to the following examples of deficiencies would result in a major amendment. This should not be considered an all-inclusive listing.

1. Manufacture of a new batch of drug product (with supporting information) for any reason; for example:

   - Composition change or reformulation
   - Change in the source of a drug substance
   - Change in manufacturing site
   - Need for a new bioequivalence study (21 CFR 320.21)
   - New in vitro study for a specific product (e.g., metered dose inhalers)
   - Change in major manufacturing process
   - New strength of the product
   - Unacceptable impurities or impurity levels (21 CFR 314.94(a)(9))
   - Unacceptable excipients found during the review (21 CFR 314.94(a)(9))
   - Failed stability data
   - Change in the container-closure system (other than solid oral dosage forms)

2. New bioequivalence study (21 CFR 320.21) that is not related to manufacture of a new batch of the drug product

3. New analytical methods and full validation data (21 CFR 314.94(a)(9))

Any other circumstances that might be considered to be a major amendment should get division level concurrence, including an assessment that the application is of such overall poor quality that substantive review is not possible.

Many of the deficiencies that would be categorized as a major amendment for chemistry would also pertain to the sterility assurance and/or microbiology review (i.e., change in

facility or container-closure system). Generally, the microbiology review would not affect the designation determined through the CMC review. However, in rare instances, the sterility assurance and/or microbiology reviews, rather than chemistry, may determine the major amendment designation. This could occur, for example, when extensive validation work is necessary (21 CFR 314.94(a)(9)).

When is an amendment classified as minor?

Except for those amendments that are classified as *major* or *telephone,* amendments will be designated as *minor*. Minor amendments often consist of deficiencies that are outside the control of the applicant or deficiencies that are more easily addressed than those in a major amendment. Though most amendments will likely be *minor*, some examples include, but are not limited to:

1. Deficiencies in the drug master file (DMF)

2. Problems regarding good manufacturing practices (GMPs)

3. Incomplete dissolution data

4. Labeling deficiencies that have not been adequately addressed

Sterility assurance and/or microbiology issues that would likely take less than a full day to review would generally fall into the minor amendment category. However, as stated previously, the microbiology designation is determined by the chemistry review.

C. When is an amendment classified as a telephone amendment?[45]

If an amendment would otherwise be classified as *minor*, but the deficiencies are of a limited number or complexity, it can be classified as a telephone amendment at the discretion of the reviewer's team leader. Should this determination occur with the first review cycle of a new application, the division director's or the deputy division director's concurrence will be sought.

The applicant should provide a complete and satisfactory response within 10 calendar days of the call. Such deficiencies include:

1. Clarification of data already submitted

2. Request for a postapproval commitment

[45] OGD will accept only hard copies (2) of major and minor amendments for review (21 CFR 314.94). However, OGD will review responses to telephone amendments transmitted by facsimile provided the applicant also submits hard copies (2).

3. Final resolution of technical issues, such as finalization of specifications

To expedite the review, telephone amendments can also be requested during the final division or office level administrative review of an ANDA, immediately before tentative or final approval.

III. REVIEW CONSIDERATIONS

A. What are the timeframes for handling amendments?

OGD attempts to review major amendments within 180 days and to review minor amendments within 30 to 60 days. However, not all minor amendments can be reviewed within 60 days. The response to a telephone amendment is reviewed upon receipt.

B. When is an amendment redesignated?

There could be situations during 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 can be completed in different timeframes. If the chemistry review is completed first and it is appropriate, 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 redesignation of an amendment. For example, if an ANDA is in minor status for chemistry and it is subsequently determined that an in vivo bioequivalence study fails, a redesignation to major will occur. Redesignation to a minor amendment might also occur when a chemistry or microbiology telephone amendment request has not been responded to within 10 days of OGD's request.

C. What is the process for classifying an amendment?

Reviewers will conduct their reviews 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 tertiary reviews indicated. If an applicant requests reclassification of an amendment, the director or deputy will review that request. Applicants should respond to all requests for amendments on time and ensure that two hard copies are submitted (21 CFR 314.94) 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.