ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA

Guidance for Industry

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

September 2024
Generic Drugs
Revision 1

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Contains Nonbinding Recommendations

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

This guidance represents 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 office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to explain to applicants how the assessment goals established as part of the Generic Drug User Fee Amendments of 2022 (GDUFA III)[2] 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)).[3] This guidance describes amendment classifications and categories and explains how amendment submissions may affect an application's assessment goal dates. This guidance supersedes the July 2018 guidance for industry *ANDA Submissions – Amendments to Abbreviated New Drug Applications Under GDUFA.*

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.

[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. You may submit comments on this guidance at any time. Submit comments to Docket No. FDA-2017-D-5670 (available at https://www.regulations.gov/docket?D=FDA-2017-D-5670).

[2] See Title III of Division F (the FDA User Fee Reauthorization Act of 2022) of the Continuing Appropriations and Ukraine Supplemental Appropriations Act, 2023 (Public Law 117-180).

[3] 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 (Oct 6, 2016).

II. BACKGROUND

On July 9, 2012, the Generic Drug User Fee Amendments (GDUFA I) was signed into law.[4] GDUFA must be reauthorized every 5 years, and has been reauthorized two times since GDUFA I, most recently in the Continuing Appropriations and Ukraine Supplemental Appropriations Act, 2023. As described in the GDUFA III commitment letter[5] that accompanied the legislation, FDA has agreed to performance goals and program enhancements regarding aspects of the generic drug assessment program that build on the GDUFA program established and enhanced through previous authorizations. New enhancements to the program are designed to maximize the efficiency and utility of each assessment cycle, with the intent of reducing the number of assessment cycles for ANDAs and facilitating timely access to quality, affordable, safe, and effective generic medicines for American patients.

Under GDUFA III, FDA agreed to certain assessment goals and procedures for amendments under assessment as of or received on or after the GDUFA III effective date (i.e., October 1, 2022). The GDUFA III commitment letter reflects changes in the classification of and assessment goals for amendments to ANDAs and PASs under the Generic Drug User Fee Amendments of 2017 (GDUFA II). In general, GDUFA III amendments continue to be designated as either *standard* or *priority*,[6] 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 submission to an application under assessment to be an amendment. These submissions will be classified based on the content submitted and issued a goal date consistent with that classification, in addition to other considerations in the GDUFA III commitment letter. The types of amendments and assessment goals described in this guidance only apply to submissions that have been received for substantive assessment (i.e., assessment goals do not apply to submissions pending filing review).

Under GDUFA, FDA agreed to issue information requests (IRs) and/or discipline review letters (DRLs) for ANDAs.[7] If an amendment submitted in response to an IR or a DRL contains either information not requested by FDA (i.e., gratuitous information) or information that requires a more thorough assessment as determined by FDA (e.g., if the response contains new data or requires reanalysis, adds a new facility, and/or necessitates an internal consult between

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[4] Food and Drug Administration Safety and Innovation Act of 2012, (Public Law 112-144).

[5] The GDUFA III commitment letter titled "GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2023–2027" is available at https://www.fda.gov/media/153631/download.

[6] The terms *standard* and *priority* are defined in sections XI.X and XI.U, respectively, of the GDUFA III commitment letter. See also, section 505(j)(11)(A) of the FD&C Act and the Manual of Policies and Procedures 5240.3: Prioritization of the Review of Original ANDAs, Amendments, and Supplements, as revised, which describes how the assessment of original ANDAs, ANDA amendments, and ANDA supplements will be prioritized.

[7] Section II.B of the GDUFA III commitment letter. See the guidance for industry *Information Requests and Discipline Review Letters Under GDUFA* (October 2022). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

disciplines), the amendment will be classified as a minor or major amendment and the assessment goal will be adjusted accordingly from the submission date.[8] See section V of this guidance. Similarly, amendments that are administrative in nature and do not require a scientific assessment (i.e., *administrative amendments*) will generally not affect the goal date. See section III.C of this guidance.

III. CATEGORIES OF GDUFA AMENDMENTS

This guidance provides a detailed description of major and minor amendments. The sections below provide general descriptions and examples of the types of deficiencies that would classify an applicant's response to these deficiencies as a major or minor amendment. In addition, FDA has developed a non-exhaustive list of examples of major deficiencies, which is available in Appendix A.[9]

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 assessment, 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 or different formulation of the drug product

- Developing new analytical procedures[10] and providing full validation data

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 concurrence by the appropriate division director or their designee. This classification does not reflect the time it takes an applicant to respond to the complete response letter (CRL),

[8] 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.

[9] 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.

[10] This language is intended to align with terminology used by the International Council for Harmonisation and revisions to the Code of Federal Regulations.

IR, or DRL but is based on a determination by FDA that the content of the information or data provided will require extensive assessment.

B. Minor Amendments

Generally, minor amendments are those not classified as major or are a response to a deficiency that could be adequately resolved through an IR or certain DRLs. Minor amendments often consist of responses to deficiencies that are more easily addressed than those in a major amendment and typically require less extensive assessment by FDA.[11] Examples of minor amendments include responses to:

- Minor deficiencies in the drug substance
- Incomplete dissolution data
- Labeling deficiencies that have not been adequately addressed in response to an IR

C. Unsolicited Amendments

An *unsolicited amendment* is an amendment with information not requested by FDA except for those unsolicited amendments considered routine or administrative in nature that do not require scientific review (e.g., requests for final ANDA approval, patent amendments, and general correspondence).[12] The unsolicited amendment will be classified as either major or minor based on the content of the amendment. For example, if an unsolicited amendment contains information that addresses any of the major deficiencies identified in this guidance, the unsolicited amendment will be classified as major.

IV. ASSESSMENT GOALS

The GDUFA III commitment letter identifies the assessment goals for amendments submitted to ANDAs and PASs.[13] These assessment goals are based in part on whether the ANDA or PAS is subject to standard assessment or priority assessment and whether the amendment is classified as major or minor. Further, the setting of an assessment goal considers whether the submission requires a preapproval inspection and, if a priority submission does require a preapproval

[11] A previous FDA guidance from December 2001, that has since been withdrawn, described 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.

[12] Section XI.Z of the GDUFA III commitment letter.

[13] The assessment goals identified in this guidance apply to amendments to original ANDAs or PASs that are submitted either on or after Oct 1, 2022.

inspection, whether the applicant submitted a timely, complete, and accurate presubmission facility correspondence (PFC).[14]

A. Amendments to Original ANDAs

1. Major Amendments

a. ANDA amendments subject to standard assessment

FDA will assess and act on[15] 90 percent of standard major ANDA amendments within 8 months of the amendment submission date[16] if FDA does not require a preapproval inspection.[17] FDA will assess and act on 90 percent of standard major ANDA amendments within 10 months of the amendment submission date if FDA requires a preapproval inspection.[18]

Example: On November 27, 2024, 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 assessment. 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 assessment goal. Therefore, the assessment goal for this amendment is September 27, 2025.

Example: On July 24, 2024, an applicant submits an amendment in response to a Risk Evaluation and Mitigation Strategy IR. FDA determines that the amendment is subject to a standard assessment. FDA classifies the amendment as a major amendment that does not require a preapproval inspection and sets an 8-month assessment goal. Therefore, the assessment goal for this amendment is March 24, 2025.

b. ANDA amendments subject to priority assessment

FDA will assess and act on 90 percent of priority major ANDA amendments within 6 months of the amendment submission date if preapproval inspection is not required.[19] FDA will also assess

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[14] See the draft guidance for industry *ANDAs: Pre-Submission Facility Correspondence Related to Prioritized Generic Drug Submissions* (December 2022). When final, this guidance will represent FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

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

[16] 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* (February 2014).

[17] Section I.A.4.a of the GDUFA III commitment letter.

[18] Section I.A.4.b of the GDUFA III commitment letter.

[19] Section I.A.5.a of the GDUFA III commitment letter.

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 PFC not later than 60 days prior to the date of amendment submission and FDA finds the PFC to be complete and accurate.[20] Finally, FDA will assess 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) one or more of the following conditions occur:

- The applicant submits a PFC later than 60 days prior to the date of the amendment or does not submit a PFC,
- FDA finds that the information in a PFC is incomplete or inaccurate,
- The applicant submits information in the amendment that differs significantly from what the applicant submitted in the PFC, or
- FDA, upon assessment of a final BE study report submitted in the amendment, determines that an inspection of the relevant site or sites is necessary.[21]

Example: On December 20, 2024, an applicant submits an amendment in response to a CRL that identified major deficiencies in its ANDA. FDA determines that the submission is subject to a priority assessment. The applicant submitted a complete and accurate PFC on October 1, 2024. The applicant subsequently added a new facility and placed information about the new facility in its December 20, 2024, submission. FDA classifies the amendment as a major amendment requiring a preapproval inspection and sets a 10-month assessment goal. Therefore, the assessment goal for this amendment is October 20, 2025.[22]

2. Minor Amendments

FDA will assess and act on 90 percent of standard and priority minor ANDA amendments within 3 months of the amendment submission date.[23]

Example: On July 8, 2024, 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 assessment. FDA classifies the amendment as a minor amendment and sets a 3-month assessment goal. The assessment goal for this amendment is October 8, 2024.

[20] See footnote 13.

[21] Section I.A.6 of the GDUFA III commitment letter.

[22] If the Dec 20, 2024, submission did not contain a new facility and the complete and accurate PFC submitted on Oct 1, 2024, remained unchanged, FDA would have set an 8-month assessment goal.

[23] Section I.A.7 of the GDUFA III commitment letter.

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

Submission Type	Performance Goal
Standard major amendment to an ANDA	90% assessed within 8 months of the submission date if preapproval inspection is not required
	90% assessed within 10 months of the submission date if preapproval inspection is required
Priority major amendment to an ANDA	90% assessed within 6 months of the submission date if preapproval inspection is not required
	90% assessed within 8 months of the submission date if a preapproval inspection is required and the applicant meets requirements under section I(A)(5)(b) of the GDUFA III commitment letter
	90% assessed within 10 months of the submission date if a preapproval inspection is required and the applicant meets any limitations as described under section I(A)(6) of the GDUFA III commitment letter
Standard or priority minor amendment to an ANDA	90% assessed within 3 months of the submission date

3. Unsolicited Amendments

FDA will generally assess and act on an unsolicited ANDA amendment submitted during the assessment 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 assessment goals for standard and priority ANDAs.[24] FDA will generally assess and act on unsolicited ANDA amendments submitted between assessment cycles by the later of (1) the goal date for the subsequent solicited amendments or (2) the goal date assigned under the assessment goals for standard or priority ANDAs.[25,26]

Example: On August 1, 2024, 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 ANDA is subject to a priority assessment and sets an 8-month assessment goal. The assessment goal for this ANDA is April 1, 2025.

On October 15, 2024, the applicant submits an amendment containing a change in manufacturing site, but the applicant did not submit a PFC. FDA decides that the subject drug still meets the priority designation associated with the original ANDA. However, because the amendment contains a change to the manufacturing site information submitted in the original PFC, FDA classifies the amendment as a major amendment requiring a preapproval inspection and sets a 10-month assessment goal, which extends the assessment

[24] Section I.C.1 of the GDUFA III commitment letter.

[25] Section I.C.2 of the GDUFA III commitment letter.

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

goal of this ANDA. The assessment goal for this ANDA and amendment is August 15, 2025.

B. Amendments to PASs

1. Major Amendments

a. PAS amendments subject to standard assessment

FDA will assess and act on 90 percent of standard major PAS amendments within 6 months of the amendment submission date if preapproval inspection is not required.[27] FDA will assess and act on 90 percent of standard major PAS amendments within 10 months of the amendment submission date if preapproval inspection is required.[28]

Example: On March 3, 2024, 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 assessment. FDA classifies the amendment as a major amendment that does not require a preapproval inspection and sets a 6-month assessment goal. The assessment goal for this amendment is September 3, 2024.

b. PAS amendments subject to priority assessment

FDA will assess and act on 90 percent of priority major PAS amendments within 4 months of the amendment submission date if preapproval inspection is not required.[29] FDA will assess 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 not later than 60 days prior to the date of PAS submission, and FDA finds the PFC to be complete and accurate.[30] FDA will assess 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) one or more of the following conditions occur:

- The applicant submits a PFC later than 60 days prior to the date of PAS submission or does not submit a PFC,
- FDA finds that the information in a PFC is incomplete or inaccurate,
- The applicant submits information in the PAS that differs significantly from what the applicant submitted in the PFC, or

[27] Section I.B.3.a of the GDUFA III commitment letter.

[28] Section I.B.3.b of the GDUFA III commitment letter.

[29] Section I.B.4.a of the GDUFA III commitment letter.

[30] Section 1.B.4.b of the GDUFA III commitment letter.

- FDA, upon assessment of a final BE study report submitted in the PAS, determines that an inspection of the relevant site or sites is necessary.[31]

Example: On March 26, 2024, 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 assessment. 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 assessment goal. The assessment goal for this amendment is November 26, 2024.[32]

2. Minor Amendments

FDA will assess 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, 2024, 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 assessment goal. The assessment goal for this amendment is August 1, 2024.

Example: On June 10, 2024, the applicant submits an unsolicited amendment. FDA classifies the unsolicited amendment as a minor amendment and sets a 3-month assessment goal, extending the assessment goal for the current assessment. The assessment goal for both amendments is September 10, 2024.

[31] Section 1.B.4.c of the GDUFA III commitment letter.

[32] If FDA identifies a facility in the Mar. 26, 2024, submission that was not identified in the complete and accurate PFC, FDA will set a 10-month assessment goal.

[33] Section 1.B.5 of the GDUFA III commitment letter.

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

Submission Type	Performance Goal
Standard PAS	90% assessed within 6 months of the submission date if preapproval inspection is not required
	90% assessed within 10 months of the submission date if preapproval inspection is required
Priority PAS	90% assessed within 4 months of the submission date if preapproval inspection is not required
	90% assessed within 8 months of the submission date if preapproval inspection is required and applicant meets requirements under section I(B)(2)(b) of the GDUFA III commitment letter.
	90% assessed within 10 months of submission date if preapproval inspection is required and applicant meets any limitations as described under section I(B)(2)(c) of the GDUFA III commitment letter.
Standard PAS major amendments	90% assessed within 6 months of submission date if preapproval inspection is not required
	90% assessed within 10 months of submission date if preapproval inspection is required
Priority PAS major amendments	90% assessed within 4 months of submission date if preapproval inspection is not required.
	90% assessed within 8 months of submission date if preapproval inspection is required and applicant meets requirements under section I(B)(4)(b) of the GDUFA III commitment letter.
	90% assessed within 10 months of submission date if preapproval inspection is required and applicant meets any limitations as described under section I(B)(4)(c) of the GDUFA III commitment letter.
Standard or priority minor PAS amendments	90% assessed within 3 months of the submission date

3. Unsolicited Amendments

Like unsolicited amendments to ANDAs, FDA will generally assess and act on unsolicited PAS amendments submitted during the assessment 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 assessment PASs. FDA will generally assess and act on unsolicited PAS amendments submitted between assessment 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]

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

Example: On November 26, 2024, 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. Then, on January 15, 2025, 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 assessment goal and (2) the unsolicited amendment as a major amendment requiring a preapproval inspection with a 10-month assessment goal. Because the longest goal date (i.e., the 10-month goal) applies, the assessment goal for both amendments is November 15, 2025.[35]

V. APPLICATION OF ASSESSMENT GOALS

A. Changes to Classifications or Assessment 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 assessment 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 assessment of an unsolicited or solicited minor amendment, FDA will classify the submission as a major amendment and set an assessment goal of 10 months from the submission date.

Example: On November 13, 2024, 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 assessment. 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 assessment goal. The assessment goal for this amendment is September 13, 2025.

Example: On August 24, 2024, 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 assessment and that no preapproval inspection is required. FDA classifies the amendment as a major amendment and sets an 8-month assessment goal. The assessment goal for this amendment is April 24, 2025.

[35] When FDA receives an unsolicited amendment *after* a CRL is issued but *before* the applicant submits the amendment responding to that CRL, FDA does not calculate the assessment clock beginning from the date that it received the unsolicited amendment but, rather, from the date FDA receives the amendment responding to the CRL.

If an applicant does not submit a response to an IR or DRL within the time frame requested by FDA, FDA may reissue the contents of an IR or DRL as a deficiency in a CRL on completion of the current assessment cycle. If an applicant submits a response to an IR or DRL within the requested time frame, but the response contains either information not requested by FDA or information that requires a more extensive assessment as determined by FDA, FDA will classify the submission as a major or minor amendment and assign an appropriate new goal date for that amendment.

> *Example*: During the assessment 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 Form FDA 356h. On November 19, 2024, the applicant submits a timely response to the IR and provides an updated Form FDA 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 10-month assessment goal from the submission date. The assessment goal for this amendment is September 19, 2025.

Notification of a change in classification and change in the assessment goal 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 assessment cycle.[36] FDA will generally accept an unsolicited amendment submitted during the assessment cycle and adjust the goal date for the application. However, FDA may defer assessment of the unsolicited amendment if the discipline assessments are close to completion and either (1) the submitted amendment contains a significant amount of new information to be assessed or (2) the amendment is submitted after the relevant assessments 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 assessment. This discretion to assess or defer such amendments enables FDA to timely assess all GDUFA submissions. The assessment goal for unsolicited amendments is discussed in sections IV.A.3 and IV.B.3 of this guidance.

> *Example*: FDA is assessing an original ANDA with a goal date of November 13, 2024. On October 15, 2024, the applicant submits an unsolicited amendment containing a new source for the active pharmaceutical ingredient. The product quality assessment is complete, and FDA identified minor deficiencies for inclusion in a CRL. FDA determines that it will defer assessment of the unsolicited amendment until the applicant submits a response to the CRL.

[36] For responses to IRs or DRLs, if the Agency determines that it cannot assess a response before the goal date or if a CRL is otherwise ready to be issued, the assessment of the IR or DRL response may, in general, be deferred. See guidance for industry *Information Requests and Discipline Review Letters Under GDUFA* (October 2022) at 6.

FDA issues the CRL on November 1, 2024. The applicant submits its response to the CRL on December 30, 2024. FDA classifies the amendment in response to the CRL as a minor amendment with a 3-month assessment goal and classifies the unsolicited amendment as a major amendment requiring a preapproval inspection with a 10-month assessment goal. Because the longest assessment date applies (i.e., the 10-month goal), the assessment goal for both amendments is October 30, 2025.

C. Amendments Submitted to Tentatively Approved Applications

Unsolicited amendments submitted off-cycle are generally not assessed and are not assigned a goal date until the applicant submits a solicited amendment. FDA will, however, assess unsolicited amendments to ANDAs that have received tentative approval (TA), as described below.

1. Requests for Final Approval[37]

A request for final approval with no new data, information, or other changes to the ANDA generally requires 90 days for FDA assessment. 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 accurately plan the request for final approval. If a request for final approval is submitted fewer than 90 days prior to the earliest lawful approval date, FDA may not approve the ANDA by the earliest lawful approval date because of inadequate assessment 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 that adds new facilities will be classified as a major or minor amendment based on the content in the submission and will be assigned the appropriate assessment goal date. The submission of multiple amendments prior to final approval may also delay the issuance of the final approval letter. Applicants should assess the changes made to the application and updates to approval requirements or recommendations (e.g., reference listed drug labeling updates or updates to the United States Pharmacopeia monograph)[38] since the TA and consider the possible assessment goals that would be assigned to their request for final approval when determining the appropriate timing for submission of their request. This will help ensure that final approval is granted in a timely fashion to permit earliest lawful marketing.

Example: On November 3, 2024, an applicant submits a request for final 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 assessment and that the new manufacturing site requires a preapproval inspection. FDA classifies the request for

[37] See the guidance for industry *ANDA Submissions – Amendments and Requests for Final Approval to Tentatively Approved ANDAs* (January 2024).

[38] As new requirements are issued and recommendations are provided that impact received or tentatively approved ANDAs, applicants should amend their applications, as appropriate, to ensure FDA is able to take action in a timely manner.

final approval as a major amendment requiring preapproval inspection and sets a 10-month assessment goal. The assessment goal for this amendment is September 3, 2025.

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, and, in general, FDA will set an assessment goal consistent with the criteria outlined in section IV of this guidance. However, for certain amendments, FDA may delay assessment if the earliest lawful final approval date is not for several years. For example, FDA may delay assessment of a labeling update that does not require a change in patent certification for an ANDA with paragraph III certifications[39] to patents that will not expire for 5 years. FDA will not delay assessment of ANDA amendments submitted to applications under the President's Emergency Plan for AIDS Relief (PEPFAR) that have received TA because PEPFAR products that have been tentatively approved are eligible for purchase with PEPFAR funds in developing countries. For amendments that FDA will assess 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, 2024, an applicant submits an unsolicited amendment to a tentatively approved ANDA for a PEPFAR tablet product. The amendment contains information on a new container-closure system. FDA classifies the amendment as a minor amendment and sets a 3-month assessment goal. The assessment goal for this amendment is January 5, 2025.

D. Amendments Submitted in Response to Changes in the Drug Master File

Changes made to a drug master file (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 assessment goals or may result in a CRL being issued to the ANDA.

VI. SUBMISSION AND RECEIPT OF AMENDMENTS

FDA encourages applicants to follow FDA guidance on cover letters for ANDA submissions, including amendments.[40] 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:[41]

[39] See FDA's guidance cited in footnote 37.

[40] For additional background, see also the guidance for industry *Cover Letter Attachments for Controlled Correspondences and ANDA Submissions* (June 2023).

[41] Ibid.

- A statement indicating whether the amendment is unsolicited or in response to an assessment 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, IR, or DRL
- 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 assessment 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 Form FDA 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 assessment of that amendment begins.[42] 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 an inspection.

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

[42] If a previous amendment was subject to priority assessment, but a subsequent amendment is subject to standard assessment, FDA will notify the applicant of this change in classification within 14 days of receipt of the solicited amendment. See section II.C.1 of the GDUFA III commitment letter.

teleconference.[43] This goal applies only if an applicant accepts the first scheduled teleconference date offered by FDA.[44] Requests for reclassification should be submitted to the ANDA with a copy to the appropriate signatory authority to ANDAReconsideration@fda.hhs.gov.

Following final decision of a request for reconsideration at the division level, an applicant may pursue formal dispute resolution above the division level following the guidance for industry and assessment staff *Formal Dispute Resolution: Sponsor Appeals Above the Division Level* (May 2019).

[43] See section II.C.5 of the GDUFA III commitment letter. See also the draft guidance for industry *Requests for Reconsideration at the Division Level Under GDUFA* (January 2024). When final, this guidance will represent FDA's current thinking on this topic. For facility reclassification requests from major to minor, see section II.C.7 of the GDUFA III commitment letter. See also the Manual of Policies and Procedures (MAPP) 5021.5 *Assessment of Facility-Based Deficiency Major-to-Minor Reclassification Requests*. MAPPs can be found on the Manual of Policies and Procedures web page at https://www.fda.gov/about-fda/center-drug-evaluation-and-research/cder-manual-policies-procedures-mapp.

[44] Ibid.

APPENDIX A: POTENTIAL MAJOR DEFICIENCIES

This appendix contains a non-exhaustive list of examples of deficiencies that the Food and Drug Administration (FDA) may consider major. The determination of whether an application is issued a major or minor deficiency will be in the judgment of the relevant assessment discipline. Where appropriate, FDA will attempt to resolve possible deficiencies identified during the assessment cycle through information requests (IRs) and discipline review letters (DRLs) prior to sending them in a complete response letter (CRL). Unresolved deficiencies will result in a major or minor CRL.[1]

A. Pharmaceutical Quality Deficiencies

1. Drug Substance

    a. Inadequate selection or justification of starting materials that will likely result in a redesignation of the starting material

    b. Toxicological studies are needed to qualify an unqualified impurity in the drug substance

    c. Reference to an unreviewed secondary drug master file (DMF) or inclusion of a technical dossier from a third-party containing significant additional manufacturing information, which is introduced after the initial review of the primary DMF

    d. Stability-indicating or sensitive analytical methods that are not fit for purpose and require a new method to be developed and validated (or significant changes resulting in revalidation of the method), new certificates of analysis, and repeated and/or reassessed stability studies

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

    f. Significant change in the drug substance manufacturing process that provides new information to be assessed by FDA

    g. API batch inadequacies that require manufacture and testing of a new API batch

[1] Sometimes the relevant assessment discipline must internally consult with other FDA offices to complete its assessment. As noted in section II.B of the GDUFA III commitment letter, consults require significant assessment resources and generally result in a major deficiency.

2. Drug Product

    a. Toxicological studies[2] are needed to qualify an unqualified impurity in the drug product

    b. Original API source is replaced with new source

    c. A new API source is added after receipt

    d. A new strength of the finished dosage form is added after receipt[3]

    e. A new manufacturing site is needed for the finished dosage form

    f. Unacceptable physical properties for drug product (e.g., physical properties that may affect drug safety or efficacy)

    g. Additional long-term stability data is needed to establish expiration dating (failing accelerated and intermediate stability data)

    h. A new drug delivery system is needed to ensure product performance (e.g., current delivery system is not delivering the proper dose, for example, with auto injectors)

    i. Substantial revision to proposed analytical procedure is needed (e.g., proposed procedure is not stability-indicating or is not discriminating enough to address product quality such that stability studies will likely need to be repeated and reassessed)

    j. Identification or inclusion of new critical quality attributes (CQAs) or methods for controlling them is needed (e.g., CQAs related to nasogastric tube administration or abuse deterrence properties, as indicated in the reference listed drug (RLD) labeling)

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[2] Preclinical studies should not be required to support approvability of an abbreviated new drug application (ANDA). Published and publicly available preclinical data to support the effectiveness of a requested change, impurity, or level of excipient can be submitted to an ANDA as justification. The adequacy of this data will be assessed by FDA. The need for new preclinical studies suggests that an ANDA may not be the appropriate submission pathway for the proposed drug product. See 54 FR 28872 at 28880 (Jul. 10, 1989). See also the guidance for industry *Determining Whether to Submit an ANDA or a 505(b)(2) Application* (May 2019). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[3] For the definition of *additional strength*, see the Manual of Policies and Procedures (MAPP) 5200.7 Rev. 1 *ANDA Amendments and Supplements Reviewed by the Division of Filing Review.* MAPPs can be found on the Manual of Policies and Procedures web page at https://www.fda.gov/about-fda/center-drug-evaluation-and-research/cder-manual-policies-procedures-mapp.

k. Failure to provide environmental assessment for plant-derived products, when needed[4]

l. Insufficient data to demonstrate drug substance sameness (especially for complex APIs)

m. Insufficient data to support use-related risk analysis, including any human factors studies associated with the proposed product

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

o. A safety assessment of extractables and leachables is needed, assessment of extractables and leachables is inadequate, or submission of that assessment was made in an unsolicited amendment

p. A new batch needs to be manufactured due to formulation issues (e.g., nitrosamine impurity mitigation or other product stability issues)

3. Process

a. Significant change to the drug product manufacturing process to address an unresolved quality risk (e.g., change of manufacturing unit operation from wet to dry granulation to address formation of a degradant)

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

c. Significant differences between the manufacturing process proposed for commercial batches and exhibit batches (e.g., major change in the control strategy or equipment)

d. Change in or lack of information about the form of the drug substance during drug product manufacturing, which requires the manufacture of a new batch to demonstrate the CQAs are not affected

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

[4] At the filing stage, FDA assesses whether the ANDA contains either an environmental assessment or a claim of categorical exclusion in determining whether the application is substantially complete. If neither is provided, this would generally result in a minor deficiency. See the guidance for industry *ANDA Submissions – Refuse-to-Receive Standards* (December 2016). However, FDA does not substantively assess claims of categorical exclusion at the filing stage. After filing, if FDA determines an environmental assessment is needed and if the applicant did not provide one, this would generally be a major deficiency. This is a very rare occurrence.

f. Inadequately justified scale-up of a unit operation that impacts the manufacturer's ability to manufacture at commercial scale

g. Change in overall control strategy that adversely impacts product quality due to interaction of API and excipients during manufacturing

h. A new batch needs to be manufactured due to significant changes in the manufacturing process (e.g., a change from dry to wet granulation)

i. Discrepancies in the process description, in-process control, or scale-up information provided in the submission that remain outstanding at the end of the assessment cycle

j. Extractable and leachable data requires a safety assessment

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 multidose products, failure to provide either antimicrobial effectiveness test results or information to describe and demonstrate validation of a specially designed container-closure system that prevents microbial ingress during the product's in-use period

f. Failure to provide depyrogenation validation data for the container-closure system when the product has an endotoxins specification for release and/or stability

g. Failure to provide method validation studies for proposed noncompendial finished product release/stability testing (e.g., bacterial endotoxins testing, sterility testing, or container-closure integrity testing)

h. Reference to a DMF that is inadequate with respect to certain microbiological quality issues such as failure to provide sterilization validation information

5. Biopharmaceutics

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

    c. Failure to include an in vivo study (e.g., bioequivalence (BE), IVIVC, vasoconstrictor assay) when it is recommended for a postapproval change[5]

6. Facilities[6]

    a. One or more facilities were found inadequate[7]

    b. The facility was not clearly identified in Form FDA 356h at the time of submission. Identification of the facility after detailed review does not permit sufficient time to conduct a preapproval inspection or facility evaluation.

B. BE Deficiencies

1. BE

    a. Inadequate or insufficient in vivo or in vitro BE studies requiring submission of new studies

    b. Inadequate physicochemical data

    c. Deficiencies related to device comparability for nasal/inhalation products that require consult to other offices within the Agency or require additional BE studies

    d. Insufficient validation data that would require extensive review of resubmitted data and/or development of new analytical procedures with full validation data

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[5] See guidances for industry *SUPAC-MR: Modified Release Solid Oral Dosage Forms; Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation* (October 1997) and *SUPAC-IR: Immediate Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (November 1995).

[6] In addition to the deficiencies identified in this section, FDA will classify any amendment that provides for a new facility that requires comprehensive evaluation as a major amendment.

[7] Applicants can request an amendment be reclassified from major to minor if the facility issue or issues are resolved and the only major deficiency was related to facilities. See the MAPP 5021.5 *Assessment of Facility-Based Deficiency Major-to-Minor Reclassification Requests.*

e. Reintegration of chromatograms that may result in method revalidation

f. Reanalysis of samples required due to contract/clinical research organization issue, site issue, analytical issue, inadequate justification for reanalysis of samples, or other significant issues

g. Insufficient justification for protocol deviations that could impact the BE determination

h. Submission contains an in vivo study with a serious adverse event(s) or death(s) possibly related to test product

i. Inadequate in vitro dissolution testing or in vitro alcohol dose dumping study data resulting from, for example, the use of aged or expired batches or inadequate study methodology

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

k. Inadequate formulation and/or recommendation to reformulate

l. Deficiencies identified during the technical review related to excipient intake above the limit in the Inactive Ingredient Database without adequate justification

m. Deficiencies related to sugar alcohol content in a drug product formulation (e.g., sugar alcohol content differs substantially from the RLD) in cases where an in vivo comparative study is not conducted, or adequate justification is not provided

n. Consult-related deficiencies found including, but not limited to: insufficient information submitted to address safety issues (e.g., insufficient pharmacology/toxicology information to support the safety of the formulation); insufficient information to address tablet size, or a change in device/container closure; and insufficient information to support alternative study designs in relation to the product-specific guidance

o. Deficiencies related to changes in FDA's guidances for industry that result in inadequate in vivo and/or in vitro BE studies

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

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

2. Clinical BE

    a. Failure to show statistical noninferiority of the proposed product to the reference standard in the skin irritation, sensitization, and adhesion study with regard to irritation potential or adhesive performance for topical and transdermal delivery system (TDS) products

    b. When applicable, failure to show statistical noninferiority of the vehicle TDS product to the positive control (e.g., sodium lauryl sulfate) in the skin irritation and sensitization study with regard to irritation potentials[8]

    c. Failure to demonstrate BE of the test product and reference standard in the comparative clinical endpoint BE study

    d. Unacceptable comparative 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 product and reference standard over placebo in the comparative clinical endpoint BE study

    f. Wrong RLD or reference standard used in the comparative clinical endpoint BE study

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

    h. 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)

[8] See the draft guidance for industry *Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs* (April 2023). When final, this guidance will represent FDA's current thinking on this topic.

4. Clinical Consultation

    a. Inadequate information provided to ensure the safety of the proposed product in labeled clinical use would not differ from that of the RLD (e.g., proposed product contains different instructions for use than 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) or labeled duration of dosing (e.g., long term treatment vs short course therapy)

    d. Unknown safety of an inactive ingredient because it has not been used in other drug products with similar conditions of use or target populations

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

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

    g. Pharmacokinetics profile differs from RLD in a clinically significant way that may affect safety or efficacy

5. Clinical

    a. Missing or incomplete comparative analyses report

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

6. 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 prespecification of the analysis methods and statistical models to be used in the protocol and the statistical analysis plan

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

e. Failure to resolve through IRs a major issue affecting the analysis results or the ability of the FDA assessor to perform the analyses

C. Risk Evaluation and Mitigation Strategy Deficiencies

1. Risk evaluation and mitigation strategy (REMS) with elements to assure safe use

    a. Inadequate or missing proposed REMS submission[9]

D. Labeling Deficiencies

1. Labeling

    a. Proposed labeling differs substantially from the last approved labeling for the RLD, outside the scope of differences allowed under 21 CFR 314.94(a)(8)(iv) (e.g., applicant is proposing a new labeling component that does not align with the RLD)

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

[9] For more information, see the draft guidances for industry *Development of a Shared System REMS* (June 2018) and *Use of a Drug Master File for Shared System REMS Submissions* (November 2017). When final, these guidances will represent FDA's current thinking on these topics.