
POLICY AND PROCEDURES

OFFICE OF PHARMACEUTICAL QUALITY

Assessment of Facility-Based Deficiency Major-to-Minor Reclassification Requests

Table of Contents

PURPOSE1
BACKGROUND.....2
POLICY2
RESPONSIBILITIES4
PROCEDURES6
EFFECTIVE DATE11
CHANGE CONTROL TABLE.....11
 ATTACHMENT: Generic Drug User Fee Amendments
 Submission Types and Goal Dates12

PURPOSE

- This MAPP describes the policies and procedures used in the Office of Pharmaceutical Quality (OPQ), the Office of Compliance, and the Office of Generic Drugs (OGD) for the assessment of requests for reclassification of facility-based major complete response (CR) letter amendments (referred to as facility-based deficiency major-to-minor reclassification requests elsewhere) for original abbreviated new drug applications (ANDAs) and associated prior approval supplements (PASs).
- This MAPP applies to reclassification requests received as part of a single amendment that consists of both a reclassification request for facility-based deficiencies¹ and a response to a CR letter in which the only major deficiency or deficiencies in the CR letter resulted from a facility inspection(s) or assessment.
- This MAPP applies only to requests for major-to-minor reclassifications for CR letters issued on or after October 1, 2022 (the implementation date of the Generic Drug User Fee Amendments of 2022 program (GDUFA III)).²

¹ There could be more than one official action indicated for a facility issue leading to a major complete response.

² See the GDUFA III commitment letter titled “Reauthorization Performance Goals and Program Enhancements Fiscal Years 2023-2027” available on the FDA website at <https://www.fda.gov/media/153631/download>.

BACKGROUND

- The Generic Drug User Fee Amendments of 2012 (GDUFA I)³ amended the Federal Food, Drug, and Cosmetic Act to authorize FDA to assess and collect user fees to provide FDA with resources⁴ to help ensure patients have access to quality, affordable, safe, and effective generic drugs. GDUFA fee resources bring greater predictability and timeliness to the review of generic drug applications. GDUFA has been reauthorized every 5 years to continue FDA's ability to assess and collect GDUFA fees, and this user fee program has been reauthorized two times since GDUFA I, most recently in the Generic Drug User Fee Amendments of 2022.⁵ As described in the GDUFA III commitment letter applicable to this latest reauthorization,⁶ FDA has agreed to performance goals and program enhancements regarding aspects of the generic drug assessment program that build on previous authorizations of GDUFA. 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 generic medicines for American patients.
- In accordance with the GDUFA III commitment letter, when OPQ and OGD staff receive and accept an amendment that consists of a facility-only major-to-minor reclassification request and a response to the CR letter, they work collaboratively to determine whether to grant or deny the request.

POLICY

- FDA will accept for review a request for reclassification from major to minor if:
 - The CR letter was issued on or after October 1, 2022 (the implementation date of GDUFA III).⁷
 - The reclassification request is submitted with a CR letter response amendment in a single submission.
 - The facility issue is the only major deficiency.

³ Title III of the Food and Drug Administration Safety and Innovation Act, Public Law 112-144.

⁴ User fees are available for obligation in accordance with appropriations Acts.

⁵ Enacted as Title III of Division F (the FDA User Fee Reauthorization Act of 2022) of the Continuing Appropriations and Ukraine Supplemental Appropriations Act, 2023.

⁶ See footnote 2.

⁷ Ibid.

-
- The CR letter’s major amendment classification is based on observations from a surveillance inspection (e.g., official action indicated (OAI) classification of a facility from a surveillance inspection). This includes surveillance inspections conducted by foreign regulatory authorities where the information is shared under a mutual recognition agreement.⁸
 - The reclassification request is easily identified in the cover letter for the amendment submitted in response to the CR letter.
 - FDA determines that the words “Facility-Only Reclassification Request” are included in the submission.
 - FDA verifies that the submission includes one of the following:
 - The voluntary action indicated (VAI) or the no action indicated (NAI) current good manufacturing practice (CGMP) classification letter issued by FDA to the facility or facilities subsequent to the OAI classification referenced in the CR letter⁹
 - If the OAI facility or facilities are being withdrawn, a statement verifying that the facility or facilities are being withdrawn and that the withdrawn¹⁰ facility or facilities did not generate data to support a regulatory action (e.g., exhibit batches, stability batches)
 - The CR letter is less than 1 year old¹¹ (from the date the CR letter was signed), or it is more than 1 year old and one of the following applies:
 - The product is on the drug shortage list or is a public health emergency product.
 - The facility deficiency is the only deficiency in the CR letter (i.e., the facility issue is the only (i.e., single) major deficiency, and there are no minor deficiencies).

⁸ Mutual recognition agreements between FDA and foreign regulatory authorities allow drug inspectors to rely on information from drug inspections conducted within each other’s borders (available at <https://www.fda.gov/international-programs/international-arrangements/mutual-recognition-agreement-mra>).

⁹ See Q5 of the *Questions and Answers: Integration of FDA Facility Evaluation and Inspection Program for Human Drugs: A Concept of Operations* FDA web page (available at <https://www.fda.gov/drugs/pharmaceutical-quality-resources/questions-and-answers-integration-fda-facility-evaluation-and-inspection-program-human-drugs-concept>).

¹⁰ When a facility is withdrawn from an application, data generated by that facility can no longer serve as the primary basis of approval (see 21 CFR 314.94), even if the data remains in the electronic common technical document as supportive information.

¹¹ See Section II.C.6. of the GDUFA III commitment letter.

-
- If accepted for review based on the above criteria, FDA will grant the request for reclassification only when FDA determines that the facility issues have been addressed (e.g., facility has been classified as an NAI or a VAI), and there is no need for an inspection or an alternative tool to resolve facility issues for the subject drug.¹²
 - FDA will generally **deny** a request for reclassification from major to minor if:
 - The facility CR deficiency was issued based on an inspection other than a surveillance inspection or assessment (e.g., a withhold recommendation based on a preapproval inspection (PAI) or the use of alternative tools).¹³
 - The facility deficiency has not been adequately resolved for the subject drug (e.g., FDA intends to conduct additional follow-up to verify that a corrective and preventive action(s) plan(s) was appropriate and fully implemented).
 - The facility or facilities that are the subject of the major deficiency are being withdrawn and generated data to support a regulatory action. In such cases, because data from those facilities can no longer serve as the primary basis of approval, FDA will need to assess the impact of the withdrawal or withdrawals on the completeness of the application. This assessment will require significant time and resources.
 - The submission does not include the VAI or the NAI CGMP classification letter issued by FDA.
-

RESPONSIBILITIES

OGD Responsibilities

- **The Office of Regulatory Operations (ORO) will:**

For OGD-Managed Submissions:

- Triage the facility-only major-to-minor reclassification request and assign it to OPQ's Office of Program and Regulatory Operations (OPRO).

¹² In certain cases, the Office of Pharmaceutical Quality should confirm with the Office of Manufacturing Quality in the Office of Compliance to ensure that there is no need for an inspection or use of an alternative tool to evaluate a facility before reclassification.

¹³ See the draft guidances for industry *Conducting Remote Regulatory Assessments Questions and Answers* (July 2022) and *Alternative Tools: Assessing Drug Manufacturing Facilities Identified in Pending Applications* (September 2023). When final, these guidances will represent the 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>.

-
- Draft a formal correspondence that includes acknowledgment of the reclassification request and issue it to the applicant.
 - Provide an update to the OPQ assessment team on the prioritization decision that determines whether the request has a 30- or 60-day decisional period (referred to as decisional period elsewhere).
 - Draft the final grant or deny decision and issue it to the applicant.

OPQ Responsibilities

- **OPRO will:**

- Assign the facility-only major-to-minor reclassification request to the regulatory business process manager (RBPM).

For OGD-Managed Submissions:

- **The RBPM will:**

- Assign the reclassification request and notify OPQ's Office of Pharmaceutical Manufacturing Assessment (OPMA) to evaluate the reclassification request.
- Review the rationale for OPMA's grant or deny decision.

For OPQ-Managed Requests for Chemistry, Manufacturing, and Controls Supplements:

- **The RBPM will:**

- Draft a formal correspondence that includes acknowledgment of the reclassification request and issue it to the applicant.
- If applicable, provide an update to the OPQ assessment team on the prioritization decision that determines whether the request has a 30- or 60-day decisional period.
- Draft the final grant or deny decision and issue it to the applicant.

- **OPMA will:**

- Confirm the current status of the facility or facilities identified in the reclassification request and determine whether to grant or deny the request where the facility or facilities are not being withdrawn.

- Confirm that the facility did not manufacture or conduct analyses associated with one or more batches that are intended to support approval of the application where the facility or facilities are being withdrawn.
- If the reclassification request is denied, provide the rationale to the RBPM to include in the denial letter.

Office of Compliance Responsibilities

- **The Office of Manufacturing Quality (OMQ) will:**
 - Provide input on the classification status of the facility when requested by OPMA.
-

PROCEDURES

Original ANDAs and OGD-Managed ANDA PASs

1. The ORO regulatory project manager (RPM) receives and reviews the amendment submission cover letter for the facility-only major-to-minor reclassification request.
2. The ORO RPM determines whether to accept or not accept the reclassification request for review. The ORO RPM accepts the request for review if all the criteria in bulleted items a) through f) are met:
 - a) The reclassification request is submitted with a CR letter response amendment in a single submission.
 - b) The reclassification request is submitted with the VAI or the NAI CGMP classification letter issued by FDA to the facility, or a statement is provided indicating that the facility is being withdrawn and did not manufacture batches or conduct analyses intended to support approval of the application.
 - c) The reclassification request is easily identified by inclusion of the words “Facility-Only Reclassification Request” in the cover letter for the amendment submitted in response to the CR letter.
 - d) The reclassification request is specific to a facility deficiency, and that specific deficiency is the only basis for the CR letter’s major classification. (Amendment may contain other minor deficiencies, except as noted below for a CR letter that is more than 1 year old and does not meet other criteria for acceptance.)

-
- e) The CR letter was issued on or after October 1, 2022 (the implementation date of GDUFA III).¹⁴
 - f) The CR letter is less than 1 year old at the time the request for reclassification is submitted (from the date the CR letter was signed), or it is more than 1 year old and one of the following applies:
 - 1) The product is the subject of a response to a public health emergency as declared by the Secretary of the U.S. Department of Health and Human Services under section 319 of the Public Health Service Act (42 U.S.C. 247d).
 - 2) The product is on the drug shortage list under section 506E of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356e).
 - 3) The facility deficiency is the only deficiency in the CR letter (i.e., the facility issue is the only major deficiency (i.e., single), and there are no minor deficiencies).
- 3. The ORO RPM triages the CR letter amendment that includes the reclassification request.
 - 4. The ORO RPM notifies the applicant via a formal correspondence indicating whether its reclassification request is accepted for review and provides a decisional date indicating when the reclassification request decision will be made.
 - 5. The ORO RPM notifies OPRO of the facility-only deficiency major-to-minor reclassification request and the decisional period (based on the priority or standard designation)¹⁵ by assigning it to OPRO.
 - 6. OPRO assigns the reclassification request to the RBPM. Then, the RBPM assigns the reclassification request to an OPMA assessor(s) for review.
 - 7. The assigned OPMA assessor evaluates the reclassification request by determining whether the facility deficiency, including any deficiency pertaining to the specific application, is resolved (including the impact of a facility withdrawal, if applicable).
 - a) If the deficiency is resolved, the assessor determines whether a PAI or the use of alternative tools is required to complete the assessment of the facility. If further assessment via an inspection or the use of alternative tools is not necessary in support of the application, the request will be granted.

¹⁴ See footnote 2.

¹⁵ See MAPP 5240.3 Rev. 6 *Prioritization of the Review of Original ANDAs, Amendments, and Supplements* (available at <https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cder-manual-policies-procedures-mapp>).

-
- b) If the deficiency remains unresolved or if a PAI or the use of alternative tools is necessary to address the current concerns, the request will be denied. If the most recent facility inspection designation was VAI, but FDA is continuing to evaluate the facility's remediation of prior OAI deficiencies, OPMA consults with the assigned OMQ compliance officer. Within the agreed-upon timeline, OMQ provides this information to OPMA. (Note: This step does not apply to withdrawn facilities.)
- c) If the facility or facilities that are the subject of the major deficiency are being withdrawn and were listed on Form FDA 356h¹⁶ and did not generate data to support the primary basis for approval, the request will be granted (e.g., withdrawal of an alternate facility).
- d) If the facility or facilities that are the subject of the major deficiency are being withdrawn and generated data to support a regulatory action, data from those facilities can no longer serve as the primary basis of approval. In this case, the OPMA assessor evaluates the impact of the withdrawal or withdrawals on the completeness of the application. This assessment will require significant time and resources; consequently, the request should be denied.
8. The OPMA assessor communicates to the OPRO RBPM the decision regarding whether to grant or deny the request. If the decision is to grant the request, the OPMA assessor will reach out to OMQ, as needed, for input on the final classification decision. Regardless of the outcome, the OPMA assessor documents the decision and rationale in a memo and uploads the memo to the archival database.
9. OPRO informs the ORO RPM of the decision.
10. The ORO RPM drafts and issues to the applicant the decisional letter that includes the applicable GDUFA goal date of the ANDA amendment(s)¹⁷ as stated in the GDUFA III commitment letter. See tables 1 and 2 in the Attachment, Generic Drug User Fee Amendments Submission Types and Goal Dates.

¹⁶ See Form FDA 356h, available at <https://www.fda.gov/media/72649/download>.

¹⁷ The Office of Regulatory Operations regulatory project manager reviews and processes solicited and unsolicited ANDA or drug master file amendments independently from the facility-based major-to-minor reclassification request, including those that are received during the reclassification decisional period. In addition, the Office of Regulatory Operations regulatory project manager reviews and classifies any content deemed as major within the complete response letter response containing the facility-based reclassification request independently from the facility-based reclassification request. If any such amendment or major content affects the GDUFA goal date, the Office of Regulatory Operations regulatory project manager issues an acknowledgment letter after issuing the facility-based reclassification grant or deny letter.

OPQ-Managed ANDA PASs

1. OPRO receives the facility-only major-to-minor reclassification request and assigns it to the RBPM.
2. The OPRO RBPM reviews the cover letter and determines whether to accept or not accept the reclassification request for review. The OPRO RBPM accepts the reclassification request for review if all the criteria in bulleted items a) through f) are met:
 - a) The reclassification request is submitted with a CR letter response amendment in a single submission.
 - b) The reclassification request is submitted with the VAI or the NAI CGMP classification letter issued by FDA to the facility, or a statement is provided indicating that the facility is being withdrawn and did not manufacture batches or conduct analyses intended to support approval of the application.
 - c) The reclassification request is easily identified by inclusion of the words “Facility-Only Reclassification Request” in the cover letter for the amendment submitted in response to the CR letter.
 - d) The reclassification request is specific to a facility deficiency, and that specific deficiency is the only basis for the CR letter’s major classification. (Amendment may contain other minor deficiencies, except as noted below for a CR letter that is more than 1 year old and does not meet other criteria for acceptance.)
 - e) The CR letter was issued on or after October 1, 2022 (the implementation date of GDUFA III).¹⁸
 - f) The CR letter is less than 1 year old at the time the request for reclassification is submitted (from the date the CR letter was signed), or it is more than 1 year old and one of the following applies:
 - 1) The product is the subject of a response to a public health emergency as declared by the Secretary of the U.S. Department of Health and Human Services under section 319 of the Public Health Service Act or is anticipated to be subject to the same criteria as applied to such a declaration at the time of submission.
 - 2) The product is on the drug shortage list under section 506E of the Federal Food, Drug, and Cosmetic Act.

¹⁸ See footnote 2.

-
- 3) The facility deficiency is the only deficiency in the CR letter (i.e., the facility issue is the only major deficiency (i.e., single), and there are no minor deficiencies).
 3. The OPRO RBPM triages the CR letter amendment that includes the reclassification request and assigns it to OPMA.
 4. After a priority or standard designation has been made, the OPRO RBPM communicates the decisional period to the OPQ assessment team.
 5. The OPRO RBPM notifies the applicant via a formal correspondence indicating whether its reclassification request is accepted for review and provides a decisional date indicating when the reclassification request will be made.
 6. The assigned OPMA assessor evaluates the reclassification request and makes a grant or deny decision by determining whether the facility deficiency, including any deficiency pertaining to the specific application, is resolved (including the impact of a facility withdrawal, if applicable).
 - a) If the deficiency is resolved, the assessor determines whether a PAI or the use of alternative tools is required to complete the assessment of the facility. If further assessment via an inspection or the use of alternative tools is not necessary in support of the application, the request will be granted.
 - b) If the deficiency remains unresolved or if a PAI or the use of alternative tools is necessary to address the current concerns, the request will be denied. If the most recent facility inspection designation was VAI, but FDA is continuing to evaluate the facility's remediation of prior OAI deficiencies, OPMA consults with the assigned OMQ compliance officer. Within the agreed-upon timeline, OMQ provides this information to OPMA. (Note: This step does not apply to withdrawn facilities.)
 - c) If the facility or facilities that are the subject of the major deficiency are being withdrawn and were listed on Form FDA 356h¹⁹ and did not generate data to support the primary basis for approval, the request will be granted (e.g., withdrawal of an alternate facility).
 - d) If the facility or facilities that are the subject of the major deficiency are being withdrawn and generated data to support the change proposed in the supplement, in such cases, because data from those facilities can no longer serve as the primary basis of approval, the OPMA assessor evaluates the impact of the withdrawal or withdrawals on the completeness of the supplemental application. This assessment will require significant time and resources; consequently, the request should be denied.

¹⁹ See footnote 16.

7. The OPMA assessor communicates to the OPRO RBPM the decision regarding whether to grant or deny the request and documents the decision and rationale in a memo and uploads the memo to the archival database.

8. The OPRO RBPM drafts and issues to the applicant the decisional letter that includes the applicable GDUFA goal date of the ANDA amendment(s)²⁰ as stated in the GDUFA III commitment letter. See tables 1 and 2 in the Attachment, Generic Drug User Fee Amendments Submission Types and Goal Dates.

EFFECTIVE DATE

- This MAPP is effective on January 15, 2024.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
6/27/2023	Initial	N/A
1/15/2024	Rev. 1	Updated to include information that delineates how to assess the impact of a facility withdrawal on the reclassification request

²⁰ The Office of Program and Regulatory Operations regulatory business process manager reviews and processes solicited and unsolicited ANDA or drug master file amendments independently from the facility-based major-to-minor reclassification request, including those that are received during the reclassification decisional period. In addition, the Office of Program and Regulatory Operations regulatory business process manager reviews and classifies any content deemed as major within the complete response letter response containing the facility-based reclassification request independently from the facility-based reclassification request. If any such amendment or major content affects the GDUFA goal date, the Office of Program and Regulatory Operations regulatory business process manager issues an acknowledgment letter after issuing the facility-based reclassification grant or deny letter.

ATTACHMENT: Generic Drug User Fee Amendments Submission Types and Goal Dates

As described in the GDUFA III commitment letter,¹ the goal dates for decisions on requests for reclassification and for amendment assessments for which a request for reclassification is submitted are as follows:

Table 1. Goal Dates for Reclassification Requests (Original ANDAs*)

Submission Type	FDA Response Regarding Major-to-Minor Reclassification Requests	New ANDA Goal Date if Reclassification Granted	ANDA Goal Date if Reclassification Denied**
Standard major amendment	Within 60 days of submission date	Within 5 months of submission date	Within 8 months of submission date if a PAI* is not required
			Within 10 months of submission date if a PAI is required
Priority major amendment	Within 30 days of submission date	Within 4 months of submission date	Within 6 months of submission date if a PAI is not required
			Within 8 months of submission date if a PAI is required and applicant meets the requirements under section I(A)(5)(b)*** (i.e., adequate presubmission facility correspondence)
			Within 10 months of submission date if a PAI is required and applicant meets any limitations as described under section I(A)(6)*** (i.e., presubmission facility correspondence not adequate)

* ANDA = abbreviated new drug application; PAI = preapproval inspection.

** Goal date for PASs will be different. See table 2 below.

*** See the GDUFA III commitment letter.

¹ See the GDUFA III commitment letter titled “Reauthorization Performance Goals and Program Enhancements Fiscal Years 2023-2027” available on the FDA website at <https://www.fda.gov/media/153631/download>.

Table 2. Goal Dates for Reclassification Requests (PASs*)

Submission Type	FDA Response Regarding Major-to-Minor Reclassification Requests	New PAS Goal Date if Reclassification Granted	PAS Goal Date if Reclassification Denied**
Standard major amendment	Within 60 days of submission date	Within 5 months of submission date if no inspection is required	Within 6 months of submission date if a PAI* is not required
			Within 10 months of submission date if a PAI is required
Priority major amendment	Within 30 days of submission date	Within 4 months of submission date if no inspection is required	Within 4 months of submission date if a PAI is not required
			Within 8 months of submission date if a PAI is required and applicant meets the requirements under section I(B)(4)(b)*** (i.e., adequate presubmission facility correspondence)
			Within 10 months of submission date if a PAI is required and applicant meets the requirement under section I(B)(4)(c)*** (i.e., presubmission facility correspondence not adequate)

* PAS = prior approval supplement; PAI = preapproval inspection.

** Goal date for ANDAs will be different. See table 1 above.

*** See the GDUFA III commitment letter.