POlicy and procedures

Office of Pharmaceutical Quality

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

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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(ies) 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 resources\(^4\) 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 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.
  – The CR letter’s major amendment classification is based on observations from a surveillance inspection (e.g., official action indicated (OAI) classification of a

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\(^3\) 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.

\(^7\) See footnote 2.
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 and verifies that the submission includes 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 letter.\(^9\)

- The CR letter is less than 1 year old\(^10\) (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).

- 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.\(^11\)

- FDA will generally deny a request a request for reclassification from major to minor if:

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\(^8\) 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 ([https://www.fda.gov/international-programs/international-arrangements/mutual-recognition-agreement-mra](https://www.fda.gov/international-programs/international-arrangements/mutual-recognition-agreement-mra)).


\(^10\) See section II.C.6. of the GDUFA III commitment letter.

\(^11\) 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.
– 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).12

– 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 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).

  – 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).

12 See the draft guidance for industry Conducting Remote Regulatory Assessments Questions and Answers (July 2022). When final, this guidance 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.
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.
  - 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 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 of 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.

c) The reclassification request is easily identified 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).13

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).


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.

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13 See footnote 2.
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) 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 a deficiency pertaining to the specific application, is resolved.

8. When the archival system indicates that FDA’s evaluation of the site is ongoing (e.g., in-process remediation), although a VAI letter has been issued, the OPMA assessor contacts the assigned Office of Manufacturing Quality compliance officer to gain additional information about the scope of the open evaluation. Within 2 U.S. business days, OMQ will provide this information to OPMA.

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 required in support of the application, the request will be granted.

b) If the deficiency remains unresolved (e.g., although the most recent facility inspection designation was VAI, FDA is continuing to evaluate the facility’s remediation of prior OAI deficiencies) or if a PAI or the use of alternative tools is necessary to address the current concerns, the request will be denied.

9. 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.

10. OPRO informs the ORO RPM of the decision.

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14 See MAPP 5240.3 Rev. 6 Prioritization of the Review of Original ANDAs, Amendments, and Supplements.
11. The ORO RPM drafts and issues to the applicant the decisional letter that includes the applicable GDUFA goal date of the ANDA amendment(s)\(^{15}\) 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.

**OPQ-Managed ANDA PASs**

1. OPRO receives the facility-only major-to-minor recategorization request and assigns it to the RBPM.

2. The OPRO RBPM reviews the cover letter and determines whether to accept or not accept the recategorization request for review. The OPRO RBPM accepts the recategorization request for review if all the criteria in bulleted items a) through f) are met:
   
   a) The recategorization request is submitted with a CR letter response amendment in a single submission.
   
   b) The recategorization request is submitted with the VAI or the NAI CGMP classification letter issued by FDA to the facility.
   
   c) The recategorization request is easily identified in the cover letter for the amendment submitted in response to the CR letter.
   
   d) The recategorization 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).\(^{16}\)
   
   f) The CR letter is less than 1 year old at the time the request for recategorization is submitted (from the date the CR letter was signed) or it is more than 1 year old and one of the following applies:

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\(^{15}\) 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 recategorization request, including those that are received during the recategorization 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 recategorization request independently from the facility-based recategorization 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 recategorization grant or deny letter.

\(^{16}\) See footnote 2.
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.


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 the request 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.

   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 (e.g., although the most recent facility inspection designation was VAI, FDA is continuing to evaluate the facility’s remediation of prior OAI deficiencies) or if a PAI or the use of alternative tools is necessary to address the current concerns, the request will be denied.

7. The OPMA assessor communicates to the OPRO RBPM the decision of 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) 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 June 27, 2023.

CHANGE CONTROL TABLE

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Revision Number</th>
<th>Revisions</th>
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<tbody>
<tr>
<td>6/27/2023</td>
<td>Initial</td>
<td>N/A</td>
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</tbody>
</table>

17 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, 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*)

<table>
<thead>
<tr>
<th>Submission Type</th>
<th>FDA Response Regarding Major-to-Minor Reclassification Requests</th>
<th>New ANDA Goal Date if Reclassification Granted</th>
<th>ANDA Goal Date if Reclassification Denied**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard major amendment</td>
<td>Within 60 days of submission date</td>
<td>Within 5 months of submission date</td>
<td>Within 8 months of submission date if a PAI* is not required</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Within 10 months of submission date if a PAI is required</td>
</tr>
<tr>
<td>Priority major amendment</td>
<td>Within 30 days of submission date</td>
<td>Within 4 months of submission date</td>
<td>Within 6 months of submission date if a PAI is not required</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>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)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>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)</td>
</tr>
</tbody>
</table>

* 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*)

<table>
<thead>
<tr>
<th>Submission Type</th>
<th>FDA Response Regarding Major-to-Minor Reclassification Requests</th>
<th>New PAS Goal Date if Reclassification Granted</th>
<th>PAS Goal Date if Reclassification Denied**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard major amendment</td>
<td>Within 60 days of submission date</td>
<td>Within 5 months of submission date if no inspection is required</td>
<td>Within 6 months of submission date if a PAI* is not required</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Within 10 months of submission date if a PAI is required</td>
</tr>
<tr>
<td>Priority major amendment</td>
<td>Within 30 days of submission date</td>
<td>Within 4 months of submission date if no inspection is required</td>
<td>Within 4 months of submission date if a PAI is not required</td>
</tr>
<tr>
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<td>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)</td>
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<td>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)</td>
</tr>
</tbody>
</table>

* PAS = prior approval supplement; PAI = preapproval inspection.
** Goal date for ANDAs will be different.
*** See the GDUFA III commitment letter.