POLICY AND PROCEDURES

Office of Pharmaceutical Quality

Prioritization of Solicited DMF Amendments Associated With ANDAs or PASs not Concurrently Under Assessment

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PURPOSE

This MAPP describes how the Office of Pharmaceutical Quality (OPQ) intends to prioritize assessments of CDER solicited Type II Drug Master File (DMF) amendments[1,2] that are submitted to the Agency prior to the submission of a referencing off-cycle[3] abbreviated new drug application (ANDA).[4] The applicable referencing ANDAs include an original ANDA, an amendment to an ANDA (containing a response

[1] A solicited amendment refers to the response from the drug master file (DMF) holder to the CDER DMF complete response letter (CRL) or DMF deficiency letter. It excludes responses to DMF Information Request (IR) Letters and DMF Additional Comment Letters.

[2] For details on information typically provided as part of a Type II DMF amendment, refer to the draft guidance for industry: *Drug Master Files* (November 2019). When final, this guidance will represent the FDA's current thinking on the 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.

[3] An off-cycle assessment is conducted on a DMF when there is no referencing ANDA with an open assessment cycle. Note that there is no goal date for an off-cycle assessment.

[4] The processes described in this MAPP will not be initiated if the solicited Type II DMF amendment is referenced *only* by an NDA or supplement to an NDA *and not any referencing ANDA.*

to a complete response letter (CRL)), or a prior approval supplement (PAS) to an ANDA (hereinafter referred to collectively as the "referencing ANDA").

This MAPP outlines the prioritization criteria that are applicable to solicited Type II DMF amendments received under the provisions of the Generic Drug User Fee Amendments (GDUFA) III[5] on or after October 1, 2022. These criteria specifically pertain to the drug substance (DS) quality discipline and any associated consults.[6]

BACKGROUND

To facilitate the approval of a referencing ANDA, the DMF for the DS referenced in the ANDA should be assessed and determined to be adequate to support the ANDA as early as possible. An "adequate" status indicates that the DMF has no open issues related to the assessment of the referencing ANDA. Often, when a DMF is determined to be inadequate to support the ANDA, a solicited amendment addressing the deficiencies in a DMF CRL is submitted before the amendment to the ANDA (containing a response to a CRL) is submitted. Under GDUFA I and II, the assessment of solicited DMF amendments was generally initiated only after the associated referencing ANDA was submitted.

Under GDUFA III, the Agency will consider initiating the assessment of solicited DMF amendments related to referencing ANDAs upon receipt, even if the ANDA referencing the DMF is not under assessment (referred to as an off-cycle DMF assessment). The program enhancements described in the GDUFA III commitment letter seek to make better use of the off-cycle time by initiating the assessment of a solicited DMF amendment upon submission rather than waiting for the associated referencing ANDA to be submitted to the Agency.[7]

POLICY

1. Priority will be given to off-cycle solicited DMF amendments for which an "adequate" status may result in a referencing ANDA receiving final approval during the subsequent assessment cycle.

2. Consideration will be given to the type of any CRL issued for the referencing ANDA (i.e., major or minor).

[5] GDUFA III commitment letter: https://www.fda.gov/media/153631/download.

[6] This MAPP does not apply to the microbiology assessment discipline, as microbiology assessments cannot be conducted outside the context of an open ANDA application cycle.

[7] This MAPP aligns with the commitments under paragraphs VI.F.1 and 2. in the GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2023-2027 (GDUFA III commitment letter).

3. The assessment of off-cycle solicited DMF amendments will generally be initiated based on the applicable priority criteria below:[8]

   a. High-priority:

   i. The referencing ANDA is associated with a drug shortage[9] or related to a public health emergency.[10]

   OR

   ii. The referencing ANDA may be eligible for a full approval (with an acceptable DMF assessment) in the subsequent assessment cycle, with the exception of those ANDAs categorized as low-priority.

   b. Low-priority:

   i. Cases involving a complex DS where the DMF amendment is addressing DS sameness deficiencies.

   ii. The referencing ANDA is associated with major deficiencies from a discipline other than DS quality in the previous assessment cycle.[11]

   iii. The referencing ANDA has an associated facility in Official Action Indicated (OAI) status at the time of DMF amendment triage.

   iv. The referencing ANDA is not eligible for a full approval in the subsequent assessment cycle based on patent and/or exclusivity protections (i.e., the anticipated action is tentative approval).

4. Off-cycle solicited DMF amendments deemed high-priority will be assigned for assessment as described in the procedures section below.

5. Off-cycle solicited DMF amendments deemed low-priority will be assigned for assessment based on the availability of resources.

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[8] The prioritization also applies to any associated consults.

[9] Submissions that could help mitigate or resolve a drug shortage and prevent future shortages, including submissions related to products that are listed on the FDA's Drug Shortage List with "Currently in Shortage" status at the time FDA determines prioritization. The list of drug products currently in shortage and discontinuations reported to FDA are available at: https://www.accessdata.fda.gov/scripts/drugshortages/.

[10] 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).

[11] Note that for the purpose of triaging the DMF amendment, if the deficiencies in the Drug Product (DP) Quality discipline are identified as "major" solely due to the DMF, the deficiencies will not be classified as "major" for the discipline.

6. For multiple associated referencing ANDAs, the criteria will be considered independently for each application. If any associated application meets the criteria for high-priority, then the priority for the off-cycle solicited DMF amendment will be deemed high.

RESPONSIBILITIES

Office of Pharmaceutical Quality (OPQ)/Office of Program and Regulatory Operations (OPRO)-DMF Triager:

- Triages the off-cycle solicited DMF amendments
- Determines the priority for initiating the assessment of such amendments
- Assigns the off-cycle solicited DMF amendment a DMF Review Target Date (DTD),[12] as appropriate
- Adds assignments to relevant systems
- Communicates the DTD to the DMF holder

OPQ/OPRO-Regulatory Business Process Manager (RBPM):

- Issues communications resulting from off-cycle solicited DMF assessments

OGD (Office of Generic Drugs)/Office of Generic Drug Policy (OGDP)-Patent and Exclusivity Team (PET) Reviewer:

- Analyzes the patent and exclusivity landscape for the referencing ANDA during the off-cycle solicited DMF amendment triage process

PROCEDURES

1. Generally, OPQ receives the notification for the off-cycle solicited DMF amendment from the DMF holder via the DMFOGD@fda.hhs.gov mailbox (see Attachment 1).

2. The OPQ/OPRO DMF triager will monitor the DMFOGD@fda.hhs.gov mailbox for any notifications of off-cycle solicited amendments.

3. The OPQ/OPRO DMF triager will triage and assign the priority for the off-cycle solicited DMF amendment within 10 business days of the receipt date for the DMF amendment or the receipt of the notification email to DMFOGD@fda.hhs.gov, whichever is later.

[12] The DMF Review Target Date refers to the due date assigned to the DMF assessment team. For an off-cycle assessment, this date is not linked to a GDUFA performance goal date.

4. If a referencing ANDA that references the DMF is received by the FDA during the 10-business day triage and assignment processing period, then the off-cycle solicited DMF amendment will be assigned a DMF Review Target Date (DTD) consistent with the open ANDA application cycle.

5. The DMF triager will apply the prioritization criteria, which encompass DS quality and application-related factors, as provided in the policy section above (also see Attachment 2) to determine the priority for the off-cycle solicited DMF amendment.

6. If none of the first four criteria apply (see Attachment 2), the DMF triager will contact the PET within OGDP to determine whether the referencing ANDA may be eligible for a full approval in the subsequent assessment cycle.

7. Once an off-cycle solicited DMF amendment has been deemed high-priority, the OPRO DMF triager will assign the DMF amendment to the assessment team, per established procedures for DMF amendment assignments. The DMF triager will set the DTD for high-priority amendments to 120 days from the receipt date of the DMF amendment or notification of response email, whichever is later.

8. Once the high-priority DMF amendment has been triaged and assigned a DTD, the DMF triager will communicate with the DMF holder (i.e., the sender of the notification email) that the DMF assessment is in progress and provide the DTD to the DMF holder.

9. The DMF assessment team will generally initiate any needed consults for high-priority off-cycle solicited DMF amendments that require a pharmacology/ toxicology or clinical evaluation.

10. If an associated referencing ANDA opens a new assessment cycle after the solicited off-cycle DMF amendment has been assigned a DTD and:

    - an earlier DTD is required to align with the application goal date, the DMF amendment, and any associated consult, the triager will have the due date adjusted to the earlier DTD.

      OR

    - the application goal date would result in a later DTD, the high-priority amendment and its associated consult will retain the original DTD as described in this MAPP.

11. If the assessment team determines DMF deficiencies remain upon assessment of the off-cycle solicited DMF amendments and there are no open ANDA application assessment cycles, the OPQ-OPRO RBPM will issue an information request (IR) letter to the DMF holder. When the response to an IR is received and

the DMF amendment remains off-cycle, then the triager will set the new DTD to 120 days from the IR response receipt date.

12. If DMF deficiencies remain upon assessment of the off-cycle solicited DMF amendments and there are open ANDA application assessment cycles, the OPQ-OPRO RBPM will issue a DMF CRL to the DMF holder.

13. Once a DMF has undergone a full scientific review and has no open issues related to the assessment of the referencing ANDA, the triager will issue a first adequate letter to the DMF holder. These letters will be issued in accordance with the established procedure.

14. Unsolicited amendments[13] to the DMF that were received prior to the receipt of the solicited amendment will be evaluated by the DMF assessment team concurrently with the solicited amendment, with the contents factored into the prioritization decision. Unsolicited amendments to the DMF received after the solicited amendment will either be evaluated during the ongoing assessment of the off-cycle solicited DMF amendment, held for the subsequent DMF assessment cycle, or be subject to an extension to the DTD at the discretion of the DMF assessment team.

REFERENCES

- Guidance for industry: *ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA* (July 2018)

- Draft guidance for industry: *Drug Master Files* (November 2019). When final, this guidance will represent the FDA's current thinking on the 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

- FDA drug shortages list: https://www.accessdata.fda.gov/scripts/drugshortages/

- GDUFA III commitment letter: https://www.fda.gov/media/153631/download

EFFECTIVE DATE

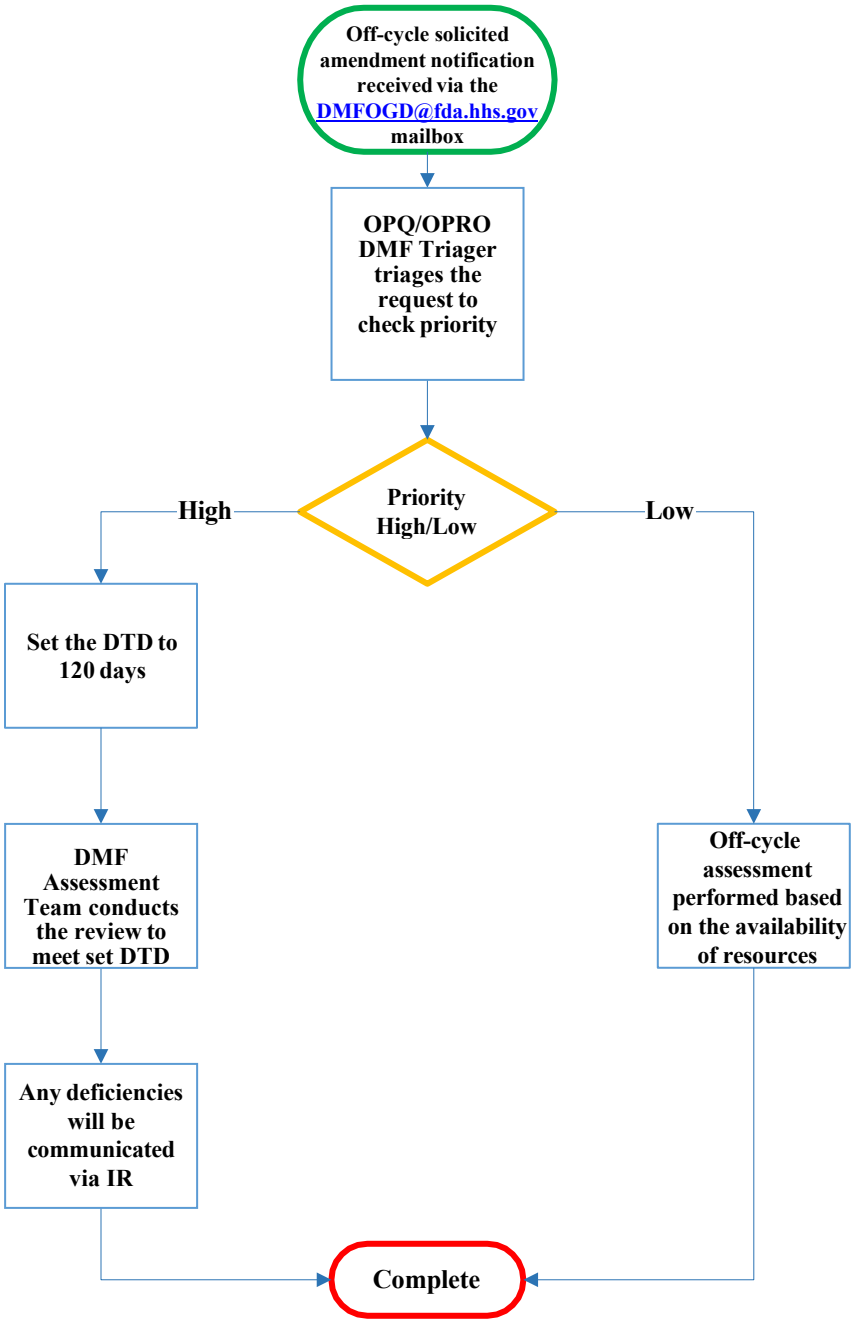
- This MAPP is effective on May 28, 2024.

[13] An unsolicited amendment refers to a gratuitous submission of information or data from the DMF holder that was not requested by the Agency.

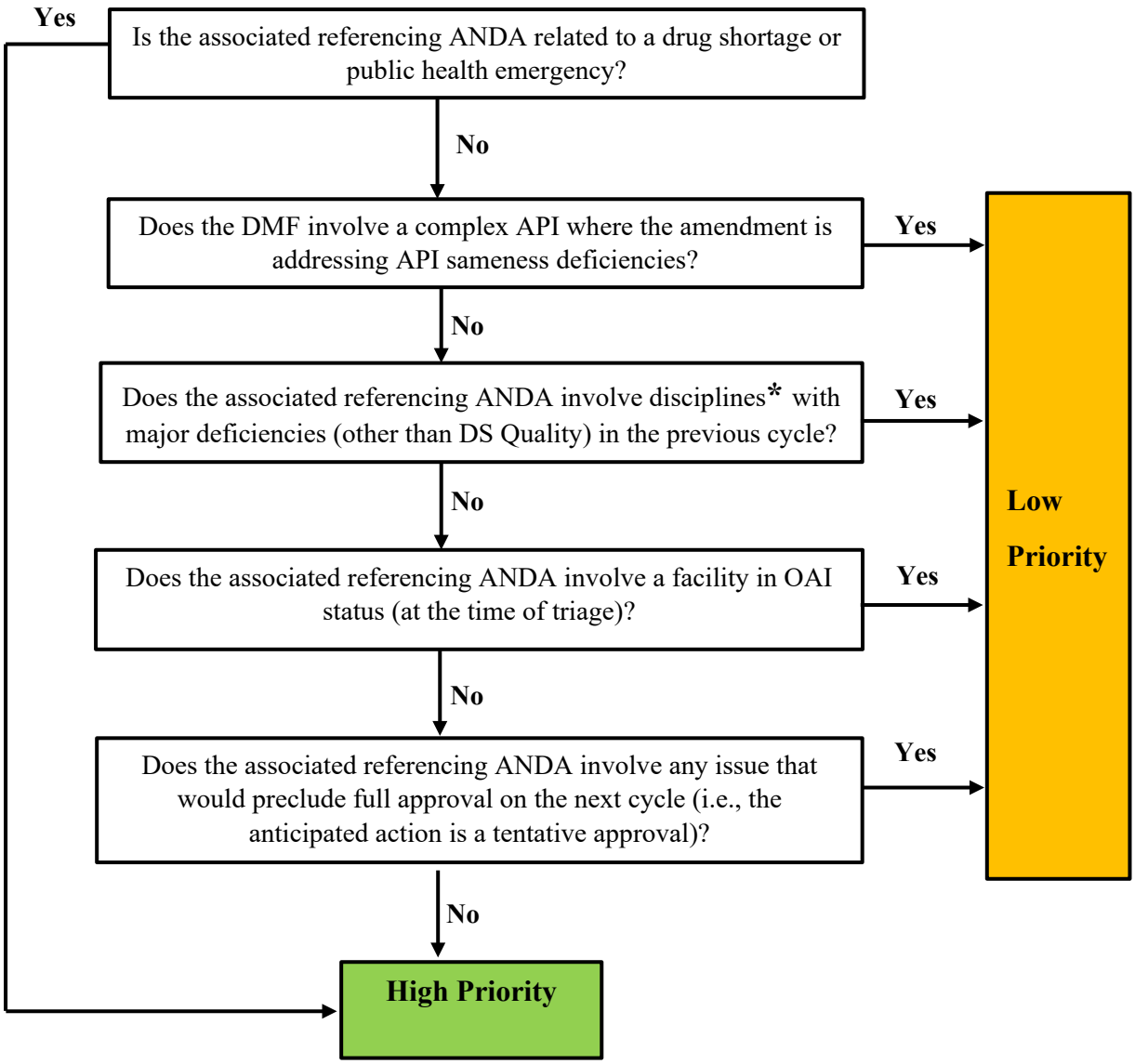
CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
5/28/2024	Initial	N/A

ATTACHMENT 1: PROCESS FLOWCHART



ATTACHMENT 2: PRIORITY CRITERIA DECISION TREE



***Note:** If the Drug Product (DP) Quality discipline is identified as "major" solely due to the DMF, the deficiencies will not be classified as "major" for the discipline.*