Review of Drug Master Files in Advance of Certain ANDA Submissions Under GDUFA

Guidance for Industry

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

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Contains Nonbinding Recommendations

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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 for holders of Type II active pharmaceutical ingredient (API) drug master files (DMFs) that will be referenced in an abbreviated new drug application (ANDA), or a prior approval supplement (PAS) to an ANDA. This guidance explains how FDA incorporates a program enhancement agreed upon by the Agency and industry as part of the negotiations relating to reauthorization of the Generic Drug User Fee Amendments (GDUFA), as described in "GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2023-2027" (GDUFA III commitment letter).[2] Specifically, this guidance describes instances when an early assessment,[3] or "DMF prior assessment," could be requested by a DMF holder and the circumstances under which FDA would commence an early assessment[4] of Type II API DMFs 6 months prior to an ANDA or PAS submission referencing the DMF. It also provides recommendations for such DMF holders when making a request.

The guidance does not apply to Type II API DMFs used to support new drug applications (NDAs), submissions related to ANDAs that are not described above, or any other types of DMFs.[5]

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

[1] This guidance has been prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research at the Food and Drug Administration.
[2] The GDUFA III commitment letter is available at https://www.fda.gov/media/153631/download.
[3] In this guidance, the terms "assessment" and "review" are used interchangeably.
[4] For the purposes of this guidance, DMF assessment consists of evaluation of all chemistry-related quality information for the API, including all related consults. It does not include assessment of sterility assurance information for a sterile API, which should be reviewed concurrently with an application submission.
[5] For additional information on the types of DMFs, see FDA draft guidance for industry Drug Master Files (October 2019). When final, the Drug Master Files 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.

the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The Generic Drug User Fee Amendments of 2012 (GDUFA I)[6] amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) to authorize FDA to assess and collect user fees to provide FDA with resources[7] 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 must be 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.[8] As described in the GDUFA III commitment letter applicable to this latest reauthorization,[9] 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.

One of the enhancements included in the GDUFA III commitment letter is a mechanism to enable assessment of DMFs in advance of certain ANDA and PAS submissions. This early assessment of DMFs is understood by FDA to, in general, address Type II API DMFs and, accordingly, subsequent references to DMFs in this guidance are references to Type II API DMFs.

The purpose of this guidance is to provide information and recommendations on the early assessment of certain Type II DMFs 6 months prior to the submission of certain ANDAs or PASs. It describes the process outlined in the GDUFA III commitment letter in greater detail and provides recommendations on how to provide the relevant information to FDA.

III. CONDITIONS FOR REQUESTING ASSESSMENT OF DMF PRIOR TO AN ANDA SUBMISSION

This section describes in detail the conditions set forth in the GDUFA III Commitment Letter applicable to a DMF, and the planned ANDAs or PASs that reference it, in order for the DMF holder to request an assessment of the DMF 6 months prior to the planned submission of certain ANDAs or PASs under the GDUFA III agreement.

Though the DMF holder should submit the DMF prior assessment request, close communication and coordination with the ANDA applicant is strongly encouraged to maximize the chance of a successful request by ensuring that all appropriate materials are provided with the request. For

[6] Title III of the Food and Drug Administration Safety and Innovation Act, Public Law 112-144.
[7] User fees are available for obligation in accordance with appropriations Acts.
[8] 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.
[9] See footnote 2.

example, the DMF holder is encouraged to obtain sufficient information from the ANDA applicant so the DMF holder can provide the information detailed under the conditions listed in sections A and B below.

As described in section VI.E.3 of the GDUFA III Commitment Letter, to be eligible for this assessment, a DMF holder would submit with its request the following:

a. At least one Letter of Authorization (LOA) with one pre-assigned ANDA number;

b. A reference to the corresponding reference listed drug (RLD)[10] listed in in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book);[11] and

c. Documentation that the DMF holder has paid a GDUFA DMF fee as described in section 744B(a)(2)(A) of the FD&C Act (21 U.S.C. 379j-41(a)(2)(A)).

Regarding condition a, if the LOA was previously submitted to the DMF, it does not need to be re-submitted with the request. Regarding condition b, a reference to the RLD listed in the Orange Book is only needed when the request is to support an original ANDA. A reference is not needed when the request is to support an ANDA amendment or supplement.

A. Request for assessment of a DMF 6 months prior to submission of an ANDA or its amendments

Under the terms of the GDUFA III commitment letter, a holder of a DMF may submit a request for assessment of the DMF 6 months prior to the planned submission date for: 1) an original ANDA, 2) an ANDA amendment containing a response to a Complete Response Letter (CRL), or 3) an amendment seeking approval of an ANDA that previously received a tentative approval. In each case, as described in section VI.E.1 of the GDUFA III Commitment Letter, the submission would include reference to a DMF for which FDA has not conducted a substantive assessment, and one of the following conditions should be met:

1. All patents and exclusivities will expire within 12 months of the planned submission date;

2. The submission is for a drug product for which there are not more than three approved drug products listed in the Orange Book, for which there are no blocking patents or unexpired exclusivities listed for the RLD, and the ANDA applicant is not seeking approval for less than all of the conditions of use on the RLD labeling, i.e., a "carve-out." In other words, there are fewer than four approved therapeutically equivalent drug products, including the RLD, listed in the Orange Book, no blocking patents or unexpired exclusivities for the RLD in the Orange Book, and the applicant is not seeking to "carve out" any conditions of use;

[10] An RLD "is the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA." 21 CFR 314.3(b).
[11] The Orange Book is available at: https://www.accessdata.fda.gov/scripts/cder/ob/.

3. The submission is for a drug product that could help mitigate or resolve a drug shortage and prevent future shortages,[12] including submissions related to products that are listed on FDA's Drug Shortage List[13] at the time of the submission of the DMF assessment request;

4. The submission is for a drug product that either could help address a public health emergency declared by the Secretary of the U.S. Department of Health and Human Services under section 319 of the Public Health Service Act (PHS Act),[14] or anticipated under the same criteria as apply to such a declaration; or

5. The submission is for a drug product for which (a) there is only one approved drug product listed in the Prescription Drug Product List (i.e., the "Active Section") of the Orange Book and that product is approved under an ANDA (i.e., the RLD is in the "Discontinued Section" and there is not more than one ANDA in the "Active Section"); (b) the approved ANDA for the drug product listed in the "Active Section" was not approved pursuant to a suitability petition under section 505(j)(2)(C) of the FD&C Act; (c) there are no blocking patents or exclusivities for the RLD; and (d) the submission does not qualify for prioritization under any other factor listed in MAPP 5240.3: Rev. 5 *Prioritization of the Review of Original ANDAs, Amendments, and Supplements*.

Regarding condition 1, this includes all of the patents listed in the Orange Book for the RLD identified as the basis of submission for the ANDA, and all exclusivities associated with the RLD. Regarding condition 2, for the purposes of the DMF prior assessment, a blocking patent is any unexpired patent for the RLD listed in the Orange Book.

B. Request for assessment of a DMF 6 months prior to submission of a PAS to add a new API source

As also described in the GDUFA III Commitment Letter, a holder of a DMF may submit a request for assessment of the DMF 6 months prior to the planned submission date for a PAS that requests to add a new API source, provided that:

1. The PAS is for a drug product that could help mitigate or resolve a drug shortage and prevent future shortages,[15] including submissions related to products that are listed on FDA's Drug Shortage List[16] at the time of the submission; or

2. The PAS is for a drug product that either could help address a public health emergency declared by the Secretary of the U.S. Department of Health and Human Services under

[12] Additional information about drug shortages can be found at: https://www.fda.gov/drugs/drug-safety-and-availability/drug-shortages.

[13] List of drug products currently in shortage and discontinuations reported to FDA are available at: https://www.accessdata.fda.gov/scripts/drugshortages/.

[14] See 42 U.S.C. 247d.

[15] See footnote 11.

[16] See footnote 13.

section 319 of the PHS Act, or anticipated under the same criteria as applies to such a declaration.

IV. ADDITIONAL INFORMATION

Under the GDUFA III commitment letter, DMF prior assessment is only available for API information submitted in a DMF. DMF prior assessment is not available for the review of drug substance information in an ANDA. Prior assessment requests should be limited to one DMF per API for each application because only one source per API is required for approval. Multiple prior assessment requests for a single API will not be accepted. However, if the drug product has multiple APIs, i.e., it is a fixed-combination product, one DMF prior assessment request can be submitted for each API. In addition, any secondary DMFs[17] referenced by a primary DMF that is granted prior assessment will be assessed during the DMF prior assessment period.

To assist DMF holders in submitting these requests, a list of elements FDA recommends be included in the cover letter of the prior assessment request is provided in the appendix. The appendix checklist also recommends that the DMF holder state explicitly the basis on which the DMF holder believes their request qualifies for DMF prior assessment. For the sake of clarity and efficiency, DMF holders are encouraged to use the appendix as a checklist when submitting the request.

Once the prior assessment request is received by FDA, the DMF staff will evaluate the request and make a determination to grant or deny the request. If the determination is to grant the request, a grant letter will be sent to the DMF holder. The DMF staff will subsequently conduct the review to meet the date indicated in the grant letter.[18] Any needed clarifications will be communicated via Information Request[19] to the DMF holder. If the determination is to deny the request, a deny letter including the reason for the denial will be sent to the DMF holder.

[17] A secondary DMF is a DMF that is incorporated by reference into a primary DMF.
[18] Unsolicited amendments submitted to the DMF after the prior assessment is granted may extend the target date.
[19] As defined in the GDUFA III Commitment Letter, Information Request means a communication that is sent to an applicant during an assessment to request further information or clarification that is needed or would be helpful to allow completion of the discipline assessment (GDUFA III Commitment Letter section XI.Q).

APPENDIX: RECOMMENDED CONTENT FOR A PRIOR ASSESSMENT REQUEST

FDA recommends that the following elements be included in the cover letter of a prior assessment request submission to the DMF:

1. Statement that the submission is a "GDUFA DMF Prior Assessment Request."[20]

2. A clear statement that the DMF holder is granting FDA permission to perform a substantive scientific review of the DMF.

3. Statement indicating the type of ANDA submission that the DMF will support, for example, original ANDA, ANDA amendment, or a PAS.

4. Statement certifying that the DMF is active and the GDUFA DMF user fee has been paid. DMF holders may submit a copy of Form FDA 3794 in the request submission to document payment of the GDUFA fee.

5. Statement that there is at least one valid Letter of Authorization (LOA) in the DMF intended to support the planned application submission.[21]

6. If the prior assessment request is to support an original ANDA submission, a citation to the Reference Listed Drug (i.e., the application number for the RLD), as provided in the Orange Book, and the drug product(s), including the strength(s), that will be included in the ANDA submission.

7. The planned submission date of the ANDA, ANDA amendment, or PAS. This date should be at least 6 months from the date the request is submitted to the DMF.[22]

8. (i). For an original ANDA, an ANDA amendment containing a response to a Complete Response Letter (CRL), or an amendment seeking approval of an ANDA that previously received a tentative approval, the applicable justification for the request from ***III.A items 1-5*** in this guidance[23] should be clearly stated in the cover letter.

[20] If DMF Form FDA 3938 is included with the submission, select "other" in field 7 and enter "GDUFA DMF Prior Assessment Request." Also select Letter of Authorization (LOA) in field 7 if one or more LOAs are included with the submission.

[21] For a planned original ANDA submission, provide the pre-assigned ANDA number and the authorized party in the cover letter. For an ANDA amendment containing a response to a CRL which references a new original DMF, an amendment seeking approval of an ANDA that previously received a tentative approval that references a new original DMF, or a PAS to add a new API source, provide the ANDA number and the authorized party.

[22] For drug shortage or products that could help address a public health emergency, a request to waive this condition may be included in the cover letter when the DMF holder is unable to provide the request 6 months in advance.

[23] FDA strongly encourages DMF holders to communicate with their customers (applicants) regarding the proper justification for the prior assessment request.

(ii). For a PAS to add a new API source, the applicable justification for the request from ***III.B items 1-2*** in this guidance[24] should be clearly stated in the cover letter.

Note that the prior assessment request should be signed by the responsible official at the DMF holder company and not the DMF agent. In addition, upon the submission of a GDUFA DMF Prior Assessment Request, please send a notification email to DMFOGD@FDA.HHS.GOV to ensure timely processing.

[24] Ibid.