Facility Readiness: Goal Date Decisions Under GDUFA

Guidance for Industry

DRAFT GUIDANCE

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

October 2022
Generic Drugs

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Facility Readiness: Goal Date Decisions Under GDUFA Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides information to applicants on how FDA intends to assign a goal date based on a facility's readiness for inspection as certified on Form FDA 356h[2,3] submitted as part of an original abbreviated new drug application (ANDA)[4] under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)). 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).[5]

Under the commitment letter related to the GDUFA authorization for fiscal years 2018 through 2022 (under the Generic Drug User Fee Amendments of 2017),[6] a goal date was assigned without regard to facility readiness. In the GDUFA III commitment letter, FDA agreed to incorporate facility readiness into goal date assignment, such that FDA generally assigns a 15-month goal date and defers substantive assessment if a facility is not ready for an inspection at the time of application submission.[7,8] FDA may not be able to complete substantive assessment of an application unless all facilities are ready for inspection. Therefore, this change

[1] This guidance has been prepared by the Office of Pharmaceutical Quality (OPQ) and the Office of Generic Drugs (OGD) in the Center for Drug Evaluation and Research at the Food and Drug Administration.
[2] Form FDA 356h, titled *Application to Market a New or Abbreviated New Drug or Biologic for Human Use*, is available at https://www.fda.gov/media/72649/download.
[3] Form FDA 356h fulfills the 21 CFR 314.94(a)(1) application form requirement.
[4] For the purposes of this guidance, the term *original ANDA* refers exclusively to the application assessed during the first review cycle, including an application resubmitted after a refuse-to-receive action.
[5] The GDUFA III commitment letter is available at https://www.fda.gov/media/153631/download.
[6] Title III of the FDA Reauthorization Act of 2017, Public Law 115-52.
[7] See section I.A.3. of the GDUFA III commitment letter.
[8] OPQ and OGD generally use the terms *assessment* and *review* interchangeably. In this guidance, assessment means the process of both evaluating and analyzing submitted data and information to determine whether the application meets the requirements for approval and documenting that determination.

helps FDA to focus resources on substantially complete[9] applications that contain facilities ready for inspection.

This guidance does not apply to:

- Facilities involved in bioequivalence and clinical studies used to support an application
- Amendments submitted after a complete response or tentative approval letter
- Supplements or amendments to a supplement

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.

II. BACKGROUND

The Generic Drug User Fee Amendments of 2012 (GDUFA I)[10] amended the FD&C Act to authorize FDA to assess and collect user fees to provide FDA with resources[11] 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.[12] As described in the GDUFA III commitment letter applicable to this latest reauthorization, 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.

[9] An application's substantial completeness is evaluated consistent with 21 CFR 314.101; information on FDA's policies and procedures for conducting a filing review to determine if an ANDA is substantially complete is available in the Manual of Policies and Procedures (MAPP) 5200.14 *Filing Review of Abbreviated New Drug Applications* (available at https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cder-manual-policies-procedures-mapp).

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

[11] User fees are available for obligation in accordance with appropriations acts.

[12] 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.

A number of GDUFA III commitments are intended to reduce first assessment cycle facility-related delays that could delay application approval. The commitment outlined in this guidance sets the goal date to 15 months for an original ANDA containing a certification that a facility on Form FDA 356h is not ready for inspection. An applicant can amend its original ANDA to reset the 15-month goal date to a standard or priority assessment goal, as applicable,[13] once all facilities become ready for inspection. However, the commitment letter also explains that for an application that continues to include a facility not ready for inspection 30 days before the 15-month goal date expiration, FDA will reset the goal date for an additional 15 months (i.e., 30 months from the date of original ANDA submission). FDA agreed to assess and act on 90 percent of such ANDAs within 30 months of the date of the original submission as applicable.[14] Through the implementation of this commitment, FDA and industry aim to incentivize the submission of applications that include facilities ready for inspection to facilitate their timely assessment.

III. FACILITY READINESS: ASSESSMENT AND REPORTING

Under the GDUFA III commitment letter, FDA uses a facility's readiness for inspection designation in the Establishment Information section of Form FDA 356h to assign an application's goal date. Applicants should examine the accuracy of the facility information they submit on Form FDA 356h.

A. Applicant Assessment of Facility Readiness

Applicants should assess whether each facility is ready for inspection before checking the appropriate box on Form FDA 356h. FDA considers a facility that is ready for inspection to be one that complies with current good manufacturing practice (CGMP) requirements[15] and meets the following criteria related to the application product:

- Facility operations, methods, and product formulation are the same as those described in the application

[13] FDA considers an ANDA to be a priority ANDA if it meets the criteria listed in either section 505(j)(11) of the FD&C Act (which governs for ANDAs subject to that provision) or MAPP 5240.3 Rev. 5 *Prioritization of the Review of Original ANDAs, Amendments, and Supplements*. Section 505(j)(11)(D) of the FD&C Act reaffirms FDA's authority to "prioritiz[e] the review of other applications as [FDA] determines appropriate."

[14] GDUFA III commitment letter, section I.A.3.b., page 5

[15] For the purposes of this guidance, CGMP refers to the requirements in section 501(a)(2)(B) of the FD&C Act and 21 CFR parts 4, 210, and 211, as applicable.

- Data at the facility are complete and accurate, and are consistent with data in the application[16]

- The facility is ready for commercial manufacturing[17]

To assess these criteria during an inspection, FDA uses Compliance Program (CP) 7346.832 *Preapproval Inspections*.[18] Applicants may also find the considerations in CP 7346.832 (Part III, section 1, NDA/ANDA Inspectional/Audit Coverage, Objectives, and Techniques) useful when assessing facility readiness.[19] FDA provides additional facility readiness recommendations in the guidance for industry *Good ANDA Submission Practices* (January 2022), section V.D., Facilities.

FDA has experienced cases where facilities were not aware they were listed on Form FDA 356h.[20] This often results in a greater likelihood that a facility will be unprepared for an inspection. FDA recommends that applicants notify each facility that the facility is listed on the applicant's Form FDA 356h and inform the facility whether the applicant has checked the "yes" or "no" box in the Establishment Information Field 28 of Form FDA 356h to identify the inspection readiness of each manufacturing or testing facility listed.

When signing Form FDA 356h, an applicant certifies that the information in the application is complete and accurate. Inaccurate representation of facility readiness may cause a delay in or refusal to approve an application.[21]

B. Reporting Facility Readiness on Form FDA 356h

Form FDA 356h should be used to convey application-related facility information for manufacturing, packaging, and control sites for drug substance and drug product facilities.[22] Applicants should check the "yes" or "no" box in the "Is the site ready for inspection?" section of Field 28 (Establishment Information) on Form FDA 356h to identify the inspection readiness for each manufacturing or testing facility listed, including any reference to a manufacturing or testing facility associated with a drug master file.

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[16] See the guidance for industry *Data Integrity and Compliance With Drug CGMP; Questions and Answers* (December 2018). 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.

[17] FDA considers *ready for commercial manufacturing* to mean that the establishment has a quality system that is designed to achieve sufficient control over the facility and commercial manufacturing operations for the product, among other elements further described in FDA Compliance Program 7346.832 *Preapproval Inspections*.

[18] Drug Compliance Programs are available at https://www.fda.gov/drugs/guidance-compliance-regulatory-information/drug-compliance-programs.

[19] FDA considers it a best practice for all manufacturing facilities listed in an application to be ready for inspection at the time of submission. These considerations are useful when assessing facility readiness for a preapproval inspection.

[20] If a facility identified in an ANDA believes it was included in error and seeks to be removed from that ANDA, the facility should work with the ANDA applicant to be removed from the application.

[21] See section 505(j)(4)(A) and (K) of the FD&C Act; 21 CFR 314.127.

[22] For more information regarding which facilities should be listed on Form FDA 356h, see the guidance for industry *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER, Questions and Answers* (October 2019).

The "Is the site ready for inspection" section of Field 28 also includes an "N/A" box, but this box should not be checked for original ANDA submissions. Applicants should check the "N/A" box when they withdraw a facility from the application. FDA will not consider an applicant's estimated date of readiness (noted in Field 28) when assigning a goal date.

If the boxes in Field 28 are blank or incorrectly marked "N/A," both of which prevent a determination of facility readiness, FDA will seek clarification by issuing the applicant an information request (IR) letter. FDA will assign the application a 15-month goal date by default if the applicant does not respond within the time frame prescribed in the IR letter.[23]

IV. GOAL DATE ASSIGNMENT

When an original ANDA is submitted with a completed Form FDA 356h, FDA reviews the submission for facility readiness information, receives the application if substantially complete,[24] assigns the appropriate goal date,[25] and issues an acknowledgement letter.[26]

To implement the GDUFA III commitment,[27] FDA modified its procedures to incorporate facility readiness in goal date assignment. In cases when one or more facilities are not ready for inspection, FDA generally assigns a 15-month goal date and defers substantive assessment of the original ANDA and any unsolicited amendments until receipt of an amendment with an updated Form FDA 356h stating all facilities are ready for inspection.

Upon receipt of an amendment with Form FDA 356h certifying that all facilities are ready for inspection, FDA will reassign the appropriate standard or priority goal date (as applicable) calculated from the amendment receipt date. To facilitate goal date reassignment, FDA

[23] The GDUFA III commitment letter provides for FDA to communicate minor technical deficiencies (e.g., document legibility) and deficiencies potentially resolved with information in the ANDA at original submission within 10 days of original ANDA submission. If the applicant resolves those deficiencies within 10 days of such communication from FDA, those deficiencies will not be a basis for a refuse-to-receive decision under the terms of the commitment letter. See GDUFA III commitment letter, section II.A.2., at page 12 (https://www.fda.gov/media/153631/download).

[24] See 21 CFR 314.101(b)(2). See also the guidance for industry *Providing Regulatory Submissions in Electronic Format — Receipt Dates* (February 2014). These submissions are deemed to be submitted to FDA on the day when transmission to the Electronic Submissions Gateway (ESG) is completed, except when the submission arrives on a weekend, Federal holiday, or a day when the FDA office that will assess the submission is otherwise not open for business. In that case, the submission is deemed to be submitted on the next day when that office is open for business. Additional information concerning the FDA ESG is available at https://www.fda.gov/industry/electronic-submissions-gateway.

[25] GDUFA III commitment letter, section I.A.

[26] See 21 CFR 314.101(b)(2). FDA sends an ANDA acknowledgement letter when it has determined that the ANDA can be received for assessment.

[27] GDUFA III commitment letter, section I.A.3., page 5.

recommends the applicant state in the cover letter "**Facility Ready For Inspection**" along with the ANDA number.[28,29]

If the applicant does not submit an amendment with Form FDA 356h certifying all facilities are ready for inspection by 30 days before the goal date, FDA resets the goal date for an additional 15 months (i.e., 30 months from the date of original ANDA submission) and commences substantive assessment. FDA agreed to assess and act on 90 percent of such ANDAs within 30 months of the date of the original submission as applicable.[30]

[28] See the guidance for industry *ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA* (July 2018) for additional recommendations on information to be included on the first page of the submission. See also the draft guidance for industry *Cover Letter Attachments for Controlled Correspondences and ANDA Submissions* (December 2021) (when final, this guidance will represent the FDA's current thinking on this topic).

[29] The application goal date is reset based on the calendar day after FDA receives the amendment certifying that all facilities are ready for inspection.

[30] GDUFA III commitment letter, section I.A.3.b., page 5.

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

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For questions regarding this draft document, contact (CDER) Ziyang Su 240-402-6004.

U.S. Department of Health and Human Services
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October 2022
Pharmaceutical Quality / CMC

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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: 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 12.
[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. Any needed clarifications will be communicated via Information Request[18] 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] 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."[19]

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.[20]

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.[21]

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[22] should be clearly stated in the cover letter.

[19] 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.

[20] 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.

[21] 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.

[22] 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[23] 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.

[23] Ibid.

Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules

Guidance for Industry

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

October 2022
Pharmaceutical Quality/CMC

Revision 1

Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules

Guidance for Industry

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

October 2022
Pharmaceutical Quality/CMC

Revision 1

Contains Nonbinding Recommendations

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Contains Nonbinding Recommendations

Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules 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

Tablets and capsules are widely manufactured and prescribed and may provide a number of advantages over other dosage forms, including ease of storage, portability, ease of administration, and accuracy in dosing.

While generic formulations of these drug products are required to be both pharmaceutically and therapeutically equivalent to a reference listed drug (RLD),[2] we are concerned that differences in physical characteristics (e.g., size and shape of the tablet or capsule) may affect patient compliance and acceptability of medication regimens or could lead to medication errors. We believe these patient safety concerns are important, and we are recommending that generic drug manufacturers consider physical attributes when they develop quality target product profiles (QTPPs) for their generic product candidates.

The recommendations in this guidance apply to abbreviated new drug applications (ANDAs) and their supplements for additional strengths that are submitted to the Office of Generic Drugs (OGD).

This guidance does not apply to approved ANDAs (generic drugs) already on the market.[3] However, if the Agency determines that an approved product should be modified because the

[1] This guidance has been prepared by the Office of Generic Drugs and the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] *Reference listed drug* means the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA. See 21 CFR 314.3(b). FDA publishes the identification of RLDs in the Approved Drug Products with Therapeutic Equivalence Evaluations (i.e., Orange Book), available at https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book.

[3] If the manufacturer of an RLD makes a postapproval change to the size or shape of a previously approved tablet or capsule, the generic versions generally will not need to be modified. However, the Agency could ask for modifications to the product if there are safety concerns because of the differences in physical characteristics.

size or shape of a product poses a risk to public health, we will notify the holder of the ANDA. This guidance is not intended to apply to other oral dosage forms (e.g., chewable tablets, oral tablets for suspension/solution, orally disintegrating tablets, sublingual tablets, troches, gums).

This guidance revises the guidance of the same name issued in June 2015 to clarify that the largest dimension of a tablet should not exceed 22 mm and that capsules should not exceed a standard 00 size. This guidance also includes updated references.

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.

II. BACKGROUND

A. Differences in Size and Shape of Tablets and Capsules between a Reference Listed Drug and a Drug Product Subject to an Abbreviated New Drug Application

1. Size

Difficulty swallowing tablets and capsules can be a problem for many individuals and can lead to a variety of adverse events and patient noncompliance with treatment regimens. It is estimated that over 16 million people in the United States have some difficulty swallowing, also known as dysphagia.[4,5] For these individuals, swallowing a tablet or a capsule can be particularly challenging. A survey of adults on difficulties swallowing tablets and capsules suggests that this problem goes well beyond the patient population with clinically recognized dysphagia and may affect as many as 40 percent of Americans. Of those who experience difficulty swallowing medications, less than a quarter discuss the problem with a health care professional, 8 percent admit to skipping a dose of prescribed medication, and 4 percent have discontinued therapy because the tablets and/or capsules were difficult to swallow.[6] Individuals who find it difficult to swallow tablets and capsules frequently cite the size as the main reason for the difficulty in swallowing.[7,8]

Size and shape of tablets and capsules affect the transit of the product through the pharynx and esophagus and may directly affect a patient's ability to swallow a particular drug product. Larger tablets and capsules have been shown to have a prolonged esophageal transit time. This

[4] Agency for Health Care Policy and Research, 1999, Diagnosis and Treatment of Swallowing Disorders (Dysphagia) in Acute-Care Stroke Patients: Summary, Evidence Report/Technology Assessment: Number 8.
[5] Robbins J, Langmore S, Hind JA, and Erlichman M, 2002, Dysphagia Research in the 21st Century and Beyond: Proceedings From Dysphagia Experts Meeting, J Rehabil Res Dev, 39(4):543–548.
[6] Harris Interactive Inc., 2003, Pill-Swallowing Problems in America: A National Survey of Adults, New York, NY: Harris Interactive Inc. for Schwarz Pharma, 1–39.
[7] See footnote 4.
[8] Bhosle M, Benner J, DeKoven M, and Shelton J, 2009, Difficult to Swallow: Patient Preferences for Alternative Valproate Pharmaceutical Formulations, Patient Prefer Adherence, 3:161–171.

can lead to disintegration of the product in the esophagus and/or cause injury to the esophagus, resulting in pain and localized esophagitis and the potential for serious sequelae including ulceration, stricture, and perforation.[9,10] Other adverse events such as pain, gagging, choking, and aspiration are related to swallowing difficulties in the oropharyngeal phase of swallowing and increasingly occur at larger tablet and capsule sizes.[11,12]

Studies in adults evaluating the effect of tablet and capsule size on ease of swallowing suggest that increases in size are associated with increases in patient complaints related to swallowing difficulties at tablet sizes greater than approximately 8 mm in diameter.[13,14,15] The size of the tablet or capsule influences esophageal transit, irrespective of patient factors and administration techniques (i.e., use of fluids, patient position). Smaller tablets generally have been shown to have significantly faster transit times in these studies. Channer and Virjee specifically compared the transit time of 8 mm diameter round tablets to 11 mm diameter round tablets and 14 mm x 9 mm oval tablets and found the transit times for the 8 mm round tablet to be significantly shorter than for 11 mm round and 14 mm x 9 mm oval tablets ($p<.02$ and $p<.04$, respectively).[16] In addition, significantly more patients were aware of the larger round tablets (>8 mm) sticking in the esophagus compared with the 8 mm round tablets.[17] Although there has been less research quantifying the effects of size difference on the oropharyngeal phase of swallowing, increasing tablet or capsule size is believed to correlate with increasing difficulty with oropharyngeal transfer.

2. Shape

For any given size, certain shapes may be easier to swallow than others. In vitro studies suggest that flat tablets have greater adherence to the esophagus than capsule-shaped tablets.[18] Studies in humans have also suggested that oval tablets may be easier to swallow and have faster esophageal transit times than round tablets of the same weight.[19,20] Patient compliance with medication regimens may be influenced by the size and shape of a tablet or capsule.

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[9] Drug and Therapeutics Bulletin, 1981, Tablets and Capsules that Stick in the Oesophagus, Drug Ther Bull, 19(9):33–34.
[10] Channer K and Virjee JP, 1986, The Effect of Size and Shape of Tablets on their Esophageal Transit, J Clin Pharmacol, 26(2):141–146.
[11] Kelly J, D'Cruz G, and Wright D, 2010, Patients With Dysphagia: Experiences of Taking Medication, J Adv Nurs, 66(1):82–91.
[12] Jackson LD, Little J, Kung E, Williams EM, Siemiatkowska K, and Plowman S, 2008, Safe Medication Swallowing in Dysphagia: A Collaborative Improvement Project, Healthc Q, 11:110–116.
[13] See footnote 10.
[14] Wamberg T, Jorgensen F, Hasselbalch H, and Hey H, 1983, The Prejudgement of the Esophageal Transfer of Tablets and Capsules, Archiv der Pharmazie Chemistry in Life Sciences, Ed., 11:24–31.
[15] Brotherman DP, Bayraktaroglu TO, and Garofalo RJ, 2004, Comparison of Ease of Swallowing of Dietary Supplement Products for Age-Related Eye Disease, J Am Pharm Assoc, 44(5):587–593.
[16] See footnote 10.
[17] Ibid.
[18] Marvola M, Rajaniemi M, Marttila E, Vahervuo K, and Sothmann A, 1983, Effect of Dosage Form and Formulation Factors on the Adherence of Drugs to the Esophagus, J Pharm Sci, 72(9):1034–1036.
[19] See footnote 10.
[20] Hey H, Jorgensen F, Sorensen K, Hasselbelch H, and Wamberg T, 1982, Oesophageal Transit of Six Commonly Used Tablets and Capsules, Br Med J, 285(6356):1717–1719.

3. Patient Factors

The Agency recognizes that a variety of other factors may affect a patient's ability to swallow a tablet or a capsule. For example, age could be a factor. Children and adolescents, as well as the elderly, are more likely to have difficulty swallowing tablets or capsules. Body position, fluid intake, and the presence of certain medical conditions (e.g., multiple sclerosis, muscular dystrophy, Parkinson's disease) may also affect a patient's ability to swallow tablets and capsules.

Although not all patient factors can be addressed through pharmaceutical design and manufacture, the physical characteristics of a product can be addressed. These physical characteristics influence the ability of certain patients to swallow the product, particularly in vulnerable populations. We believe that tablets and capsules can be effectively developed and manufactured to minimize swallowing difficulties, which can encourage and improve patient compliance with medication regimens. FDA recommends that applicants design and develop generic drugs with this in mind.

B. Other Physical Attribute Considerations

The presence and composition of a coating can also potentially affect the ease of swallowing tablets or capsules. The lack of a film coating can decrease or prevent tablet mobility compared with a coated tablet of the same size and shape. Coating also can affect other factors that contribute to patient acceptance, such as palatability and smell.

The weight of the tablet or capsule also may affect transit time, with heavier tablets or capsules having faster transit times compared to similarly-sized, lighter tablets or capsules. Surface area, disintegration time, and propensity for swelling when swallowed are additional parameters that can influence esophageal transit time and have the potential to affect the performance of the drug product for its intended use. These physical attributes should also be considered when developing a QTPP for generic drug products intended to be swallowed intact.

III. RECOMMENDATIONS

The recommendations in this guidance are based on published literature regarding patient experiences swallowing tablets and capsules and Agency experience with NDAs and ANDAs submitted for oral tablets and capsules. If a tablet or capsule intended to be swallowed intact differs from the criteria recommended in this guidance document, then the applicant should contact OGD with supportive information and justification before establishing the QTPP.

A. Size

For comparable ease of swallowing as well as patient acceptance and compliance with treatment regimens, the Agency recommends that generic oral tablets and capsules intended to be swallowed intact should be of a similar size to the corresponding RLD. The Agency recommends limiting size differences between therapeutically equivalent tablets as follows:

- If the RLD is less than 17 mm in its largest dimension,[21] the generic product should be:
  - No more than 20 percent larger than the RLD in any single dimension (the resulting single dimension of the generic should not exceed 17 mm).
  - No more than 40 percent larger than the volume of the RLD.[22]

- If the RLD is equal to or greater than 17 mm in its largest dimension, the generic product should be:
  - No larger than the RLD in any single dimension.
  - No larger than the volume of the RLD.

- We recommend that the largest dimension of a tablet should not exceed 22 mm and that capsules should not exceed a standard 00 size.[23]

Additional flexibility may be given for products that are 8 mm or smaller in their largest dimension, but efforts should be made to develop tablets and capsules that are of a similar size and shape to the RLD.

Under the standard capsule size convention, the allowances described above will generally allow an increase of one capsule size, when the RLD capsule is of size 3 or smaller. When the RLD capsule is of size 2 or larger, an increase of one capsule size should only be considered when adequate justification can be provided for the size increase. These recommendations would allow an increase of one capsule size when the capsule size is less than capsule size 00.

The Agency recognizes that two drug products may have different recommended upper size limits, but size should be considered as part of a single product risk/benefit profile. When establishing therapeutic equivalence, the applicant should compare their generic product only to the RLD.

B. Shape

In addition to the size recommendations described above, we recommend manufacturing tablets and capsules that have a similar shape or have a shape that has been found to be easier to swallow compared with the shape of the RLD. Evaluating and comparing the largest cross sectional areas of the RLD and generic product is one strategy to quantify changes in shape.[24] Tablets and capsules that have a larger cross sectional area (e.g., tablets that are rounder) would generally be more difficult to swallow than tablets or capsules of the same volume but with smaller cross sectional areas.

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[21] The largest dimension refers to the length of oval or capsule shaped tablets or the diameter of round tablets.
[22] For the purposes of this guidance, volume refers to the volume occupied by the tablet or capsule.
[23] An internationally accepted numbering system for capsule sizes is used in approved U.S. drug products. For the purpose of this guidance, a liquid fill capsule is considered a capsule.
[24] For the purposes of this guidance, the largest cross sectional area is defined by the largest cross sectional area of the tablet that lies in a plane perpendicular to the longest axis of the tablet. If the shape of tablet is unconventional (e.g., pentagon, triangle, diamond, heart), then the largest cross sectional area will be defined as the area of the smallest circle, oval, or ellipse that would completely enclose this largest cross sectional shape.

There are a variety of techniques that may be used to determine the volume measurements of a tablet or capsule, including use of pycnometers, or calculations based on physical measurements of the tablet or the die used to produce the tablet. For the purpose of this guidance, spatial imaging and/or the use of computer models is recommended, because they are more accurate and applicable to a variety of shapes, although other appropriately validated methods may be used if properly justified.

The size of a tablet or capsule should be provided in the common technical document (CTD) format,[25] section 3.2.P.1, *Description and Composition of the Drug Product* of the ANDA. Any studies and/or related information should be provided in the CTD section, 5.3.1.2, *Comparative Bioavailability and Bioequivalence Study Reports.* The Agency may request samples for evaluation of the physical attributes of a tablet or capsule.

C. Other Physical Attributes

Other physical attributes of tablets and capsules should be considered in the context of their effect on ease of swallowing. For example, tablet coating, weight, surface area, disintegration time, and propensity for swelling should be considered when developing a QTPP for generic tablets.

Description of these physical characteristics should be provided in the CTD section 3.2.P.1, *Description and Composition of the Drug Product* of the ANDA. A summary of any studies to support sizes outside the recommendation provided in this guidance should be provided in the CTD section 3.2.P.2, *Pharmaceutical Development* or CTD section 3.2.P.5.6, *Justification of Specifications*.

D. Biowaivers

A biowaiver (i.e., the waiver of in vivo bioequivalence data) for additional strengths of a solid oral dosage form is generally granted if it meets one of the criteria set forth in the regulations,[26] one of which is proportional similarity between strengths in active and inactive ingredients. Compositional proportionality may be particularly relevant when considering tablet size and tablet formulation for other strengths (both lower and higher) of the same dosage form to be considered for a waiver of the in vivo bioequivalence study requirement. Although compositional proportionality may exist when all active and inactive ingredients are in the same proportion between different strengths, other methods of achieving compositional proportionality may be more amenable to maintaining appropriate tablet sizes for generic products when compared with the RLD. A detailed description of how the Agency defines proportional similarity can be found in the draft guidance for industry *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (August 2021).[27]

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[25] See the International Council for Harmonisation (ICH) guidance for industry *M4Q: The CTD — Quality* (August 2001). 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.

[26] See 21 CFR 320.22(d).

[27] When final, this guidance will represent the FDA's current thinking on this topic.

FDA recommends that applicants consider Agency published guidance, product specific guidance,[28] and relevant regulations[29] on the waiver process when designing and formulating other strengths of the same dosage form that will be studied with bioequivalence studies. For specific questions related to biowaivers, you should contact the appropriate review division within OGD.

[28] Available at https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development.
[29] See 21 CFR 320.22.