
Completeness Assessments for Type II API DMFs Under GDUFA Guidance for Industry

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

**October 2017
Pharmaceutical Quality/CMC/Generics**

Revision 1

Completeness Assessments for Type II API DMFs Under GDUFA Guidance for Industry

*Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov*

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

or

*Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010
Email: ocod@fda.hhs.gov*

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

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

**October 2017
Pharmaceutical Quality/CMC/Generics**

Revision 1

TABLE OF CONTENTS

I.	INTRODUCTION.....	1
II.	BACKGROUND	2
III.	COMPLETENESS ASSESSMENT	2
A.	Information Confirmed During the Completeness Assessment.....	3
B.	Check of Completeness Assessment Elements.....	4
IV.	COMPLETENESS ASSESSMENT OUTCOMES.....	5
V.	API INFORMATION INCLUDED IN A GENERIC DRUG SUBMISSION.....	6
VI.	SUMMARY	6
	DEFINITIONS	7
	APPENDIX 1.....	8

Completeness Assessments for Type II API DMFs Under GDUFA Guidance for Industry¹

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 are or will be referenced in an abbreviated new drug application (ANDA), an amendment to an ANDA, a prior approval supplement (PAS) to an ANDA, or an amendment to a PAS (generic drug submissions). The guidance explains that, as of October 1, 2012, under the Generic Drug User Fee Amendments of 2012, commonly referred to as GDUFA:²

- DMF holders are required to pay a DMF fee when first authorizing the reference of their DMF in a generic application³
- Type II API DMFs must undergo an FDA completeness assessment (CA)

The guidance makes recommendations about the information that should be included in the DMF to facilitate a GDUFA CA. The guidance does not apply to Type II API DMFs used to support new drug applications (NDAs), biologics license applications (BLAs),⁴ other submissions that are not generic drug submissions, 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 the word *should* in Agency guidances means that something is suggested or recommended, but not required.

¹ This guidance has been prepared by the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research at the Food and Drug Administration.

² Public Law 112-144, Title III.

³ For these purposes, such authorization is deemed to have occurred when the DMF "is referenced on or after October 1, 2012, in a generic drug submission by an initial letter of authorization," Section 744B(a)(2)(A) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 379j-42(a)(2)(A)).

⁴ Type II API, API intermediate, and drug product DMFs are not used to support BLAs submitted pursuant to sections 351(a) and 351(k) of the Public Health Service Act (42 U.S.C. 262).

⁵ See section 744A(7) of the FD&C Act (21 U.S.C. 379j-41(7)).

Contains Nonbinding Recommendations

II. BACKGROUND

Under GDUFA, beginning October 1, 2012, the holder of a Type II API DMF must pay a one-time DMF fee when the DMF is first referenced in a generic drug submission submitted to FDA on the basis of a letter of authorization (LOA) from the DMF holder.⁶ Also under GDUFA, holders of Type II API DMFs that were evaluated *before* October 1, 2012, must pay a one-time fee for the DMF when their DMF is first referenced in a new ANDA, an ANDA or PAS amendment, or an ANDA PAS on or after October 1, 2012.⁷ Only Type II API DMFs for use in generic drug submissions incur this one-time fee.

Under GDUFA, Type II API DMFs intended for reference in a generic drug submission for which the fee is paid will undergo a CA. Section 744B(a)(2)(D)(iii) of the FD&C Act requires FDA to make publicly available on its Web site a list of DMF numbers that correspond to DMFs that, having successfully undergone a CA in accordance with criteria to be published by FDA, are available for reference.

Although the requirement for a CA for Type II API DMFs is new, FDA has previously evaluated DMFs in accordance with the criteria set out in the GDUFA Completeness Assessment Checklist for Type II API DMFs (CA Checklist), attached to this guidance as Appendix 1. In order to ensure adequate time for the CA, FDA strongly encourages the DMF holder to submit a complete DMF and pay the DMF fee at least 6 months prior to the submission of an ANDA or PAS that will rely on the DMF. When submitting a DMF, the DMF holder should also submit Form FDA 3794, the Generic Drug User Fee Cover Sheet, which includes the minimum information necessary for FDA to determine whether a DMF holder has satisfied all relevant user fee obligations.⁸

DMF holders are encouraged to submit their DMFs using the Electronic Common Technical Document (eCTD) format.⁹ More information is available on the eCTD format on FDA's Web site.¹⁰

III. COMPLETENESS ASSESSMENT

⁶ Section 744B(a)(2) of the FD&C Act (21 U.S.C. 379j-42(a)(2)). For discussion of LOAs, see 21 CFR 314.420(b) and 314.50(g)(1).

⁷ The fee amount will be announced in the *Federal Register* not later than 60 days before the start of the fiscal year (generally on or about August 1 of the previous fiscal year).

⁸ See <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM322676.pdf>.

⁹ Note that 24 months after the guidance for industry *Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specification* is finalized (i.e., May 5, 2017), DMFs will be required to be submitted using the eCTD format pursuant to the implementation timeline identified in the final guidance.

¹⁰ See information about electronic submissions at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>.

Contains Nonbinding Recommendations

FDA will perform a CA once a DMF holder files a Type II API DMF¹¹ with the Form FDA 3794 and there is an initial verification of the fee payment. The CA does not replace the full scientific review, which determines whether the information contained in the DMF is adequate to support an ANDA regulatory action.

In brief, FDA will undertake a CA to determine the following:

- Is the DMF active?
- Has the fee been paid?
- Has the DMF been previously reviewed?
- Does the DMF pertain to a single API?
- Does the DMF contain certain administrative information?
- Does the DMF contain all the information necessary to enable a scientific review?¹²
- Is the DMF written in English?¹³

FDA will conduct the CA by determining the answers to a series of questions listed in the CA Checklist, which is included in Appendix 1. DMFs for which the fee has been paid and which have been found complete in accordance with the criteria for a CA set out in the CA Checklist will be identified on FDA's public Web site as available for reference in support of a generic drug submission.

For complex APIs, in addition to the recommendations in the CA Checklist, DMF holders should ensure the DMF provides the data necessary for the Agency to review the DMF with respect to active ingredient sameness. Information on active ingredient sameness is discussed in the product's specific bioequivalence (BE) guidance when it becomes available on FDA's Web site.¹⁴

In accordance with the Generic Drug User Fee Amendments Reauthorization Performance Goals and Program Enhancements (GDUFA II Commitment Letter),¹⁵ FDA committed to complete the initial CA review for 90% of Type II API DMFs within 60 days of the later of the date of DMF submission or DMF fee payment.

A. Information Confirmed During the Completeness Assessment

¹¹ See FDA's Web site on Drug Master Files at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/default.htm>.

¹² Id.

¹³ If any part of the application is in a foreign language, an accurate and complete English translation shall be appended to such part. See 21 CFR 314.101(d)(5).

¹⁴ For example, for enoxaparin sodium: listed sameness equivalence criteria in the draft guidance include mode of depolymerization, source material, physicochemical properties, disaccharide building blocks, fragment mapping, sequence of oligosaccharide species, and biological and biochemical assays. If the appropriate product-specific data is not in the DMF, the DMF will be deemed incomplete.

¹⁵ Available at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM370352.pdf>.

Contains Nonbinding Recommendations

FDA will use the CA Checklist to perform the CA. At the top of the cover page of the CA Checklist, FDA will fill in basic information about the DMF, including its name, number, receipt date, and whether the DMF was submitted in electronic or paper format.

The FDA will also note whether the primary DMF the ANDA references refers to any other DMFs (subject DMFs). A primary DMF can reference subject DMFs, which provide additional information needed to completely describe the manufacture of an API.¹⁶ Before submitting its DMF, the primary DMF holder should check with the holders of any referenced subject DMFs to make sure the subject DMFs are filed with FDA and FDA still considers them active.

1. Is the DMF Active?

Before assigning a DMF to a reviewer for a CA, FDA will confirm that the DMF is active.¹⁷ If the primary DMF or any referenced subject DMFs on file at FDA are inactive, FDA will consider the primary DMF incomplete and send a letter notifying the DMF holder.

2. Has the DMF fee been paid?

Before assigning a DMF to a reviewer for a CA, FDA will confirm that the DMF fee has been paid. If it has not, FDA will not assign the DMF for CA. ANDA applicants that reference a DMF for which a fee is due will be notified that the DMF holder has not paid the fee. If the DMF fee is not paid within 20 days after notification, FDA will refuse to receive the ANDA referencing the DMF.

3. Has the DMF been previously reviewed for chemistry, manufacturing, and controls (CMC) by FDA in the context of a review of a prior application?

If FDA has reviewed the DMF for CMC after November 30, 2007, the DMF will be considered to have passed the CA without further analysis. If the DMF was reviewed for CMC prior to November 30, 2007, a CA assessment will need to be performed. For all DMFs that have not previously received a full CMC review, a CA assessment will need to be performed. If the DMF has not previously received this full review, it will be assigned to a reviewer for a CA.

B. Check of Completeness Assessment Elements

FDA will complete the administrative part of the CA Checklist (i.e., “General Information”) during the CA. If the DMF is incomplete, FDA will send the DMF holder a GDUFA DMF Incomplete Letter. With certain exceptions specified in this guidance document, this letter will provide comments about each element that resulted in an incomplete designation for the CA.

If an item is marked “n/a” and does not apply to the DMF, the element is treated the same as if it were marked “yes.”

¹⁶ For example, a subject DMF may describe the manufacture of a material used in producing the active ingredient. If a subject DMF does not meet the definition of a Type II API DMF, it will not incur a DMF fee.

¹⁷ “Active” is defined in the Definitions section of this guidance.

Contains Nonbinding Recommendations

1. Is the subject of the DMF a single API produced by one manufacturing process?

The subject of a DMF should be limited to one API and one manufacturing process. If a DMF includes information on more than one API or more than one manufacturing process for an API, the DMF will be deemed incomplete. If the DMF describes multiple APIs, the DMF holder should file separate DMFs for each API. Similarly, if there are multiple manufacturing processes for an API, the DMF holder should file separate DMFs for each manufacturing process.

2. Does the DMF holder need to submit a complete update?

If the DMF is in paper format and it has been five years or more since the DMF received a complete update,¹⁸ or if there have been more than five amendments to the DMF, the DMF holder should provide a complete and comprehensive update to it. If such a DMF has not received an update, FDA will consider the DMF incomplete. The DMF holder must submit a complete update for FDA to determine whether it passes the CA.¹⁹

FDA believes that the remainder of the CA Checklist is self-explanatory.

IV. COMPLETENESS ASSESSMENT OUTCOMES

Following the CA, FDA will find the DMF either complete or incomplete.

- If the DMF is found complete, FDA will post the DMF number on a publicly available list on FDA's Web site to indicate the DMF is available for reference by generic drug submission applicants.²⁰
- If the DMF is found incomplete, the CA findings and comments will be compiled in a GDUFA DMF Incomplete Letter to the DMF holder that explains why the DMF was deemed incomplete. Information about the CA status of a DMF, other than the lack of a public listing on the FDA's Web site, will not be provided to anyone except the DMF holder and, as necessary, any generic drug submission applicant that the DMF holder has authorized to rely on the DMF.
- To remedy a GDUFA DMF Incomplete Letter and pass the CA, the DMF holder should submit an amendment to its DMF to correct the deficiencies identified in the Incomplete Letter, or, if FDA has determined that the DMF should undergo a complete update, the DMF holder should resubmit the DMF with that update. FDA will then assess the

¹⁸ All changes must be reported as amendments. Annual reports are **NOT** to be used to report changes in the DMF.

¹⁹ The requirement for a complete update does not apply to the DMF if the entire DMF is in eCTD format, which always presents the DMF in its current state. The Agency highly encourages DMF holders to convert the entire DMF into an eCTD submission, which does not require reference to any previous paper submission.

²⁰ For the public list of DMFs available for reference, see <http://www.fda.gov/gdufa>.

Contains Nonbinding Recommendations

revised DMF's completeness. If there are no deficiencies at this time, FDA will declare the DMF to be complete and to have passed the CA.

- Although a DMF may be deemed incomplete upon its first CA, FDA will work with DMF holders to provide guidance on how to revise the DMF so it may be found complete after resubmission. Once the DMF passes the CA, FDA will make the DMF number publicly available on its Web site.²¹

V. API INFORMATION INCLUDED IN A GENERIC DRUG SUBMISSION

If a generic drug submission contains all the necessary API information and does not rely on information contained in a DMF, no CA will be performed. Instead, this information will be evaluated during the ANDA filing review.²² However, because GDUFA requires collection of a one-time fee for API information included in a generic drug submission (i.e., an (a)(3)(F) fee),²³ the applicant submitting the generic drug submission containing the API information must pay this fee.

VI. SUMMARY

Once the DMF fee is received, FDA will evaluate the DMF to make sure it meets the CA criteria.

- If the DMF passes the CA, it will be found complete and the DMF number will be made publicly available on FDA's Web site.
- If the DMF fails the CA, FDA will send a GDUFA DMF Incomplete Letter describing to the DMF holder the missing elements in its DMF.
- If the DMF holder addresses all the deficiencies and amends the DMF or completely updates the DMF per the CA request, the FDA will complete its CA. If the DMF is then found complete, the DMF number will be made publicly available on FDA's Web site.
- If a generic drug submission contains all the necessary API information and does not reference a DMF, the generic drug submission applicant will be required to pay the (a)(3)(F) fee. No CA will be conducted.

²¹ Under GDUFA, a condition for a Type II API DMF to be considered available for reference is that it "has not failed an initial completeness assessment" (Section 744B(a)(2)(D)(ii)(II) of the FD&C Act). FDA does not interpret that provision as disqualifying a DMF if it has ever failed a CA. Instead, FDA considers this condition to be satisfied when, after submission of an amendment or resubmission of the DMF to address deficiencies identified by FDA, FDA finds that the DMF has passed the CA.

²² See guidance for industry *ANDA Submissions – Refuse-to-Receive Standards*.

²³ Section 744B(a)(3)(F) of the FD&C Act.

Contains Nonbinding Recommendations

DEFINITIONS

Active pharmaceutical ingredient²⁴ (as defined by GDUFA):

- (A) A substance, or a mixture when the substance is unstable or cannot be transported on its own, intended
 - (i) to be used as a component of a drug; and
 - (ii) to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the human body; or
- (B) a substance intended for final crystallization, purification, or salt formation, or any combination of those activities, to become a substance or mixture described in subparagraph (A).

Active DMF: A drug master file (DMF) for which the FDA has made a determination that the DMF was acceptable for filing administratively and is up to date.

DMF holder:²⁵ Designated owner of the DMF, which may be different from the U.S. agent listed as the contact.

Generic drug submission:²⁶ An abbreviated new drug application (ANDA), an amendment to an ANDA, a prior approval supplement (PAS) to an ANDA, or an amendment to a PAS.

Letter of authorization (LOA):²⁷ A written statement by the holder or designated U.S. agent or representative permitting FDA to refer to information in the DMF in support of another person's²⁸ generic drug submission.

Type II Active Pharmaceutical Ingredient Drug Master Files:²⁹ The submission of API information to the FDA by the DMF holder who intends to authorize generic drug applicants to rely on the information to support submissions to the FDA without the holder having to disclose the information to the generic drug applicants.

²⁴ Section 744A(2) of the FD&C Act.

²⁵ See 21 CFR 314.420(a).

²⁶ Section 744A(7) of the FD&C Act.

²⁷ See FDA's Web site on Drug Master Files at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/default.htm>.

²⁸ The word "person" includes individual, partnership, corporation, and association (section 201(e) of the FD&C Act.

²⁹ Section 744A(12) of the FD&C Act; also see 21 CFR 314.420(a)(2).

Contains Nonbinding Recommendations

APPENDIX 1

**GDUFA COMPLETENESS ASSESSMENT CHECKLIST FOR
TYPE II API DMFs**

DMF NUMBER: DMF HOLDER: DRUG NAME (subject): SUBMIT DATE: RECEIVED DATE: Electronic or paper submission: DMF(s) referenced by the primary DMF being assessed, if applicable: <input type="checkbox"/> EXPEDITED ASSESSMENT per REQUEST from FDA by: (requestor name here)
--

Primary reviewer: Date:	Review recommendation for completeness assessment: <input type="checkbox"/> COMPLETE <input type="checkbox"/> INCOMPLETE
--------------------------------	--

1. Has the GDUFA fee been paid? Enter date paid:

Yes No

2. Is the DMF active?

Yes No

If no, DMF is INCOMPLETE per policy. Issue Incomplete Letter to DMF holder.

3. Has the DMF been reviewed, after November 30, 2007, for chemistry, manufacturing, and controls (CMC) by FDA in the context of a review of a prior application?

Yes No

If "yes," the DMF is COMPLETE per policy.

If "no," review DMF with checklist.

ADDITIONAL COMMENTS REGARDING THE DMF:

--

Contains Nonbinding Recommendations

Checklist Review

GENERAL INFORMATION

			NOTE(S)
	<p>1. Subject of the DMF is a single API produced by one manufacturing process.</p> <p>2. For previously submitted DMFs, the DMF holder has submitted a complete update.</p> <p>3. Provides current Good Manufacturing Practice (cGMP) Statement of Commitment.</p> <p>4. Provides complete name, address, and contact information for holder.</p> <p>5. Designates U.S. Agent for non-U.S. DMF holders, with appropriate designation letter.</p> <p>6. Contains Letters of Authorization for any DMFs referenced to support this DMF.</p> <p>7. All DMFs referenced in this DMF have been filed with the Agency and are active.</p> <p>8. Contains label with storage conditions and expiry/retest date.</p> <p>9. Contains bovine spongiform encephalopathy (BSE)/transmissible spongiform encephalopathy (TSE) certification, if animal-sourced.</p> <p>10. Contains information on adventitious agents, if animal-sourced.</p> <p>11. Contains information on presence of pesticides, if plant-sourced.</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> n/a</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> n/a</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> n/a</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> n/a</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> n/a</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> n/a</p>	<p>For #1: The DMF is limited to: (i) one API, although multiple manufacturing sites for a single API are permitted when the same process is used in each of those sites; (ii) one manufacturing process, although certain process alternatives/changes may be permissible with sufficient supportive information provided. Examples include: validated reprocess/rework procedures; micronization leading to different particle sizes (excluding nano particles); addition of a stabilizing agent for stability purposes; and minor process variation that leaves the chemical transformation the same, with little risk to the impurity profile.</p> <p>A separate DMF should be filed for: different salt form; different synthetic route; and significant process variation resulting in a different impurity profile and requiring a different control strategy.</p> <p>For the definition of API and the Agency's interpretation, refer to GDUFA Q&A guidance.</p> <p>For #2: Five years or five amendments are a good guide to determine the necessity for submission of a complete update, because a large number of amendments with significant changes make it difficult to determine the current state of the information in the DMF. The complete update should reflect the current state of the process and not require reference to any previous submission for information.</p> <p>The requirement for a complete update does not apply to the DMF if the entire DMF is in electronic common technical document (eCTD) format, which always presents the DMF in its current state. We highly encourage DMF holders to convert</p>

Contains Nonbinding Recommendations

			the entire DMF into an eCTD submission, which does not require reference to any previous paper submission.
--	--	--	--

MODULE 2: SUMMARIES³⁰

eCTD No.			NOTE(S)
2.3	12. Contains a Quality Overall Summary (QoS).	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> n/a	For #12: If a QoS is provided, the Question-based Review (QbR) format is highly encouraged.

MODULE 3: QUALITY

3.2 Body of Data

3.2.S API [name, manufacturer]

eCTD No.			NOTE(S)
3.2.S.1	<p>General Information</p> <p>Contains complete <u>General Information</u> on the following:</p> <p>13. Nomenclature.</p> <p>14. Structure.</p> <p>15. General Properties: basic information regarding the general properties of the API.</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>	

³⁰ DMF holders are highly encouraged to submit files in eCTD format. See information about electronic submissions at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm> and ICH M4Q: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4_R1_Quality/M4Q_R1_.pdf. Note that 24 months after the guidance for industry *Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specification* is finalized (i.e., May 5, 2017), DMFs will be submitted using the eCTD format pursuant to the implementation timeline identified in the final guidance.

Contains Nonbinding Recommendations

eCTD No.			NOTE(S)
3.2.S.2	<p>Manufacture</p> <p>3.2.S.2.1 Contains complete <u>Manufacturer Information on the following for each site:</u></p> <p>16. Name and full address(es) of the manufacturing facility(ies), contact name of on-site individual, phone and fax numbers, and e-mail address.</p> <p>3.2.S.2.2 Contains <u>Description of Manufacturing Process and Process Controls</u> addressing the following:</p> <p>17. If the API is synthetic/semi-synthetic, provides complete synthetic scheme from <u>appropriately supported starting materials</u>. Scheme includes structural representation with reagents, reaction conditions, molar ratio, etc.</p> <p>18. Flow chart for every stage.</p> <p>19. Description of the manufacturing process.</p> <p>3.2.S.2.3 Contains information on the <u>Control of Materials</u>, as follows:</p> <p><i>Starting Material:</i></p> <p>20. Starting material, clearly designated, with appropriate justification.</p> <p>21. Name of each manufacturer.</p> <p>22. Specification.</p> <p>23. Analytical method.</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> n/a</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>	<p>For #16: Separate facilities used for release testing of the API and for additional processing (e.g., micronization) should also be listed.</p> <p>Central File Number (CFN), Facility Establishment Identifier (FEI), and Data Universal Numbering System (DUNS) numbers should be provided if available.</p> <p>For #17: For a fermentation process, information pertaining to the quality and control of the microorganism, cell bank systems, and media components should be provided.</p> <p>For #20: Justification for designation of each starting material should be in agreement with the general principle outlined in International Conference on Harmonisation (ICH) Q11. This can include information, if applicable, on:</p> <ul style="list-style-type: none"> • Name, address, and contact information of the manufacturer(s) of each proposed starting material. • A flow diagram and description outlining the synthetic route and conditions of each proposed starting material. • Discussion of the impurities (including residual solvents and inorganic impurities) arising from

Contains Nonbinding Recommendations

eCTD No.			NOTE(S)
	<p>24. Certificate of Analysis (CoA) from manufacturer.</p> <p>25. CoAs from the DMF holder.</p> <p><i>Reagents/Solvents:</i></p> <p>26. Specifications.</p> <p>27. Representative CoAs.</p> <p>3.2.S.2.4 Contains information for <u>Controls of Critical Steps and Intermediates</u>, as follows:</p> <p>28. In-process controls and tests, described for each critical step.</p> <p><i>Intermediates:</i></p> <p>29. Specifications for each identified intermediate.</p> <p>30. Analytical methods for each intermediate.</p> <p>3.2.S.2.5 Process Validation and/or Evaluation</p> <p>31. Contains a summary of Process Validation and/or Evaluation information.</p> <p>32. Provides sterility assurance data for sterile API.</p> <p>3.2.S.2.6 Manufacturing Process Development</p> <p>33. Contains a summary of Manufacturing Process Development.</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> n/a</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> n/a</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>	<p>the manufacturing process of each proposed starting material.</p> <ul style="list-style-type: none"> • The ability of analytical procedures to detect impurities in the starting material. • The fate and purge of those impurities and their derivatives in subsequent processing steps. • How the proposed specification for each starting material will contribute to the control strategy. <p>For #26: Specifications should clearly identify the test methods. For non-compendial methods, the method description should be provided.</p> <p>For #31: If the validation has been performed, the DMF holder should provide a validation summary, including batch descriptions with traceability among steps/stages, and analytical test results for the starting materials, intermediates, in-process controls, and final API, preferably in a tabular format.</p> <p>For #32: The full sterilization process validation and the method validation of sterility tests for the sterilized API should be provided, including but not limited to: description of the specific sterilization processes for the bulk drug substance and all associated manufacturing equipment, components, and containers/closures, description of sterile processing areas, list of all filling lines/rooms/suites, legible floor plans for sterile API manufacturers, description of environmental monitoring program for sterile</p>

Contains Nonbinding Recommendations

eCTD No.			NOTE(S)
			products, validation data for sterilization of bulk API, filter validation data if applicable, validation data for the sterilization and depyrogenation of the final container/closure system, validation data for the sterilization of all manufacturing equipment and components, description of process simulation/media fill program and associated data from media fill runs and container/closure integrity testing results.
3.2.S.3	<p>Characterization</p> <p>3.2.S.3.1 Provides information to support the Elucidation of Structure and other Characteristics of the API as follows:</p> <p>34. Characterization information appropriate for the material (e.g., nuclear magnetic resonance (NMR), infrared (IR), ultraviolet (UV), mass spectrometry (MS), elemental analysis, etc.).</p> <p>3.2.S.3.2 Provides information on Impurities, as follows:</p> <p>35. A table including the name(s), structure(s), origin (degradant, process impurity) of observed/potential organic impurities.</p> <p>36. Information on potential inorganic impurities (inorganic) (e.g., metal catalysts, reagents).</p> <p>37. Potential residual solvents.</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>	<p>For #34: Data interpretation should be provided; spectroscopic comparison with authenticated material (e.g., United States Pharmacopeia (USP) Convention reference standard), if available, is encouraged to confirm the structure.</p> <p>For #35: Potential genotoxic impurities can be included in this table or summarized in a separate table.</p>
3.2.S.4	<p>Provides information to support the <u>Control of the API</u>, as follows:</p> <p>38. Full test specification.</p> <p>39. Description of the analytical methods.</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>	<p>For 3.2.S.4: A summary of the control strategy, as illustrated in ICH Q11, is highly encouraged.</p> <p>For #40: Method verification reports</p>

Contains Nonbinding Recommendations

eCTD No.			NOTE(S)
	<p>40. Method validation and/or method verification reports.</p> <p>41. CoAs for representative batches (batch analysis).</p> <p>42. Justification for each specification.</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>	<p>should be provided for compendial methods, such as assay or related substance by high-performance liquid chromatography (HPLC); the method equivalency study should be provided when an in-house method is used in lieu of a compendial method.</p>
3.2.S.5	<p>Provides information to support the <u>Reference Standards or Materials</u>, as follows:</p> <p><i>API:</i></p> <p>43. The source, lot #, CoA (for primary reference standard (RS) and working standard (WS)).</p> <p>44. Qualification data on the drug substance (DS) RS.</p> <p><i>Impurities:</i></p> <p>45. The source, lot #, and CoA for RS and WS for each identified impurity.</p> <p>46. Qualification data on the impurity RS.</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>	<p>For #44: Qualification data on in-house primary RSs includes spectroscopic characterization and quantification by mass balance. When a compendial RS is used as the primary RS, the lot number and certificate are sufficient. WSs should be adequately qualified against the primary RS. Spectroscopic comparison with compendial reference standards, when available, is highly encouraged. Data can be cross-referenced to 3.2.S.3.2, if appropriate.</p> <p>For #46: See note for #44 above.</p>
3.2.S.6	<p>Provides information to support the <u>Container/Closure System</u>, as follows:</p> <p>47. Description of container/closure system (including contact material and secondary material).</p> <p>48. Certification statements for contact materials for use in food and drugs.</p> <p>49. Manufacturer, specifications, and representative CoA for primary contact material and functional secondary packaging component.</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>	<p>For #48: The certification statement from the supplier should state that each primary packaging material for the DS is safe to use in contact with food, with an appropriate reference to the indirect food additive regulations (21 CFR 174-186).</p>
3.2.S.7	<p>Provides information to support the <u>Stability of the API</u>, as follows:</p>		

Contains Nonbinding Recommendations

eCTD No.			NOTE(S)
	<p>3.2.S.7.1 Stability Summary and Conclusions</p> <p>50. Indicates clearly the retest date or expiration date of API.</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No	
	<p>3.2.S.7.2 Postapproval Stability Protocol and Stability Commitment</p> <p>51. Provides stability protocol.</p> <p>52. Provides stability commitment.</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> No	
	<p>3.2.S.7.3 Stability Data</p> <p>53. Provides Stability Data.</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No	

MODULE 3: 3.2.R REGIONAL INFORMATION (API)

eCTD No.			NOTE(S)
3.2.R	<p>Provides regional information, as follows:</p> <p>3.2.R.1.S Executed Batch Records for API</p> <p>54. Provides representative executed batch records, with translation, where appropriate.</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No	<p>For #54: Yields, results of in-process controls, and intermediate analysis should be provided where appropriate.</p>