Drug Master Files
Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Rick Ensor 240-402-2733, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

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)

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Revision 1

Drug Master Files
Guidance for Industry

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TABLE OF CONTENTS

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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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 FDA's current thinking on drug master files (DMFs), which are submissions to FDA that may be used to provide confidential, detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of human drug products. DMFs can contain other types of information as well (e.g., toxicology information, shared system REMS (risk evaluation and mitigation strategy)).

DMF holders can authorize one or more applicants or sponsors to incorporate by reference information contained in the DMF without having to disclose that information to the applicants or sponsors. DMFs are submitted solely at the discretion of their holders and are not required by statute or regulation. They are not typically submitted for nonproprietary materials. Ordinarily, FDA neither independently reviews nor approves DMF submissions. Instead, FDA customarily reviews the technical contents of DMFs only in connection with the review of applications that reference them.[2]

DMFs can be used to support (but are not substitutes for) applications reviewed by FDA. This guidance focuses on the following submissions to the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER):

- DMFs under 21 CFR 314.420 that are used to support new drug applications (NDAs), abbreviated new drug applications (ANDAs), and investigational new drug applications (INDs) under the Federal Food, Drug, and Cosmetic Act (FD&C Act).

- DMFs and other master files under 21 CFR 601.51(a) that are used to support biologics license applications (BLAs) under the Public Health Service Act (PHS Act).

[1] This guidance has been prepared by the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research and in consultation with the Center for Veterinary Medicine at the Food and Drug Administration.

[2] In this guidance, the term *review* also means *assessment.* Both terms refer to the process of evaluating and analyzing submitted data and information to determine whether the application meets the requirements for approval and documenting that determination.

Additionally, information contained in DMFs can generally be referenced in premarket submissions for devices (e.g., premarket approvals) and animal drugs (e.g., new animal drug applications). Although the focus of this guidance is on the submissions to CDER and CBER described above, in general, FDA believes the contents of this guidance will assist other master file holders in providing complete and up-to-date master files to FDA.

This guidance provides information about preparing and submitting DMFs. It describes DMF types, the information needed in DMF submissions, and FDA's DMF review processes. For additional information, see FDA's DMF web pages.[3]

This guidance revises the guidance for industry *Drug Master Files: Guidelines* that published in September 1989. Most of the information contained in the 1989 guidance has been retained here, with significant reorganization.

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. TYPES OF DMFS

Four types of DMFs are covered by § 314.20, as illustrated in the table below.

Types of DMFs

DMF Type*	Subject of Information Provided in the DMF
Type II**	Drug substance, drug substance intermediate, and materials used in their preparation, or drug product
Type III	Packaging material
Type IV	Excipient, colorant, flavor, essence, or material used in their preparation
Type V	FDA-accepted reference information

* Type I DMFs were discontinued in 2000 but the numbering of the other DMF types has not changed. FDA's approach to the terminology for types of master files used for products subject to approval under the PHS Act has generally tracked its approach to the types of DMFs (e.g., Type II, Type III) used for products regulated under the FD&C Act.

** Although FDA's approach to the use of master files in BLAs under the PHS Act largely parallels its approach to the use of DMFs in applications under the FD&C Act, there is a significant difference: a BLA holder is generally expected to have knowledge of and control over the manufacturing process for the biological product for which it has a license. For biological products in BLAs under the PHS Act, FDA has, as a scientific matter, generally not

[3] For CDER, see https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs; for CBER, see https://www.fda.gov/vaccines-blood-biologics/new-drug-application-nda-process-cber/drug-master-files-cber-regulated-products.

permitted applicants to incorporate information about drug substance, drug substance intermediate, or drug product by reference to a master file; rather, FDA generally expects such information to be submitted directly to the BLA.

III. DMF SUBMISSIONS

This section describes the format and delivery of DMF submissions, outlines the content of original and subsequent DMF submissions, offers submission recommendations specific to the four types of DMFs, and ends with some broader recommendations for DMF holders to consider when submitting DMFs.

A. Format and Delivery

DMF submissions are subject to the electronic submission requirements as set forth in guidance implementing section 745A of the FD&C Act, including the guidance for industry *Providing Regulatory Submissions in Electronic Format—Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (Rev. 6)* (*Providing Regulatory Submissions* guidance).[4] The *Drug Master Files* guidance is not issued under section 745A of the FD&C Act and does not establish legally enforceable responsibilities. To the extent it discusses binding requirements for DMFs, such requirements have been promulgated in previously issued guidance under section 745A and FDA regulations.

Unless otherwise stipulated in the *Providing Regulatory Submissions* guidance or successor guidance under section 745A, DMF submissions must have a DMF number, must be submitted in the electronic format specified in such guidance, and, if 10 gigabytes or smaller, must be submitted through the Electronic Submissions Gateway (ESG).[5] Submissions over 10 gigabytes can be submitted through ESG *or* they can be submitted on physical media (e.g., CD-ROM) accompanied by a cover letter as described below and with prepaid delivery charges.[6] The standard electronic format for DMFs is electronic common technical document (eCTD) format.[7]

For proper routing of DMFs, it is important to choose the appropriate center—CDER or CBER—from the menu of choices when submitting through ESG. DMF holders who wish to submit information that may be reviewed in multiple centers should consult the respective centers. See the CDER and CBER DMF web pages for contact information.[8]

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[4] Revision 7 of *Providing Regulatory Submissions* is available as a draft guidance. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[5] See the *Providing Regulatory Submissions* guidance.

[6] Ibid.

[7] For more information on electronic submissions, see FDA's Electronic Regulatory Submissions and Review web page at https://www.fda.gov/drugs/forms-submission-requirements/electronic-regulatory-submission-and-review, eCTD web page at https://www.fda.gov/ectd, ESG web page at https://www.fda.gov/industry/electronic-submissions-gateway, and *Transmitting Electronic Submissions Using eCTD Specifications* at https://www.fda.gov/media/76812/download.

[8] See footnote 3.

CDER's DMF web page links to templates for certain submissions (e.g., cover letters, annual reports) that recommend elements that DMF holders can include in these submissions.[9] This guidance refers to these templates where applicable rather than listing each element that FDA recommends be included in a particular submission.

B. Original Submissions

Before submitting an original DMF in eCTD format, DMF holders must obtain a pre-assigned number.[10] For CDER submissions, see Requesting a Pre-Assigned Application Number at https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/requesting-pre-assigned-application-number. For CBER submissions, send requests for application numbers via secure email to cberrims@fda.hhs.gov and include the sponsor/applicant name and address, point of contact name and number, product name, and anticipated submission date.

Original submissions should contain a cover letter and complete administrative and technical information in the appropriate eCTD modules. Although some eCTD module section headings refer to *change* and *sponsor/applicant*, they are applicable to original and subsequent submissions to DMFs.

This section reviews the eCTD modules and module sections that are relevant for original submissions. For a complete list of eCTD section headings, see FDA's *Comprehensive Table of Contents Headings and Hierarchy*, which can be found in the eCTD Submission Standards on FDA's eCTD website (https://www.fda.gov/ectd). For additional formatting recommendations, see the following:

- *Providing Regulatory Submissions* guidance.
- International Council for Harmonisation (ICH) guidance for industry *M4 Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use*.
- ICH guidance for industry *M4Q: The CTD—Quality*.
- Draft guidance for industry *Submitting Marketing Applications According to the ICH-CTD Format—General Considerations*.[11]

[9] Holders submitting DMFs that contain information that is intended for use by applications for biological products may also use these templates.

[10] See the *Providing Regulatory Submissions* guidance.

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

1. Module 1

a. Cover letter (eCTD section 1.2)

FDA recommends using the cover letter template for original submissions on CDER's DMF web page at https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs.[12] As laid out in this template, the cover letter should specify the submission type (e.g., original, agent appointment). A table of submission types is available on CDER's DMF web page. The cover letter should also include a statement of commitment signed by the DMF holder stating that the DMF is current and that the holder will comply with the statements made in the DMF. (Alternatively, the statement of commitment can be a separate document included in eCTD section 1.2.) See the template for additional information to include.

b. Administrative information (eCTD section 1.3)

The administrative information section should include information about the DMF holder, the agent (if applicable), the manufacturer, and debarment certification (for more information about debarment certification, see section III.B.1.b.iv in this guidance).

i. DMF holder

DMF holders should provide their name and address. Only one company should be listed as the DMF holder. Joint submissions are not accepted.

ii. Contact/Agent

DMF holders should provide the name, telephone and fax numbers, email address, and specific responsibilities of the contact person and the responsible official (if different from the contact person).

To facilitate communication, FDA strongly encourages foreign DMF holders to appoint an agent, preferably in the United States, who is familiar with FDA regulations, guidances, and procedures. However, DMF holders, not their agents, are responsible for the contents of their DMFs (e.g., all aspects of the chemistry, manufacturing, and controls (CMC) information). Agents can submit to the DMF on behalf of DMF holders. They can sign DMF submissions as well, with the following exceptions:

- Agent appointment letters.
- Statements of commitment.
- Name changes.
- Holder transfers.
- New holder acceptance letters.
- DMF closure requests.

[12] FDA is developing a form to replace the cover letter used for original and subsequent submissions. The form should be available by the time this guidance is finalized.

An agent for DMF purposes is not the same as an agent for the purposes of the Drug Listing and Registration System (DRLS). DMF holders should not include the name of the agent for registration purposes in the DMF unless the same person or company is the agent for both the DMF and DRLS.

DMF holders can have different agents for different DMFs.

DMF holders should submit agent appointment letters in their original submissions or in administrative amendments. The letter should be on the DMF holder's letterhead and should contain the agent's name, address, contact person's name (if different from the agent's name), telephone and fax numbers, and email address, among other information. FDA recommends using the agent appointment letter template on CDER's DMF web page at https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs.

iii. Manufacturer

DMF holders should provide the manufacturer's name, site address, and contact person's name, telephone and fax numbers, and email address.

iv. Debarment certification

DMF holders are included in the category of "Persons whose services were used in any capacity in connection with the application" required under section 306(k)(1) of the FD&C Act. DMF holders can submit their own debarment certifications in eCTD section 1.3.3.

For more information on debarment certifications, see draft guidance for industry *Submitting Debarment Certification Statements*.[13]

c. References (eCTD section 1.4)

i. Letter of authorization

FDA will not review a DMF until the DMF holder submits a letter of authorization (LOA) to the DMF regarding a specific application or other DMF (§ 314.420(d)). LOAs can be submitted as part of the original submission or in a subsequent submission. The LOA permits FDA to review the DMF and permits the authorized party (i.e., the company or individual who submits an application or another DMF) to incorporate information into an application or another DMF by reference (eCTD section 1.4.1). An LOA should still be submitted even if the authorized party and the DMF holder are the same company.

The DMF holder should send a copy of the LOA to the authorized party. The authorized party must include a copy of the LOA in its application (§ 314.50(a)(1)) or DMF (eCTD section 1.4.2). An LOA does not give an authorized party permission to view or access a DMF.

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

Note:

- An LOA should not be used to authorize an agent or representative to act on behalf of a company.
- An LOA should not be used to authorize DMF holder employees to submit information to the DMF.
- An LOA can be submitted by an agent but ultimately the DMF holder is responsible for the LOA.
- An LOA should not have multiple authorized parties; DMF holders should submit a separate LOA for each party.
- If the DMF holder changes its name, the DMF holder should submit a new LOA using the "Replace" function in the electronic submission.
- If an authorized party changes its name, the DMF holder should submit a new LOA using the "Replace" function in the electronic submission.
- An LOA does not need to include the name of the individual employed by the authorized party (i.e., a contact person). The name of the applicant is sufficient.
- An LOA should distinguish between those facilities that will be used for purposes of the authorization versus other facilities that are part of the DMF but are not applicable to the authorization. Unless this specification is present in the LOA, FDA will assume that all facilities listed in a DMF apply to the referencing application.

FDA recommends using the LOA template on CDER's DMF web page at https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs. As laid out in this template, the LOA should include, among other information, a statement of commitment signed by the DMF holder stating that the DMF is current and that the holder will comply with the statements made in the DMF. (Alternatively, the statement of commitment can be included in eCTD section 1.2 and referenced in the LOA.)

ii. List of authorized persons to incorporate by reference

In eCTD section 1.4.3, DMFs must list each party currently authorized to incorporate by reference any information in the DMF (§ 314.420(d)). The list should only contain authorized parties for which LOAs have been submitted and should be updated whenever a new LOA is submitted or an authorized party is withdrawn. The list should contain the following information for each authorized party:

- Name of the authorized party.

- Date of the LOA.

- Specific products, items, or processes referenced by the LOA, including submission dates, eCTD section numbers, and page numbers.

- Application number referencing the DMF (optional).

To withdraw authorization, DMF holders should submit a "Withdrawal of Authorization" letter to the DMF and notify the authorized party. The withdrawal letter should replace the LOA in eCTD section 1.4.1. FDA recommends using the withdrawal of authorization template on CDER's DMF web page at https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs.

d. Application status (eCTD section 1.5)

DMF holders can use eCTD section 1.5.5 to close a DMF. See section VI for information about DMF closures.

e. Meetings (eCTD section 1.6)

Holders of Type II active pharmaceutical ingredient (API)[14] DMFs referenced in ANDAs can request teleconferences in response to first-cycle DMF deficiency letters.[15]

f. Information amendment: Information not covered under modules 2 through 5 (eCTD section 1.11)

In general, changes reported in eCTD section 1.11 should only include a summary of changes to modules 2 through 5 or changes that do not fit in modules 2 through 5. Documents included in eCTD section 1.11 should contain references and links to any sections in modules 2 through 5 that are changed. For example, a change in the drug substance specification should be mentioned in eCTD section 1.11 but should also be changed in sections 2.3.S.4.1 and 3.2.S.4.1.

g. Other correspondence (eCTD section 1.12)

Because DMFs are neither approved nor disapproved, an environmental assessment should not be submitted in a DMF (eCTD section 1.12.14).[16] However, DMF holders should include in their DMFs a commitment to operate their facilities in compliance with applicable environmental laws.

[14] This guidance uses the terms *API* and *drug substance* interchangeably.

[15] See page 19 of "GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022" at https://www.fda.gov/media/101052/download.

[16] See 21 CFR part 25 and the guidance for industry *Environmental Assessment of Human Drug and Biologics Applications (Rev. 1).*

h. Labeling (eCTD section 1.14)

For DMFs related to drug substances, drug substance intermediates, drug products covered by Type II DMFs, and excipients covered by Type IV DMFs, DMF holders should provide a copy of the shipping label in the Labeling section.

i. Risk evaluation and mitigation strategy (eCTD section 1.16)

In the REMS section, DMF holders should provide REMS-related documents, if applicable.[17]

2. Module 2

Module 2 summarizes the appropriate module 3 sections (and 4 and 5, if applicable).

3. Module 3

See section III.D in this guidance for information to include in this module, organized by DMF type.

4. Module 4

This module is not necessary for DMFs unless nonclinical evaluations are included in the DMF. The following information is appropriate to submit in module 4:

- Nonclinical evaluations to support the safety of:
  - An excipient whose CMC information is provided in module 3 in a Type IV DMF; or
  - An impurity whose CMC information is provided in module 3 in a Type II DMF.
- Nonclinical evaluations in a Type V DMF.

5. Module 5

Module 5 should be submitted for clinical information only, such as in a Type V DMF.

C. Subsequent Submissions

Amendments and additions or deletions of information in the DMF, including LOAs, must be submitted to the DMF (§ 314.420(c)). These subsequent submissions should contain a cover

[17] For information on REMS submissions, see draft guidance for industry *Use of a Drug Master File for Shared System REMS Submissions* and the *Technical Conformance Guide for Shared System REMS Drug Master File Submissions.* When final, the guidance will represent FDA's current thinking on this topic.

letter[18] and updated administrative and technical information, as needed. DMF holder name changes and acceptance notifications should also include the statement of commitment as described in section III.B.1.a.

If information in a subsection (e.g., 3.2.S.2.3) of a DMF changes, DMF holders should replace documents in that subsection. For more information, see the *eCTD Technical Conformance Guide* at https://www.fda.gov/media/93818/download.

All amendments and LOAs should reference the updated DMF. A cumulative change history should be submitted with each subsequent submission.

DMF holders must notify affected authorized parties of any DMF changes, additions, or deletions (§ 314.420(c)) and should provide sufficient information to enable authorized parties to determine the appropriate reporting procedure for their applications (see §§ 314.60, 314.70, 314.96, and 314.97). This notification should occur well before making any changes to permit authorized parties to report application changes within an appropriate time frame.

1. Cover Letter

FDA recommends using the cover letter template for subsequent submissions on CDER's DMF web page at https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs. Among other information as laid out in this template, the cover letter should specify the change and reference the date and eCTD section or page number of any previous submission affected by the change.

In addition, the cover letter should specify the submission type: for example, changes in administrative information (e.g., change in agent) should be reported as an administrative amendment, changes in technical information (e.g., change in a test procedure) should be reported as a quality amendment (also referred to as a *technical amendment*), and changes in REMS information (e.g., major REMS modification) should be reported as a REMS–Risk Evaluation and Mitigation Strategy.

Multiple submission types (e.g., LOAs, administrative and quality amendments) can be submitted together with a single cover letter and sequence number. In these cases, the DMF holder should list each submission type in the cover letter. The DMF holder can also further delineate the submission type by amendment type (e.g., change of holder). A table of submission and amendment types is available on CDER's DMF web page at https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs.

2. Administrative Amendments

These types of amendments include, but are not limited to, the following changes.

[18] See footnote 12.

a. Name changes, acquisitions, or transfers of ownership

DMF holders must notify FDA of any name changes (§ 314.420(c)); such changes should be submitted in an administrative amendment to each DMF they own. Name changes can occur through a change in name only or because the DMF holder is acquired by or transfers ownership to another company. If an agent had been appointed by the previous DMF holder and that agent is being retained by the new DMF holder or if a new agent is being retained, the current DMF holder should submit an agent appointment letter on the DMF holder's letterhead (eCTD section 1.3.1.2).

If transfer of ownership is involved, the original DMF holder should submit a transfer notification to the DMF and the new DMF holder should submit an acceptance notification. A statement of commitment signed by the new DMF holder should be included in name change and acceptance notifications stating that the DMF is current and that the holder will comply with the statements made in the DMF. (Alternatively, the statement of commitment can be included in eCTD section 1.2 and referenced in these notifications.)

Templates for name changes, transfer notifications, and acceptance notifications are on CDER's DMF web page at https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs.

b. Changes to the DMF subject

Changes to the DMF's subject (title) should be submitted in an administrative amendment. If a title change is necessary because of a change in technical information (e.g., change in the grade of a drug substance that is the subject of the DMF), a quality amendment should also be submitted.

c. Changes to the DMF type

Changes to DMF type should be submitted in an administrative amendment. If the change in type necessitates changes in the DMF's technical information, the DMF holder should submit those changes in a quality amendment.

3. Quality Amendments

Any changes to technical information should be submitted in a quality amendment.

4. Conversion of Existing DMFs To Comply With eCTD Format

Although there is no requirement to resubmit existing DMF submissions in eCTD format, DMF holders wishing to do so should include a list of content changes occurring as a result of the conversion in an attachment to the cover letter.[19] It is not necessary to request a new DMF

[19] See the *eCTD Technical Conformance Guide* for more information on resubmission of non-eCTD documents.

number. If the existing number is four digits (e.g., 1234), the DMF holder will need to add two zeros to the front of the number to convert it to the eCTD six-digit format (e.g., 001234).

D. Submission Recommendations, by DMF Type

The information recommended below is not intended to be all-inclusive. Please refer to supplemental guidances related to information to be included in DMFs as well as the DMF website.[20]

1. Type II: Drug Substance, Drug Substance Intermediate, and Materials Used in Their Preparation, or Drug Product

Each Type II DMF should be limited to a single drug substance, drug substance intermediate, type of material used in their preparation, or drug product.[21] Drug product intermediates are also included in the category of Type II DMF. Separate DMFs should be submitted for drug substances manufactured using different processes.

DMFs for drug substances, drug substance intermediates, drug products, and drug product intermediates should state that the material covered by the DMF is manufactured under current good manufacturing practices (eCTD sections 3.2.S.2 or 3.2.P.3).

Type II DMFs for APIs submitted in support of ANDAs should follow the recommendations in guidances for industry such as *Completeness Assessments for Type II API DMFs Under GDUFA*. Such recommendations do not apply to Type II DMFs for APIs that are only used to support INDs or NDAs.

a. Drug substance or drug substance intermediate

The definition and criteria for designating starting materials and intermediates are discussed in ICH guidances for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (Rev. 1)* and *Q11 Development and Manufacture of Drug Substances* and ICH Q7 and Q11's corresponding Questions and Answers guidances.

Drug substance manufacturers should collect stability data according to their stability protocol and should continue to submit data from ongoing studies in a quality/stability amendment.[22]

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[20] See, e.g., guidances for industry *Completeness Assessments for Type II API DMFs Under GDUFA* and *Drug Master Files for Bulk Antibiotic Drug Substances*. See also draft guidance for industry *Postapproval Changes to Drug Substances*, which, when final, will represent FDA's current thinking on this topic.

[21] Although FDA's approach to the use of master files in BLAs under the PHS Act largely parallels its approach to the use of DMFs in applications under the FD&C Act, there is a significant difference. A BLA holder is generally expected to have knowledge of and control over the manufacturing process for the biological product for which it has a license. For biological products in BLAs under the PHS Act, FDA has, as a scientific matter, generally not permitted applicants to incorporate information about drug substance, drug substance intermediate, or drug product by reference to a master file; rather, FDA generally expects such information to be submitted directly to the BLA.

[22] See ICH guidance for industry *Q1A(R2) Stability Testing of New Drug Substances and Products*.

For sterilization of drug substances to be used in sterile products, the same sterility assurance information should be submitted as for sterile drug products, as outlined in the guidance for industry *Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products* (*Submission Documentation* guidance) and other supporting documents included on CDER's DMF web page.[23] Building and facility information, including floor plans, can be submitted in the Type II DMF if a Type V DMF is not cross-referenced for this information.

b. Material used in the preparation of a drug substance or drug substance intermediate

If material used in the preparation of a drug substance or drug substance intermediate requires FDA review of CMC information (e.g., defined artificial cell growth media), this information should be submitted in a Type II DMF.

c. Drug product or drug product intermediate

21 CFR 314.420 permits DMF submissions for drug products.

2. Type III: Packaging Material

Packaging materials should be identified by type (e.g., bottle) and material of construction (MOC) (e.g., high-density polyethylene). Packaging materials can be combined to prepare a container-closure system (e.g., a syringe barrel and a plunger).

Information, including safety information, about the components of an MOC can be provided directly to the authorized party without filing a DMF.

For most MOCs (e.g., plastics and glass) and the packaging materials made from them, safety and quality information can be provided by referring to appropriate sections of the Code of Federal Regulations. Additional quality information can be provided by referring to appropriate sections of the United States Pharmacopeia–National Formulary (USP–NF). MOCs should be identified by their names as listed in the appropriate regulations, where applicable.

Data supporting the protection, compatibility, and performance of a packaging material or container-closure system for its intended use should be submitted in the application for the drug product that uses the packaging material.

Type III DMFs can include information about the packaging materials or container-closure system's components, MOCs, controls for release, and intended use. The names of the suppliers or fabricators of the MOCs or components and the specifications for their acceptance can also be provided.

[23] See footnote 3; see also FDA's MAPP 5040.1 *Product Quality Microbiology Information in the Common Technical Document—Quality (CTD-Q).*

Information regarding mixtures of color additives and plastics (often called *masterbatches*) for use in manufacturing plastic packaging components (e.g., to make a bottle blue) is appropriately filed as a Type III DMF.

For sterilization and depyrogenation of packaging materials to be used in sterile products, the same sterility assurance information should be submitted as for sterile drug products, as outlined in the *Submission Documentation* guidance and other supporting documents included on CDER's DMF web page.[24] Building and facility information, including floor plans, is appropriately filed in the Type III DMF if a Type V DMF is not cross-referenced for this information.

The different eCTD sections within 3.2.S or 3.2.P should be populated as appropriate. For multi-item DMFs, each item (e.g., different MOCs) would have a different name (e.g., 3.2.S.[MOC 1], 3.2.S.[MOC 2]). It is appropriate for DMF holders to point to information that is common to different products (e.g., analytical procedures) by reference (or via links in the case of an electronic DMF) to the relevant section for that product (e.g., 3.2.P.4.2 [MOC 1]).

3. Type IV: Excipient, Colorant, Flavor, Essence, or Material Used in Their Preparation

Information for most excipients (e.g., lactose or microcrystalline cellulose) should be submitted in eCTD section 3.2.S. Information for excipients that are mixtures of multiple compounds (e.g., flavor mixtures) should be submitted in eCTD section 3.2.P.

DMFs should be submitted only for excipients for which CMC and safety information is not available through reference to appropriate regulations or quality information through the USP-NF. These include new excipients and colorants, flavors, essences, and material used in their preparation.

a. New excipients

As defined in guidance for industry *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*, new excipients are inactive ingredients that are not fully qualified by existing safety data with respect to the currently proposed level of exposure, duration of exposure, or route of administration.[25] Nonclinical evaluations to support the safety of an excipient whose CMC information is provided in module 3 of a Type IV DMF can be provided in module 4 of the same DMF. Alternatively, this information can be provided in module 4 of a separate Type V DMF.

Excipients listed in the current USP–NF (i.e., compendial excipients) are usually considered to be qualified when administered under conditions that would not be considered new, as defined

[24] See footnote 3.

[25] To search for inactive ingredients, consult FDA's web page Inactive Ingredient Search for Approved Drug Products at https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm.

above. However, use of such excipients in a drug product that leads to increased exposure may require additional safety information, either in a DMF or in the drug product application. Additionally, it is important to note that the inclusion of an excipient in a USP-NF monograph or other non-FDA document is not an indication that FDA reviewed the substance or determined it to be safe for use.

Manufacturers of excipients derived from animal sources (e.g., gelatin) should provide information regarding safety of the material from contamination by infectious agents. This information can be provided directly to the authorized party.

b. Colorant, flavor, essence, or material used in their preparation

Colorants are used to impart color to a drug product and are composed of one or more color additives and other ingredients.

Flavor or essence is an excipient that is added to a drug product whose significant function is to impart flavor and not to produce pharmacological activity.

DMFs for mixtures of materials used to prepare a flavor (e.g., artificial strawberry flavor) should include information about the components and composition of mixtures. For example, for flavors containing multiple components, a quantitative breakdown of the components in the mixture should be provided.

Refer to USP-NF for quality information. Data to support the safety of colorant and flavor mixtures can be provided by referring to FDA regulations, including:

- Color additives (21 CFR parts 70 through 82).
- Direct food additives (21 CFR parts 170 through 173).
- Indirect food additives (21 CFR parts 174 through 178).
- Food substances (21 CFR parts 181 through 186).

Components should be identified by their names as cited in FDA regulations, where applicable.

Information about the components and compositions, as well as safety information, can be provided directly to the authorized party without filing a DMF.

If provided in a DMF, information about excipients that are mixtures of multiple compounds (e.g., flavor mixtures) should be submitted in eCTD section 3.2.P. The different sections within 3.2.S or 3.2.P should be populated as appropriate. For multi-item DMFs, each product (e.g., different flavors) would have a different name (e.g., 3.2.P.[Flavor 1], 3.2.P.[Flavor 2]). In this case, the components and composition would be described in 3.2.P.1 [Flavor 1], 3.2.P.1 [Flavor 2]. DMF holders can access information that is common to different products (e.g., analytical procedures) by reference (or via links in the case of an electronic DMF) to the relevant eCTD section for that product (e.g., 3.2.P.5.2 [Flavor 1]).

4. Type V: FDA-Accepted Reference Information

If a DMF holder wishes to submit information that is not covered by Types II through IV, the DMF holder can submit a Type V DMF (e.g., shared system REMS, sterile processing facility, toxicology studies for compound X) but must first email a letter of intent to the DMF staff at dmfquestion@fda.hhs.gov.[26] FDA will then contact the DMF holder to discuss the proposed submission.

The emailed letter of intent should include:

- The specific information to be included in the DMF.
- The proposed subject (title) of the DMF.
- A clear statement regarding why this information could not be submitted in an application (i.e., why the information is considered to be confidential).
- The clinical division(s) that should review the information, if applicable.

Information regarding the manufacturing site, facilities, operating procedures, and personnel for sterile manufacturing plants can be filed as a Type V DMF without first submitting a letter of intent. The subject field should specify what the DMF covers (e.g., sterile processing facility).

E. Other Recommendations

1. English Translations

Applicants must submit an accurate and complete English translation of each part of the NDA or ANDA that is not in English (§§ 314.50(g)(2), 314.94(a)(11)). The same is true for DMFs. A *certified* translation is not required.

2. Public Availability of Information in a DMF

Public availability of the information in a DMF is determined under 21 CFR part 20 and other applicable FDA disclosure regulations, including §§ 314.420(e), 314.430, and 601.51. DMF holders and authorized parties are free to share any information with each other.

3. Holder Not the Manufacturer

In general, FDA expects the DMF holder to be the manufacturer of the material covered by the DMF. If the DMF holder is not the manufacturer, the DMF should include a statement that the DMF holder assumes full responsibility for the manufacturing of the material covered by the DMF.

[26] See § 314.420(a)(5).

4. Primary and Secondary DMFs

A primary DMF can incorporate information in a secondary DMF by reference. The secondary DMF holder can submit an LOA authorizing either the primary DMF holder or the drug product applicant to reference the secondary DMF. Where possible, consistent with confidentiality agreements, secondary DMF holders are encouraged to submit LOAs authorizing drug product applicants to reference the secondary DMF directly.

5. Referencing Own Application Material

An applicant need not create a new DMF when referencing its own material but can include the information directly in its own application.

6. Retention of Reference Copy by the Holder

DMF holders and their agents should retain a complete reference copy that is identical to, and maintained in the same chronological order as, their submissions to FDA.

When a DMF is transferred from one DMF holder to another, all documents associated with the DMF should be transferred to the new DMF holder.

IV. ANNUAL REPORTS

Annual reports should not be used to report changes in the DMF. If it is necessary to submit an amendment and an annual report, they must be submitted under separate eCTD sequence numbers.[27]

DMF holders should submit a cover letter[28] when submitting their annual report. The annual report should include a statement of commitment signed by the DMF holder stating that the DMF is current and that the holder will comply with the statements made in the DMF. (Alternatively, the statement of commitment can be included in eCTD section 1.2 and referenced in the annual report. However, agents submitting annual reports on behalf of DMF holders should not refer to eCTD section 1.2 for the statement of commitment; rather they should include a statement of commitment signed by the DMF holder with the annual report.) The annual report should also include the appropriate administrative information, dates of any amendments reporting changes since the last annual report (or original filing date), a list of authorized parties, and a list of parties whose authorization has been withdrawn and the dates of withdrawal. See the annual report template and subsequent submissions cover letter template on CDER's DMF web page at https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs.

Annual reports help assure FDA that the statement of commitment is current. Failure to submit this report annually may result in the termination of a DMF (see section VI, DMF Closure).

[27] See the *Providing Regulatory Submissions* guidance.

[28] See footnote 12.

V. FDA PROCESSING AND REVIEWING POLICIES

A. Administrative Review

If the administrative information in an original DMF is found acceptable, FDA sends an acknowledgment letter to the DMF holder (and agent, if applicable) listing the DMF number, subject (title), type, and holder's name as specified in the cover letter. For submissions with incomplete administrative information, FDA contacts the DMF holder (and the agent, if applicable) to request the missing information. The DMF will not be available for technical review until all administrative filing issues have been adequately addressed and the DMF is referenced in an application or another DMF (see section V.B).

FDA examines subsequent submissions (e.g., amendments, LOAs) to ensure that the subject, holder name, and type match the information for that DMF number on file at FDA. FDA also checks these submissions for other administrative information, such as the holder's address, agent's address (if applicable), and appropriate submission type and, if applicable, amendment type (e.g., change of holder, change of DMF subject). If administrative issues are noted, FDA contacts the DMF holder (and agent, if applicable) to request that the information be corrected or the discrepancies be resolved.

FDA does not send acknowledgment letters for subsequent submissions. If this practice changes, FDA intends to update the DMF web pages to describe which types of documents will be acknowledged.

B. Technical Review

FDA performs a complete review of the referenced technical information in a DMF when an authorized party submits a copy of the DMF holder's LOA in its application or in another DMF.[29] The review is performed to support a particular use (e.g., a drug substance used to manufacture a solid oral dosage form). Whether a DMF is acceptable depends on the specific use described in an application or in another DMF referencing the DMF.

Reviewers may find that additional information is needed to continue a review or that the DMF cannot be used to support approval of an ANDA, NDA, or BLA or, in the case of an IND, allow clinical trials to proceed. In these cases, FDA will contact the DMF holder and the agent, if applicable, regarding its concerns.

Certain Type II DMFs for APIs that require a user fee under the Generic Drug User Fee Amendments of 2017 (GDUFA II) will receive a completeness assessment.[30]

[29] See the draft guidance for industry *Assessing User Fees Under the Generic Drug User Fee Amendments of 2017.* When final, this guidance will represent FDA's current thinking on this topic.

[30] See the guidance for industry *Completeness Assessments for Type II API DMFs Under GDUFA.*

VI. DMF CLOSURE

DMFs may be closed either because the DMF holder requests closure or because FDA cannot be assured that the DMF is current. In the latter case, FDA will notify the holder or agent, as applicable, that the DMF needs to be updated. If the DMF holder or agent, as applicable, does not respond by submitting an annual report in a timely manner, FDA could close the DMF and would notify the holder or agent, as applicable, of this action.

To close a DMF, DMF holders should submit an administrative amendment requesting closure. The request should include a statement that all authorized parties have been notified of the closure (eCTD section 1.5.5). FDA recommends using the template for requesting closure on CDER's DMF web page at https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs.

A closed DMF cannot be reviewed in support of a new or amended application or another DMF, a new or amended supplement to an approved application, a new IND, or an amendment to an existing IND. Thus, an applicant can no longer incorporate the information from a closed DMF in support of its application and will need to submit an amendment or supplement to FDA to replace the information contained in the closed DMF.

If a DMF has been closed, the holder can submit a new DMF to FDA to replace the closed DMF. The new DMF should reference the closed DMF number.

VII. GLOSSARY

Active pharmaceutical ingredient (API): Any substance intended for incorporation into a finished drug product and intended 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 body; does not include intermediates used in the synthesis of the substance (21 CFR 207.1).

Agent: A legal entity, whether a company or an individual, that is not employed but is appointed to act on behalf of a DMF holder.

Authorized party: Any person who is authorized to reference a DMF.

Contact person: An employee of the DMF holder or agent to whom communication from FDA should be sent. The contact person may or may not be the same individual as the responsible official.

DMF holder: A person who owns a DMF.

Drug product: A finished dosage form (e.g., tablet, capsule, solution) that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients (§ 314.3(b)).

Drug product intermediate: A defined mixture of one or more drug substances with one or more inactive ingredients that is not a finished dosage form. This is to be distinguished from a mixture when the drug substance is unstable or cannot be transported on its own.

Drug substance: An active ingredient that is intended to furnish pharmacological activity or another direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body but does not include intermediates used in the synthesis of such an ingredient (§ 314.3(b)).

Drug substance intermediate: A material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API. Drug substance intermediates may or may not be isolated. See ICH Q7.

Letter of authorization (LOA): A letter from a DMF holder that authorizes an applicant or another DMF holder to incorporate by reference all or part of the DMF's contents to support an application, supplement, or another DMF or an amendment to any of these documents. The LOA also authorizes FDA to review applicable portions of the DMF.

Person: An individual, partnership, corporation, or association (section 201(e) of the FD&C Act).

Primary DMF: A DMF that references another DMF and itself may be referenced by an application.

Responsible official: The employee of the DMF holder or agent who is responsible for submitting information to the DMF.

Risk evaluation and mitigation strategy (REMS): A required risk management strategy that employs tools beyond prescribing information to ensure that the benefits of a drug outweigh its risks. For more information, see section 505-1 of the FD&C Act.

Secondary DMF: A DMF that is incorporated by reference into a primary DMF.

Subject: Title of the DMF.

VIII. REFERENCES

FDA, 2018, Comprehensive Table of Contents Headings and Hierarchy.

FDA, 2018, eCTD Technical Conformance Guide.

FDA, 2017, MAPP 5040.1 Product Quality Microbiology Information in the Common Technical Document—Quality (CTD-Q).

FDA, 2017, Technical Conformance Guide for Shared System REMS Drug Master File Submissions.

FDA, 2017, Transmitting Electronic Submissions Using eCTD Specifications.

Guidances for Industry

Guidance for industry *Completeness Assessments for Type II API DMFs Under GDUFA,* October 2017

Guidance for industry *Drug Master Files for Bulk Antibiotic Drug Substances*, November 1999

Guidance for industry *Environmental Assessment of Human Drug and Biologics Applications (Rev. 1),* July 1998

Guidance for industry *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*, May 2005

Guidance for industry *Providing Regulatory Submissions in Electronic Format—Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (Rev. 6)*, January 2019 (see Rev. 7 in "Draft Guidances for Industry" below)

Guidance for industry *Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product*, April 2015

Guidance for industry *Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*, November 1994

ICH guidance for industry *M4 Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human* Use, October 2017

ICH guidance for industry *M4Q: The CTD—Quality*, August 2001

ICH guidance for industry *Q1A(R2) Stability Testing of New Drug Substances and Products*, November 2003

ICH guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (Rev. 1),* September 2016

ICH guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients: Question and Answers,* April 2018

ICH guidance for industry *Q11 Development and Manufacture of Drug Substances,* November 2012

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Draft Guidances for Industry[31]

Draft guidance for industry *Assessing User Fees Under the Generic Drug User Fee Amendments of 2017,* October 2017

Draft guidance for industry *Postapproval Changes to Drug Substances,* September 2018

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Draft guidance for industry *Submitting Debarment Certification Statements*, September 1998

Draft guidance for industry *Submitting Marketing Applications According to the ICH-CTD Format—General Considerations,* August 2001

Draft guidance for industry *Use of a Drug Master File for Shared System REMS Submissions,* November 2017

[31] When final, these guidances will represent FDA's current thinking on these topics.