CDER SBIA Webinar Series

New Requirement for Electronic Submission of Drug Master Files (DMFs): What You Need to Know

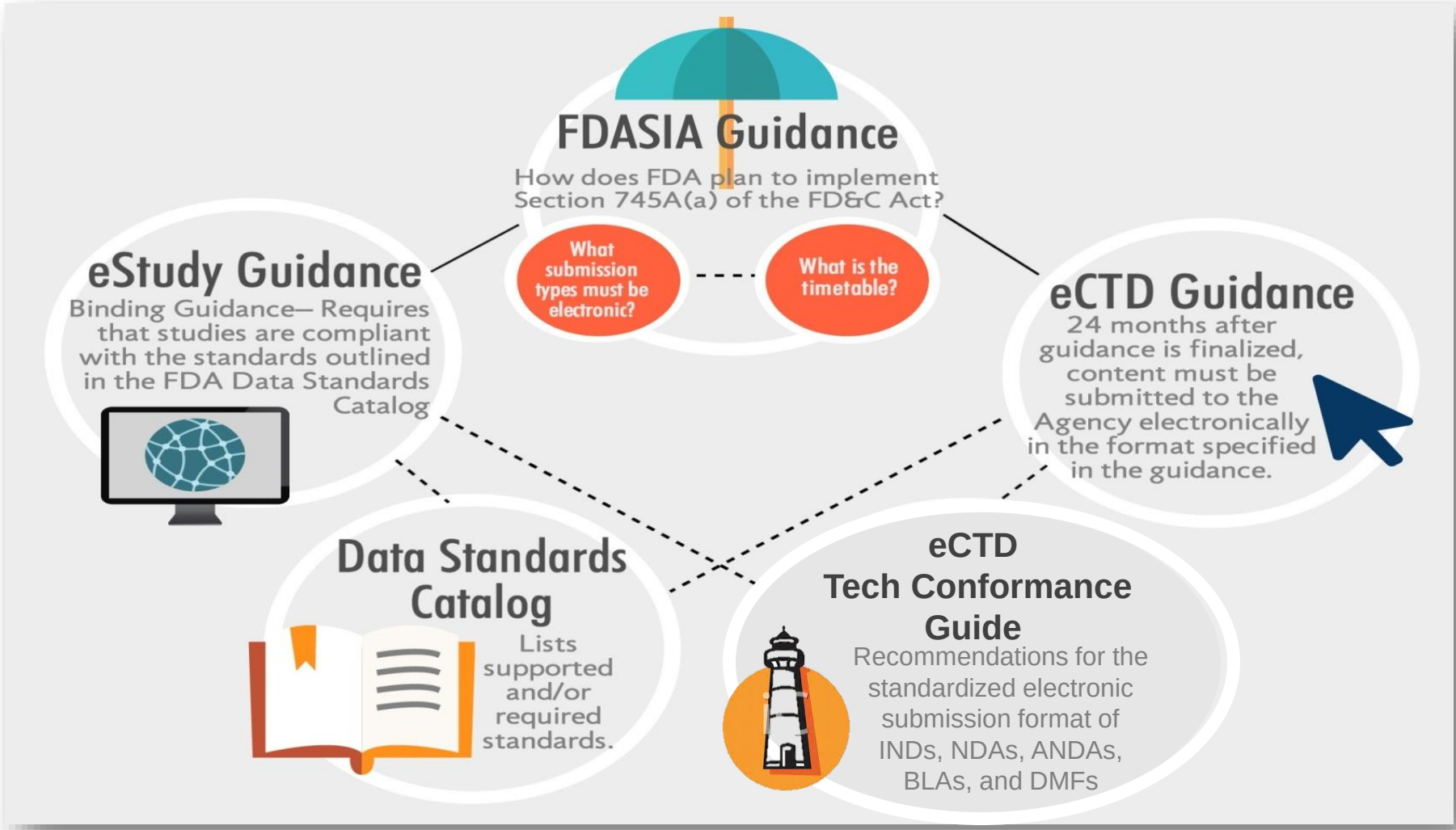
February 4, 2016

New Requirement for Electronic Submission of DMFs

Jonathan Resnick, Project Management Officer
Division of Data Management Services & Solutions
Office of Business Informatics, CDER
U.S. Food and Drug Administration

CDER SBIA Webinar Series
February 4, 2016

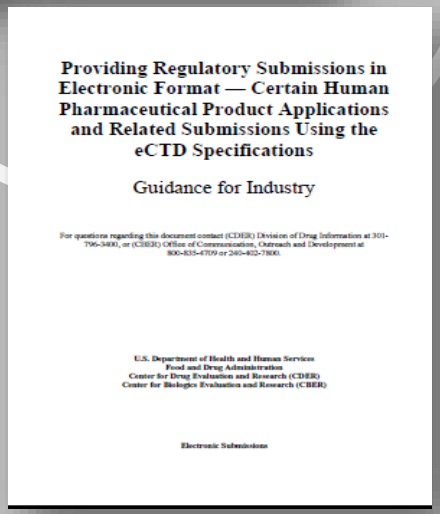
Framework for Required Electronic Submissions



When will eCTD Format be Required?

eCTD Guidance

Binding Guidance requires the electronic submission of NDAs, BLAs, ANDAs, INDs, DMFs in eCTD Format



Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications

Guidance for Industry

For questions regarding this document contact (CDER) Division of Drug Information at 301-796-3400, or (CBER) Office of Communication, Outreach and Development at 800-835-4709 or 240-402-7800.

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)

Electronic Submissions

Published May 5, 2015

24 Months*

Required May 5, 2017

Compliance

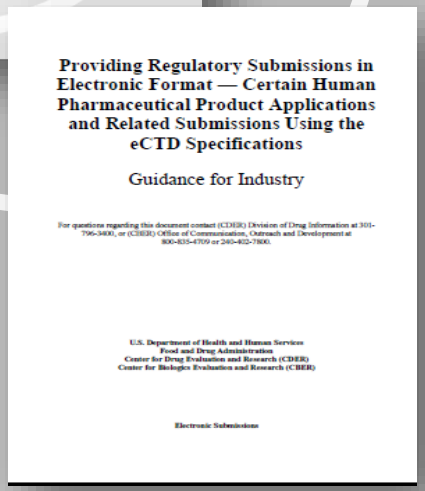
Electronic submissions using the version of eCTD currently supported by FDA. As specified in the FDA Data Standards Catalog

*36 months for Commercial INDs

What Submission Types are Applicable?

eCTD Guidance

Binding Guidance requires the electronic submission of NDAs, BLAs, ANDAs, INDs, DMFs in eCTD Format



Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications

Guidance for Industry

For questions regarding this document contact (CDER) Division of Drug Information at 301-796-3400, or (CBER) Office of Communication, Outreach and Development at 800-835-4709 or 240-402-7800.

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)

Electronic Submissions

FDASIA Section 745A(a) applies to

Submissions under section 505(b), (i), or (j) of the FD&C Act

NDAs
ANDAs
BLAs
INDs
DMFs or BPFs
Combo products

Final
Published on May 5, 2015

When will eCTD Format be Required?

May 5, 2017

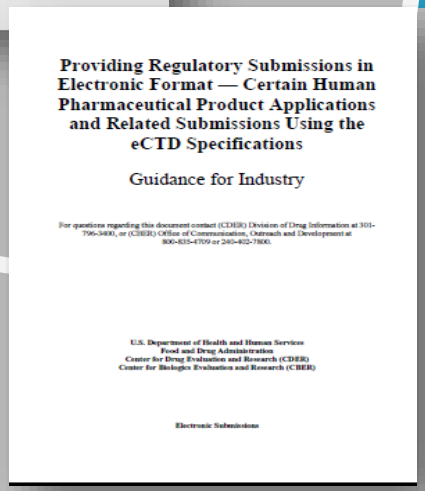
all DMF Submissions

must be in electronic, eCTD format

What are the eCTD Specifications?

eCTD Guidance

Binding Guidance requires the electronic submission of NDAs, BLAs, ANDAs, INDs, DMFs in eCTD Format



Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications

Guidance for Industry

For questions regarding this document contact (CDER) Division of Drug Information at 301-796-3400, or (CBER) Office of Communication, Outreach and Development at 800-835-4709 or 240-402-7800.

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)

Electronic Submissions

Published May 5, 2015

ICH eCTD Specs 3.2.2
ICH eCTD Study Tagging Files
FDA eCTD - Module 1
eCTD CTOC
Validation, File Format, PDF
Supportive files & more

Data Standards Catalog

Lists supported and/or required standards.

What eCTD Formats will be Required?

FDA Data Standards Catalog v4.1 (04-09-2015) - Supported and Required Standards

This table contains a listing of the data exchange, file formats and terminology standards supported at FDA. These standards have gone through all the steps necessary to make this part of the regulatory review process, including posting of regulatory guidance documents and associated implementation guidelines and technical specifications. The submission of standardized data using any standard not listed, or to an FDA Center not listed, should be discussed with the Agency in advance. This catalog is incorporated by reference in the guidance to industry, *Providing Regulatory Submissions in Electronic format-Standardized Study Data (http://www.fda.gov/downloads/Drugs/Guidances/UCM292334.pdf)*. A separate catalog will be published in the future that will contain a listing of standards that are in the development, testing, adoption or research & development (R&D) phases.

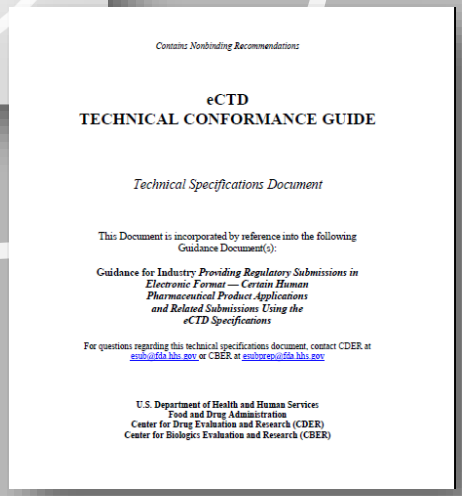
Use	Data Exchange Standard	Exchange Format	Standards Development Organization (SDO)	Supported Version	Implementation Guide Version	FDA Center(s)	Date Support Begins (MM/DD/YYYY)	Date Support Ends (MM/DD/YYYY)	Date Requirement Begins (MM/DD/YYYY)	Date Requirement Ends	Regulatory Reference and Information Sources
Regulatory Applications (IND, NDA, ANDA, BLA, master files)	Electronic Common Technical Document (eCTD)	Extensible Markup Language (XML)	International Conference on Harmonisation (ICH)	3.2.2	M2 eCTD: Electronic Common Technical Document Specifications	CDER, CBER	06/01/2008				Electronic Submissions-Electronic Common Technical Document (eCTD)
Product Labeling Submissions	Structured Product		Health Level 7			CDER,			04/01/2005 [3]		StructuredProductLabeling (SPL) Implementation Guide with Validation Procedures

How to Submit eCTD Submissions ?

Non-binding guidance

eCTD
Tech Conformance Guide

Recommendations for the standardized electronic submission format of INDs, NDAs, ANDAs, BLAs, and DMFs



Contains Nonbinding Recommendations

eCTD
TECHNICAL CONFORMANCE GUIDE

Technical Specifications Document

This Document is incorporated by reference into the following Guidance Document(s):

Guidance for Industry ***Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications***

For questions regarding this technical specifications document, contact CDER at esub@fda.hhs.gov or CBER at esubprep@fda.hhs.gov

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)

- **General Considerations**
- **Organization of eCTD**
  - **Modules 1 -5**
- **Issues and Solutions**

Published October 5, 2015

Resubmission of Material

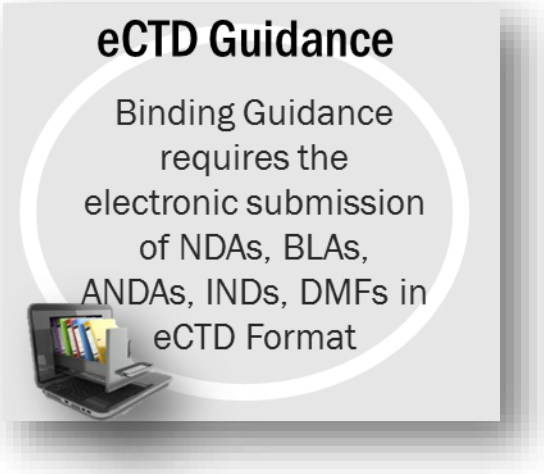
- There is NO requirement to resubmit anything that has already been submitted in paper
- *If you choose* to resubmit your entire DMF upon conversion to eCTD, that is acceptable but it is NOT required

eCTD Guidance

Binding Guidance requires the electronic submission of NDAs, BLAs, ANDAs, INDs, DMFs in eCTD Format

Will FDA Reject non-compliant submissions?

Yes.



Waivers and Exemptions

NO Waivers

NO Exemptions for DMFs

*See the Guidance for a *complete* list of the "musts"*

- **Must** submit electronic submissions using the eCTD version currently supported by FDA.
  - The version of eCTD currently supported is specified in the Data Standards Catalog
- **Must** obtain a pre-assigned application number by contacting the appropriate Center.
- **Must** follow the FDA eCTD technical specification *Table of Contents Headings and Hierarchy.*

- **Must** adhere to the formats and versions specified in the FDA *Specifications for File Format Types Using eCTD Specifications*.
- **Must** adhere to the FDA *Portable Document Format (PDF) Specifications.*
- **Must** use the eCTD *replace* operation rather than submitting the file as *new* if a document replaces a document previously submitted …

- **Must** include only FDA fillable forms (e.g., User Fee Form 3794) and electronic signatures to enable automated processing of the submission … *Scanned images of FDA forms will not be accepted.*

- **Must** not submit paper copies of the application, including review & desk copies when *submitting in eCTD format.*

- **Must** use the FDA Electronic Submission Gateway for submissions 10 GB or smaller.

Must use the FDA Electronic Submission Gateway (ESG) for submissions 10 GB or smaller

- If you are not currently an ESG submitter, set up an account now; process can take several weeks
- Most submitters use the “WebTrader Hosted Solution”
- There is no cost for an ESG account, but you must obtain a Digital Certificate for each person in your organization who will be sending files thru the ESG
- See the ESG website for complete instructions, http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm

Tips for DMF Submission Success

- Provide proper bookmarks, table of contents and hyperlinks on documents more than 5 pages long
- Pages should be properly oriented
- Scanned documents, including cover letters should be OCR'd prior to submitting
- Provide electronic submissions point of contact for technical issues
- Provide correct telephone, email or fax number for rejection notices
- Cover letter should have contact information for agent, if applicable

Tips for DMF Submission Success

- Leaf titles of documents should be clear and indicative of the document
- Cover letters should include the sequence number and if possible, date of submission (e.g. coverletter-0004-Oct-13-2015)
- Leaf titles for all annual report documents should include the reporting period (e.g. "AR-specifications-Oct-12-2014-Oct-11-2015). That way, reviewers can differentiate between one year's report from another.
- Do not include form 356h when submitting via gateway. DMFs are automatically processed without the form

Tips for DMF Submission Success

- Choose appropriate center (e.g. “CDER”) and “eCTD” as the submission type, when transmitting via ESG
- When transitioning from paper to eCTD M1 v2.01 DTD, use “original-application” as the submission type. Subsequent submissions will be coded as “amendment”.
- When transitioning from paper to eCTD M1 v3.3 DTD, there will be an additional field called submission-id which should be populated as follows:
  - If this is the first eCTD submission, populate the submission-id field with the sequence number of the submission. (e.g. 0001-submission id-“original application”- sub-type-“application”-sequence number-“0001”)
  - For a subsequent eCTD submission, populate the submission-id field with the sequence number of the first eCTD submission. (e.g. 0001-submission-id-“original application”- sub-type-“amendment”-sequence number-“0002”)

Tips for DMF Submission Success

- Be sure to apply consistent attributes for module 3.2.p and/or module 3.2.s eCTD sections for every submission. Any minor change will add another 3.2.p. and/or 3.2.s section thus, creating duplicate sections
- Always apply the correct eCTD life cycle operator (e.g. replace) when submitting updates to documents. Do not submit updated documents as “new”

Remember …

May 5, 2017

DMF Submissions

must be in eCTD format

Submissions 10GB and less must use the Gateway

Get an account NOW

Looking Forward to a Smooth Transition

Standardized electronic format = more efficient review process

Electronic Drug Master Files (eDMFs)

Presented by Arthur B. Shaw, Ph.D.
Drug Master File Expert

US Food and Drug Administration
SBIA Webinar February 4, 2016

Drug Master Files

- A Drug Master File (DMF) is a submission of information to the FDA to permit the FDA to review this information in support of a third party's application without revealing the information to the third party.

- DMFs usually cover the Chemistry, Manufacturing and Controls (CMC) of a component of a drug product e.g. drug substance, excipient, packaging material.

- Drug product information or non-CMC information (e.g., toxicology) may be filed in a DMF.

Laws and Regulations

- Laws
  - Food Drug and Cosmetic Act (FD&C Act)
  - Food and Drug Administration Safety Information Act (FDASIA) including the Generic Drug User Fee Amendments (GDUFA) and Prescription Drug User Fee Act (PDUFA)
- Regulations: Section 21 of the Code of Federal Regulations (21 CFR) Required information
  - 312 Investigational New Drug Application (IND)
  - 314 New Drug Application (NDA) and Abbreviated NDA (ANDA)
    - 314.50 Content and format of an application
    - 314.70 Changes to an Approved Application
    - 314.420 Drug Master Files

Guidances

- Guidance documents represent the Agency's current thinking on a particular subject.
- They contain RECOMMENDATIONS not requirements. One exception
- The "Guidance for Industry: Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications" contains requirements.
  - Draft Guidances are prepared by FDA, published for "Notice and Comment" in the Federal Register, and then finalized by FDA
  - FDA participates in the International Conference on Harmonization (ICH), which prepares Guidances for the US, Japan and Europe
  - Other (usually older) Guidances are for US (FDA) only)

MAPPs (Manual of Policies and Procedures)

- MAPPs are prepared for internal use by the FDA to and contain documentation of internal policies and procedures. MAPPs are made available to the public to make CDER a more transparent organization.

- MAPPs do not impose requirements on the regulated industry nor do they contain recommendations for industry guidance.

Information Sources

- DMF Web site
  http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/default.htm
  - Contains current list of DMFs, links to supporting guidances and advice for DMF holders not in DMF Guidance (1989) Guidance link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073164.htm
- DMF questions:
  - General: dmfquestion@fda.hhs.gov
  - GDUFA specific: DMFOGD@fda.hhs.gov
  - Technical questions e.g. about amount of stability data needed, designation of compound as a starting material. These are review issues and not DMF issues. Send inquiries to CDER-OPQ-Inquiries@fda.hhs.gov

Who is Required to File a DMF

Who Must File a DMF?

NOBODY

- There is no legal or regulatory requirement to file a DMF. Information can be in an Application (IND, NDA, ANDA, Biologics License Application (BLA) OR a DMF.)

Reasons for a DMF

- Maintain confidentiality of proprietary information (e.g., Manufacturing procedure) for the holder
- Permit review of information by reviewers at FDA to support applications submitted by one or more APs

However -

The manufacturer of the material can choose to submit the information necessary for review to their customers for inclusion in the IND, NDA, ANDA, or BLA

Types of DMFs

There are four types of DMFs (Type I DMFs were eliminated in 2000) but the numbering was kept the same

- II Drug substance (Active Pharmaceutical Ingredient = API), drug products, intermediates or material used in their preparation
- III Packaging materials
- IV Excipients
- V Other

Type II DMFs

- The same DMF can be used to support an NDA, IND, and/or an ANDA
- Type II DMFs can be submitted for drug products.
- Type II DMFs for “material used in their preparation” refers to material used in the preparation of drug substances, intermediates or drug products e.g., novel chromatography media, filters for sterile processing. Excipients are not “Material used in their preparation” for drug products.

Type III DMFs

- Information must be available for the review of the Container-Closure system (CCS) to show that the container closure system and its components are suitable for its intended use.
- This information can be either in the NDA/ANDA/IND/BLA or in a DMF.
- See the “Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics CHEMISTRY, MANUFACTURING, AND CONTROLS DOCUMENTATION
- Information can be provided directly to the Authorized Party for inclusion in their application. See MAPP 5015.5 CMC Reviews of Type III DMFs for Packaging Materials

MAPP 5015.5

- Procedure:
  - A referenced DMF for a packaging material for use in drug products for specified dosage forms (DFs) and routes of administration (ROAs) does not need to be reviewed if there is sufficient information in the application (IND, NDA, ANDA, or BLA) to support the suitability of the packaging material for the drug for specified materials of construction (MOCs).
  - If the information in the application is not sufficient, the applicant is asked to provide that information,
  - If the applicant does not provide the information then the reviewer reviews the DMF.
- Examples of MOCs, DFs, and ROAs covered by the MAPP:
  - High density polyethylene (HDPE) for solid oral dosage forms
  - Glass for any aqueous liquids
- Examples of information to support the suitability of the MOC:
  - Reference to the United States Pharmacopeia (USP) for glass containers.
  - Reference to appropriate food additive regulations under the Code of Federal Regulations (CFR). See 21 CFR 172-186.

Type IV DMFs

- Since CMC for compendial excipients (covered by the USP/NF) is generally not reviewed, DMFs for compendial excipients generally not reviewed.
- New excipients: See "Guidance for Industry: Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients" http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079250
  - Defined as "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.".
  - Provide CMC information and safety evaluation
- Flavor and color mixtures. Information can be provided directly to Authorized Party for inclusion in their application.

Type V DMFs

- Regulations (21 CFR 314.420(a)(5)) require that a DMF holder wishing to open a Type V DMF request permission from the FDA (pre-clearance).
  - Holder sends request to dmfquestion@fda.hhs.gov specifying topic of the DMF and reason why the information can't be in an IND or an A/NDA.
  - The request will be forwarded to the review division that will determine whether a Type V DMF is appropriate.
  - This procedure should be followed when requesting a pre-assigned number for a Type V DMF.
- Exception: Since FDA reviews manufacturing facilities (formerly in Type I DMFs) for sterile processing or biotechnology products used to support multiple applications these can be filed in a Type V DMF without pre-clearance.

Electronic DMF (EDMF)

- All submissions after May 5, 2017 MUST be in ECTD format
- Can convert paper DMF to EDMF The choice of whether to resubmit the paper DMF to electronic format is up to the individual DMF holder.
- See discussion below

Initial Submission

- Guidance

Follow the DMF Guidance and additional information on DMF Web site.

- Pre-assigned Number
  - A pre-assigned number is required for an EDMF. See “Requesting a Pre-Assigned Application number”

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm114027.htm

Initial Submission – Components

- Transmittal (cover) letter, including pre-assigned number, where applicable
- Administrative information. For complete list of information to include see DMF Guidance and DMF Web site. Make sure to include
  - Telephone number, fax number and e-mail address for the responsible individual (contact person)
  - A Statement of Commitment (Recommended in the DMF Guideline : “A signed statement by the holder certifying that the DMF is current and that the DMF holder will comply with the statements made in it.”)
  - List of Referenced applications e.g. DMF for intermediates. Include in Section 1.4.2 “Right of Reference.”
  - Note
    - There are no forms for DMFs except for User Fee Form
    - Letters of Authorization (LOAs) submitted with initial DMF submission must contain the DMF number
- Technical information

How the System Works

- A DMF goes through 2 stages of evaluation before it can be available for review of the technical content.
  - Review of electronic format
    - If the DMF is acceptable from an “electronic technical” point of view (see requirements above), it then undergoes Administrative Review
    - If the DMF is not acceptable from an “electronic technical” point of view the holder will be informed. The holder must respond adequately for DMF to proceed to Administrative Review.
  - Administrative Review (performed by DMF staff in the Office of Pharmaceutical Quality (OPQ)
    - If the DMF is acceptable from an administrative point of view (see recommendations above), OPQ sends an Acknowledgement Letter. DMF is available for review of the technical content.
    - If the DMF is not acceptable from an administrative point of view, OPQ sends an Administrative Filing Issues”(AFI) letter. The holder must respond adequately for DMF to be available review of the technical content.
- Usual processing time is 2-3 weeks

Administratively Incomplete DMFs

- Administrative Filing Issues (AFI) letter details the missing information
- Response to AFI letter should be complete.
- If response is complete then Acknowledgment Letter will be sent and DMF is available for review of the technical content.

Acknowledgement Letter

- Notifies holder of DMF number and type. The Title (Subject) and Holder of DMF will be as they appear in the cover letter of the original DMF and will be publicly available.
- Reminder of obligations of holder
  - Submit all changes as amendments
    - Notify FDA of change in holder name or address
    - Notify FDA of change in agent/representative
  - Notify authorized parties of changes
  - SUBMIT ANNUAL REPORT
  - Submit Letter of Authorization (LOA) to the DMF for each item referenced for each Authorized Party (AP.)

Submission of Technical Information

- Holder must follow appropriate regulations (21 CFR 314.50(d)(1) for ANDAs and NDAs and 21 CFR 312.23(a)(7) for INDs
- Facilities information (former Type I) not necessary Address of facility is sufficient

Guidances for CTD Information

- CTD is a structured format that permits efficient life-cycle management, which is important for DMFs and for electronic submissions
- Guidance for Industry M4Q: The CTD – Quality http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073280.pdf
- Technical content should follow recommendations in relevant Guidances
- Follow the recommendations in the Guidance for Industry Granularity Document Annex to M4: Organization of the CTD http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073261.pdf

Conversion of Paper DMFs to Electronic

- When converting from paper to electronic, the holder may submit an amendment containing all sections specified in the CTD format that are applicable to the material covered by the DMF. If a complete resubmission is being sent:
  - Each section should be complete and contain up-to-date information.
  - For drug substances and excipients all sections of 3.2.S in Module 3 and of 2.3.S in Module 2 should be submitted.
  - For drug products all sections of 3.2.P in Module 3 and of 2.3.P in Module 2 should be submitted.
  - DMFs in non-CTD paper format must be converted CTD format. Any changes in the technical content of the DMF as a result of the conversion to CTD format, e.g. addition of new information, should be specified in the cover letter of the submission.

Organization in CTD

- Each Module contains individual Sections e.g. S.1.1. Each Section contains a “Document” or “File.”
- There are no sections within S.5, S.6, P.6, or P.7

Example for Drug Substance: Each bolded element in the table is a Section and each contains a Document.

S.1 General Information	**S.1.1 Nomenclature**
	S.1.2 Structure
	S.1.3 General Properties
S.2 Manufacture	**S.2.1 Manufacturers**
	S.2.2 Description of Manufacturing Process and Process Controls
	S.2.3 Control of Materials
	S.2.4 Controls of Critical Steps and Intermediates
	S.2.5 Process Validation and/or Evaluation
	S.2.6 Manufacturing Process Development
S.3 Characterization	**S.3.1 Elucidation of Structure and other Characteristics**
	S.3.2 Impurities
S.4 Control of Drug Substance	**S.4.1 Specification**
	S.4.2 Analytical Procedures
	S.4.3 Validation of Analytical Procedures
	S.4.4 Batch Analyses
	S.4.5 Justification of Specification
S.5 Reference Standards or Materials	
S.6 Container Closure System	
S.7 Stability	**S.7.1 Stability Summary and Conclusions**
	S.7.2 Postapproval Stability Protocol and Stability Commitment
	S.7.3 Stability Data

Organization in CTD for Multi-Item DMFs

- Multi-item DMFs e.g. Type III for rubber stoppers or Type IV for flavors can be submitted in ECTD format.
- One solution: Treat each formulation as a Drug Product. P [Name]
  - P [Formulation 1]
  - P [Formulation 2]
  - Etc..

Organization in CTD for Multi-Item DMFs

- P.1 [Name] Each chemical in a flavor or rubber stopper or MOC for a packaging material is a “Component”.
- P.2 [Name] Pharmaceutical Development Usually not necessary
- P.3 [Name] Manufacturer name and address and brief summary of manufacturing process
- P.4 [Name] Specifications of the individual components listed in P.1
- P.5 [Name] Control of the finished product e.g. testing of rubber stopper, including extraction studies
- P.6 [Name] Reference standards – depends on the tests in P.5
- P.7 [Name] Container-closure used to package the product for shipping
- P.8 [Name] Summary of stability information to support recommended storage conditions and time.

Organization in CTD for Multi-Item DMFs

- Information common to different formulations can be linked to a common section.
- Examples:
  - P.3.1 Manufacturer. Usually common to all products in a DMF.
  - P.4.1 Specifications for individual components that may be common to different products in a DMF
  - P.5.2 Analytical Procedures for release of the products may be common to different products in a DMF

Organization in CTD Type V DMFs for Sterile Processing and Biotech Facilities

- Information can be in *3.2.A.1 Facilities and Equipment*
- For Sterile Processing Facilities can follow the recommendations in the following Guidances (Links on DMF Web site):
  - DMF holders submitting DMFs for Sterile Manufacturing can consult the following Guidances
  - Question-based Review (QbR) for Sterility Assurance of Aseptically Processed Products: Quality Overall Summary Outline
  - Sterility Assurance - Quality Overall Summary (SA-QOS) Outline for Terminally Sterilized Products
  - QbR for Sterility Assurance of Terminally Sterilized Products: Frequently Asked Questions

CTD Module 1

Module 1 Information that applies to DMFs

- Section 1.1 Forms: There are no forms for DMFs, except for the Generic Drug User Fee Cover Sheet (3794), only for Type II API DMFs to support ANDAs under GDUFA.
- Section 1.2 Cover Letter Include
  - Statement of Commitment.
  - Statement of Compliance with cGMP, where applicable
- Section 1.3: Administrative Information
  - 1.3.1 Contact/sponsor/ Applicant information
    - 1.3.1.1 Change of address or corporate name: Can be used to supply addresses of DMF holder and manufacturing and testing facilities
    - 1.3.1.2 Change in contact/agent: Can be used to supply the name and address of contact persons and/or agents, including Agent Appointment Letter.

CTD Module 1 (cont)

- 1.4 Reference Section
  - 1.4.1 - Letter of Authorization: Submission by the owner of information, giving authorization for the information to be used by another.
  - 1.4.2 - Statement of Right of Reference: Submission by recipient of a Letter of Authorization with a copy of the LOA and statement of right of reference. (submitted in Application or DMF that REFERENCES a DMF)
  - 1.4.3 - List of persons authorized to incorporate by reference: Submitted in DMF annual reports.
- 1.12.14 Environmental Analysis Not required for a DMF. Can include a statement that all sites comply with local environmental regulations.

CTD Module 1

- Section 1.11: Information Not Covered Under Modules 2 to 5
  - Should NOT be used for information that should be in other Modules.
  - Example: A change in Specification in response to an Information Request from FDA can be noted in this Section but Section S.4.1 must include the changed Specification.
- 1.13.5 Annual Report: Summary of manufacturing changes since last Annual Report
  - Should contain link to 1.4.3 - List of persons authorized to incorporate by reference

CTD

- Module 2 = Quality Overall Summary (QOS) Expected to be submitted.
- 3.2.S Body of Data for Drug Substance, where applicable
- 3.2.P Body of Data for Drug Product, where applicable
- 3.2.R Regional Information:
  - Executed Batch Records: At least one sample batch record (in English) is expected for drug substances and drug products.
  - Method Validation Package: Not usually submitted for DMFs. Complete Methods Validation information should be included in 3.2.S.4.3 or 3.2.P.5.3
  - Comparability Protocols: Can submitted for DMFs

Letter of Authorization (LOA)

- The DMF will be reviewed ONLY when it is referenced in an Application or another DMF.
- An LOA does two things:
  - Grants FDA authorization to review the DMF
  - Grants the Authorized Party the right to incorporate the information in the DMF by reference.
- The holder MUST submit an LOA to the DMF in Section 1.4.1
- THEN send a copy to the AP
- AP submits copy of LOA in their Application in Section 1.4.2. This is the ONLY mechanism to trigger complete technical review of the DMF.

LOA (cont.)

- For multi-item DMFs, LOA must contain a specific reference to a particular item in the DMF.
- Specify the item by its name, page number and, most importantly, DATE OF THE SUBMISSION as it appears on the cover letter of that submission (not an internal document date). This is important for multi-item DMFs e.g. flavors. Volume number not useful
- When the AP changes its name, it should request that DMF holders issue a new LOA, send it to the DMF and send a copy to new AP.
- When holder changes its name the DMF holder should issue a new LOA, send it to the DMF and send a copy to all APs.
- It is not necessary to resubmit an LOA on a periodic basis. However, the list of authorized parties should be submitted in the Annual Report

Withdrawal of Authorization

- It is not sufficient to include APs whose authorization has been withdrawn in the Annual Report.
- Holder should submit a Withdrawal of Authorization Letter (WL) to the DMF stating that they have withdrawn authorization for that AP.
- Holder should notify AP that authorization has been withdrawn.

Annual Reports (ARs)

- The Annual Report is not required in CFR but is recommended in DMF Guidance and should contain
  - List of authorized Parties, including date of LOA
  - List of parties whose authorization has been withdrawn , including date of WL
  - List of all technical and administrative changes reported since last AR
- If no changes, include a statement to that effect.
- The list of “authorized parties” is a list of the companies authorized to REFERENCE the DMF, not a list of individuals who work for the holder or their agent who are authorized to ADD material to the DMF.
- All changes in technical or administrative information (including updates to stability data) MUST be reported as amendments when they occur. See 21 CFR 314.420(c).

Reporting Changes to a DMF

- A DMF can be reviewed at any time when a review is triggered by reference in an APPLICATION (IND, NDA or ANDA).
- Therefore, DMF must be up-to-date at the time of review.
- If changes have been made but not reported to DMF, reviewer can waste valuable time reviewing obsolete information and the review of the DMF (and consequently any applications that reference the DMF) can be delayed.

Closure of DMFs

- Closure by Holder:
  - Holder submits a Closure request to DMF
  - Entry into database changes status to “Closed.” Unavailable for review.
- Closure by FDA
  - If a DMF has not had an Annual Report in three years, FDA issues an Overdue Notice Letter (ONL).
  - After ONL issued, holder can retain activity of DMF ONLY by submitting an Annual Report.
  - If no response to ONL in time period specified in ONL, FDA will notify the holder that the DMF is “Closed.” Unavailable for review
- Status of a closed DMF shows up on DMF Web site list as “Inactive”

Submissions to DMFs after Initial Submission -1

- Types of Submissions in DARRTS:
  - Annual Reports
  - Original: Includes changes in technical information (technical amendments)
  - General: Includes changes in administrative information (administrative amendments)
  - Letters of Authorization (LOAs)
- General and Original Submission Types have a number of Categories/Subcategories (CSCs). List of CSCs at DMF Web site.

Submissions to DMFs after Initial Submission -2

- Header of Cover Letter (Transmittal Letter) should identify the types of information in the submission.
- Documents covering multiple Submissions, Categories and Subcategories may be submitted at the same time as long as they are specified in the header to the Cover Letter.

Submissions to DMFs after Initial Submission-3

- Amendment = A report of a change, deletion or addition of technical or administrative information. NOT a supplement (Supplements apply only to approved applications)
- When a change is made to one Section of a DMF the entire DMF does not need to be resubmitted.
- The entire changed File in a Section should be submitted e.g. a change in the material used in the synthesis should be included in a resubmission of the File in Section S.2.3.
- All Files should be paginated within the File. Pages that replace an already-numbered page from a previous File should also contain the page number in the current File (e.g. a page replacing Page 10 in the original submission may be page 14 in the new submission). Only the pages within the changed File are subject to re-numbering.

Administrative Amendments

- Administrative:
  - Change in holder name and/or address
    - Should have two separate letters if ownership of the DMF is being transferred to another company
      - Transfer letter on the letterhead of the old owner of the DMF
      - Acceptance letter on the letterhead of the new owner of the DMF.
  - Change in subject of DMF
  - Agent appointment or termination
  - Request for closure
  - Not necessary to report personnel changes except for contact person or responsible official

Agents for DMFs

- Not required, although recommended to facilitate communication for foreign company
- Holder appoints agent in “Agent Appointment Letter” on the holder’s letterhead.
- Responsibilities of agent should be defined in Agent Appointment Letter
- Agent for DMF purposes NOT the same as agent for Drug Registration and Listing System (DRLS)
- http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/DrugRegistrationandListing/ucm084014.htm
- Agents for DRLS and DMF purposes do not have to be the same.

Review of the DMF

- DMFs ARE NEITHER APPROVED NOR DISAPPROVED
- A DMF is reviewed to determine whether it is adequate to support the particular Application that references it.

Summary

- The DMF system presents challenges for both the industry and the FDA
- Implementation of electronic DMFs will improve the efficiency of the DMF review process which can improve the speed of review of applications supported by DMFs
- Problems can be minimized if holders and Authorized Parties
  - Understand their responsibilities
  - Adhere to the regulations
  - Follow the recommendations in the Guidances
  - Communicate with each other

Resources

Click for:

- eCTD Web Page
- DMF Web Page
- Electronic Submissions Gateway
- Electronic Submissions Presentations
- PDF of these presentation slides
- Electronic submissions questions: ESUB@fda.hhs.gov
- DMF Questions: dmfquestion@fda.hhs.gov

Questions about material presented during this webinar?
CDERSBIA@fda.hhs.gov

Open Q&A begins shortly – type in your questions now.

Click for Evaluation and Certificate