## CDER SBIA Webinar Series

# Stay Compliant! Electronic Submission of Drug Master Files (DMFs) is MANDATORY starting May 5, 2017: What You Need to Know

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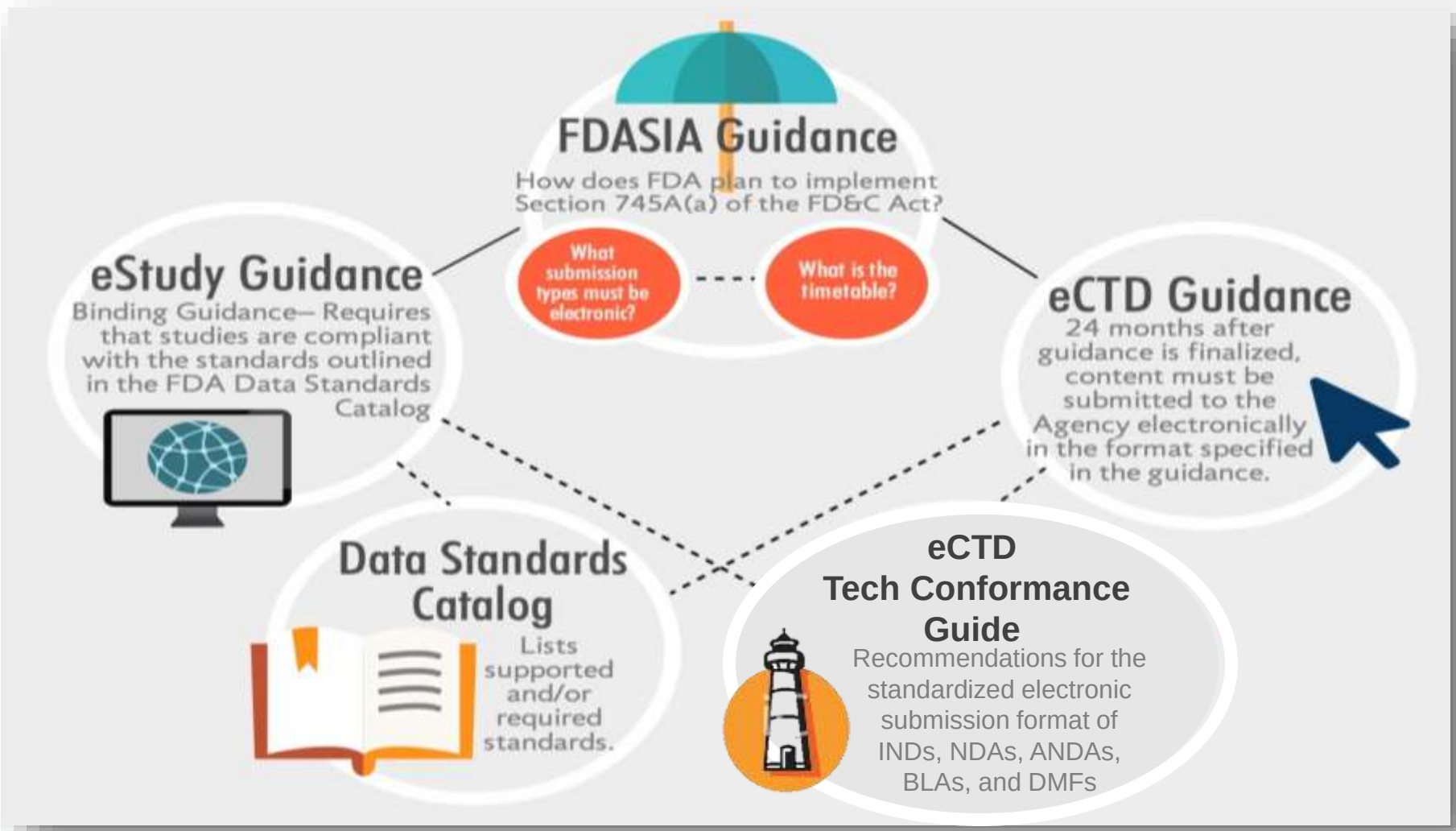
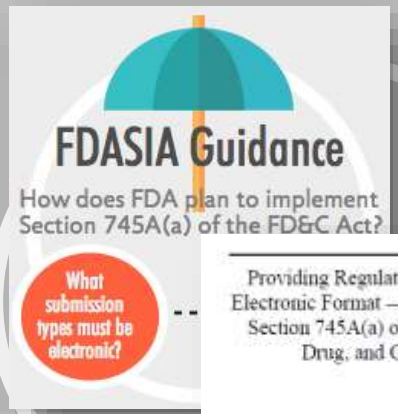
Office of Business Informatics, CDER
U.S. Food and Drug Administration

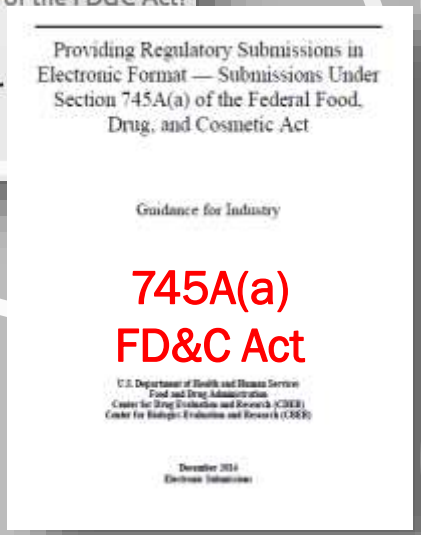
August 4, 2016

# Framework for Required Electronic Submissions



# How will eSubmissions be Implemented?




Final Published December, 2014

24 Months after Final Guidance

Individual Guidances

"745A(a) Umbrella" Implementation Guidance

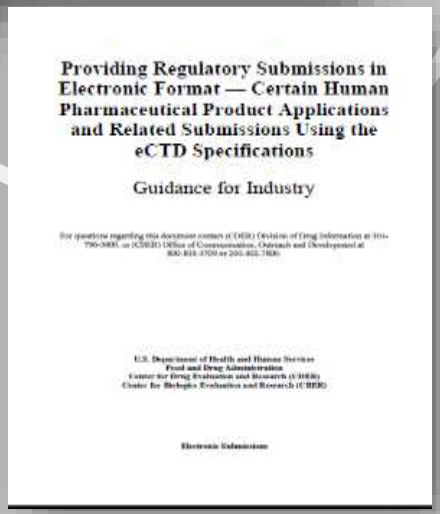
**NDAs, ANDAs, BLAs, INDs**

- Timetable
- Content
- Format

# 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

Published May 5, 2015

24 Months*

Required May 5, 2017

## Compliance

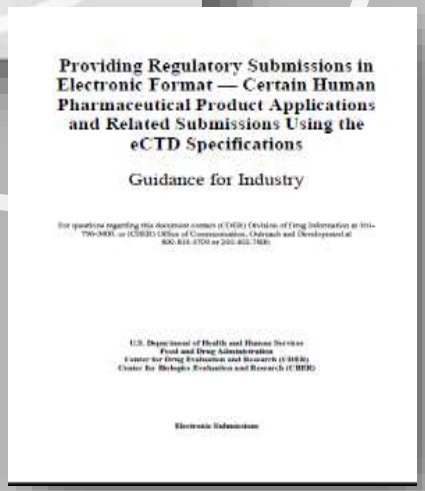
Electronic submissions using the version of eCTD currently supported by FDA. As specified in the FDA Data Standards Catalog

*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

Final Published May 5, 2015

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

## 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


Published
May 5, 2015

**ICH eCTD Specs 3.2.2**
**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.

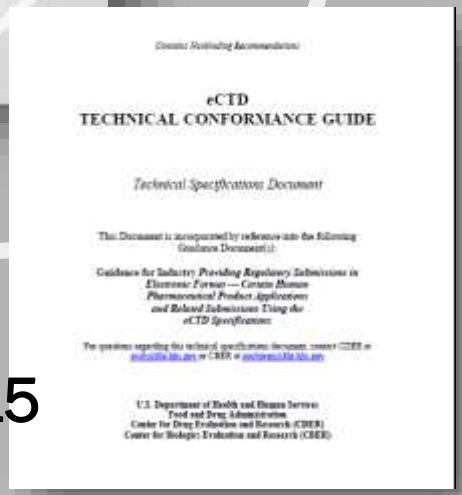
| Use | Data Exchange Standard | Exchange Format | Standards Development Organization (SDO) | Supported Version | Implementation Guide Version | FDA Center(s) | Date Support Begins (MM/DD/YYYY) | Date Support Ends (MM/DD/YYYY) | Date Requirement Begins (MM/DD/YYYY) | Date Requirement Ends | Regulatory 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


eCTD
TECHNICAL CONFORMANCE GUIDE

*Technical Specifications Document*

- **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

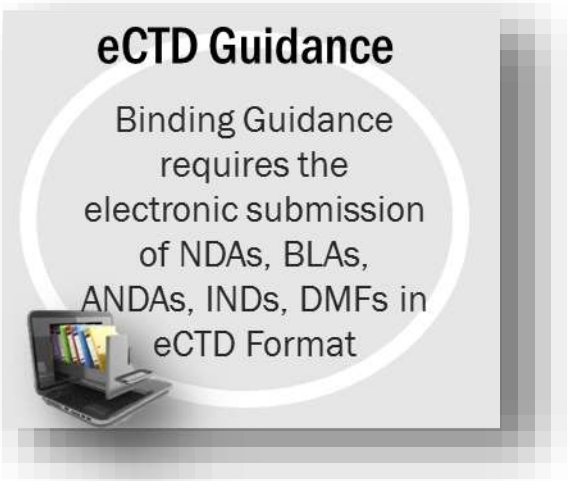
## eCTD Guidance

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

# Starting May 5, 2017

DMFs submissions in Paper will NOT be received

DMFs MUST be submitted in eCTD




# 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. *How? Go to www.fda.gov/ectd*
- **Must** follow the FDA eCTD technical specification *Table of Contents Headings and Hierarchy.*

*Find it in the eCTD Submissions Standards catalog*


*Find these specifications and more in the eCTD Submissions Standards catalog*

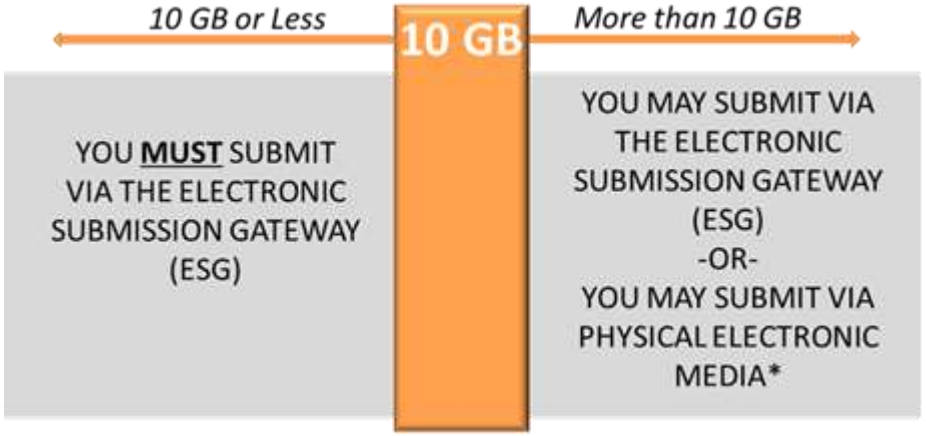
- **Must** adhere to the formats and versions specified in the FDA *Specifications for File Format Types Using eCTD Specifications*.
- **Must** adhere to the FDA *Portable Document Format (PDF) Specifications.*
- **Must** use the eCTD *replace* operation rather than submitting the file as *new* if a 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 Gateway for submissions 10 GB or smaller




* See ***Transmission Specification*** (www.fda.gov/ectd) for details

- 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/esg

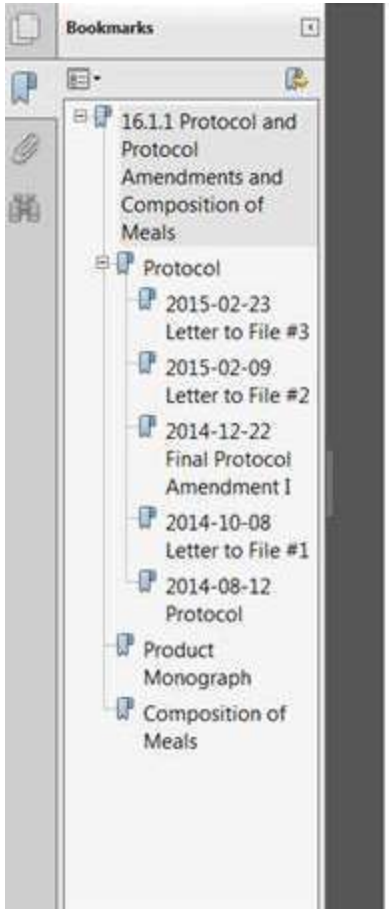
# Tips for DMF Submission Success

PDF Table of Contents and Bookmarks

- Should be the same
- For documents 5 pages or longer
- Up to 4 levels deep in hierarchy

# Tips for DMF Submission Success

**BAD – Bookmarks and TOC do not match.**
**TOC does not contain hyperlinks**

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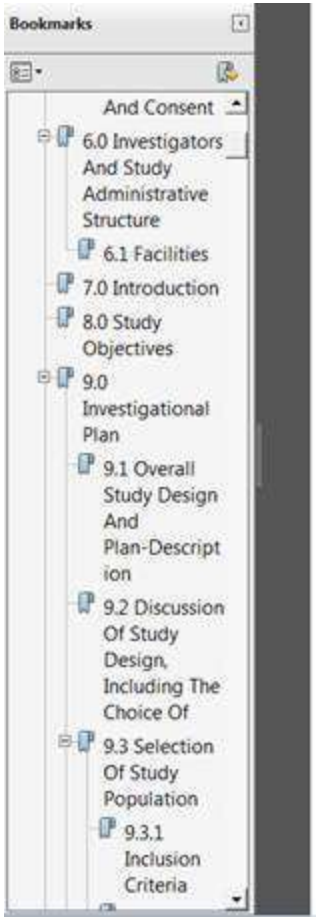
# Tips for DMF Submission Success

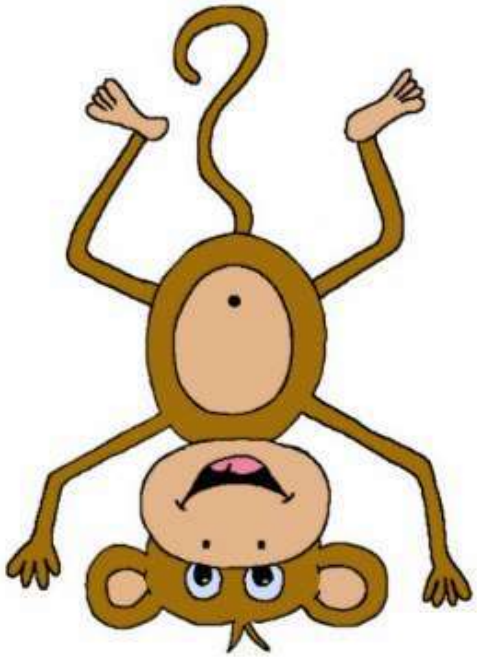
**GOOD!**



# Tips for DMF Submission Success

## Orientation

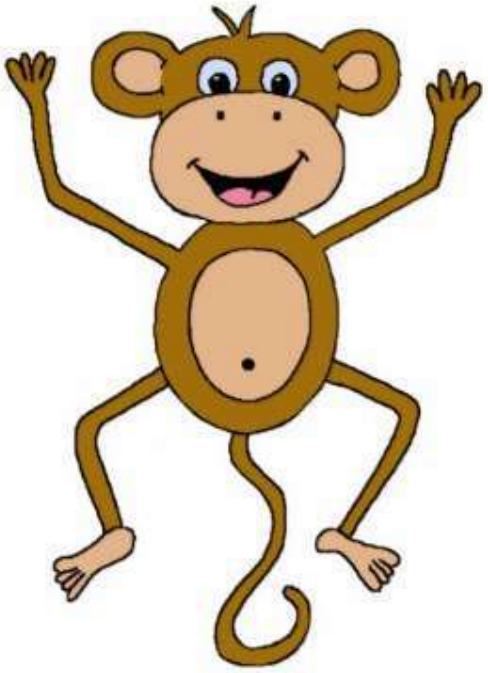
- Any documents provided in the submission should be in the correct orientation



# Tips for DMF Submission Success

Orientation

- Any documents provided in the submission should be in the correct orientation



# Tips for DMF Submission Success

- Do not include form 356h when submitting via gateway. DMFs are automatically processed without the form
- 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.

# Tips for DMF Submission Success

- Be sure to apply the correct metadata for m3.2.p and/or m3.2.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”

# Tips for DMF Submission Success

ESG Tips (Electronic Submissions Gateway)

- Get an account early
  - Account activation process contains many steps including submission of a CDER compliant test submission and passing validation. This may take multiple attempts and can take weeks.
  - Instructions are located at: www.fda.gov/esg
- When transmitting to CDER, choose “CDER” as the center and “eCTD” as the submission type
- When transmitting to CBER, choose “CBER” as the center and “DMF” as the submission type
- Questions related to the Gateway should be directed to: ESGHELPDESK@fda.hhs.gov

# DMF Paper to eCTD Examples (v2.01 DTD)

When transitioning from paper to eCTD and holder is utilizing us-regional.xml v2.01 DTD, the most common scenarios are below:

1. First eCTD submission is an amendment to the DMF
   - In this case, use a submission type of original-application

     *Subsequent amendments, including letters of authorization, submitted in eCTD should use a submission type of amendment*
2. First eCTD submission is an annual report
   - In this case, use a submission type of annual-report

TIP! FDA prefers eCTD submissions start with sequence 0001

# DMF Paper to eCTD Examples (v3.3 DTD)

When transitioning from paper to eCTD and holder is utilizing us-regional.xml v3.3 DTD, the most common scenarios are below:

1. First eCTD submission is an amendment to the DMF
   - In this case, use a submission type of original application and submission subtype of application. Use eCTD sequence number = 0001 and Submission ID = 0001.

     *Subsequent amendments, including letters of authorization, submitted in eCTD should use a submission type of original application and submission subtype of amendment. Use next available eCTD sequence number and Submission ID = 0001 (Submission ID for the first eCTD submission to the Original application)*
2. First eCTD submission is an annual report
   - In this case, use a submission type of annual report and submission subtype of report. Use eCTD sequence number = 0001 and Submission ID = 0001.

TIP! FDA prefers eCTD submissions start with sequence 0001

## 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 August 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.

# 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. The same DMF can be used to support an Investigational New Drug Application (IND), New Drug Application (NDA), Abbreviated New Drug Application (ANDA), and/or Biologics License Application (BLA )

However -

The manufacturer of the material can choose to submit the information necessary for review directly 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

- Most Type II DMFs are submitted for APIs
- 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.

# 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//NDA/ANDA/BLA.
  - The request will be forwarded to the review division that will determine whether a Type V DMF is appropriate.
  - This procedure should be followed before requesting a pre-assigned number for a Type V DMF.

# Electronic DMF (EDMF)

- All submissions after May 5, 2017 MUST be in ECTD format
- No exceptions, no waivers.
- Submissions to existing DMFs:  This means all amendments, Annual Reports, Letters of Authorization
- Can convert paper DMF to EDMF
- 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 a new EDMF. Not required when converting paper DMF to eDMF. See "Requesting a Pre-Assigned Application number"

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

  - A request for a pre-assigned DMF number for a Type V DMF should include documentation that the request for a Type V was cleared

# Initial Submission – Components

- 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
    - 1571 and 356h not applicable and shouldn't be submitted
    - Specific DMF form under consideration
    - 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 of Original DMFs (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
- Detailed 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 (M4 –Granularity) 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.
- Preferable to keep the same DMF number
- If a complete resubmission is being sent:
  - Each section should be complete and contain up-to-date information.
  - DMFs in non-CTD paper format must be converted to CTD format before submission in eCTD. 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.
- If a new electronic DMF is submitted containing information in an old paper DMF that was previously used to support and application, the new DMF should reference the applicable sections of the old DMF.

# Organization in CTD

- Module 1 Regional Information for DMFs generally administrative
- Module 2 Summary of Module 3 Example 2.3.S (drug substance) contains a summary of 3.2.S.
- Module 3 Complete Technical data
- Each Module contains individual Sections e.g. S.1.1. Each Section contains a “Document” or “File.” See next slide
- There are no sections within S.5, S.6, P.6, or P.7
- For drug substances 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.
- Type IV DMFs for a single entity should be submitted using the format in the drug substance section of the CTD.
- Type IV DMFs for mixtures such as flavor mixtures should be submitted using the format in the drug product section in the CTD.

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

- M4- Granularity (Page 5) states, referring to Module 3

"In choosing the level of granularity for this Module, the applicant should consider that, when relevant information is changed at any point in the product's lifecycle, replacements of complete documents/files should be provided in the CTD and eCTD."

Example: Three different Analytical Procedures in 3.2.S.4.2

The description of each one is a separate document, with its own pagination

  - Procedure A (i.e. document, page 1-n)
  - Procedure B (i.e. document, page 1-n)
  - Procedure C (i.e. document, page 1-n)

# CTD Module 3

- 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

# Organization in CTD for Multi-Item DMFs

- Multi-item DMFs e.g. Type III for rubber stoppers, Type IV for flavors, Type II for cell culture media 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 Type III and Type IV DMFs for mixtures

- 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):
  - 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. Can be updated as each new LOA is issued. When the list of authorized parties is submitted in the Annual Report, the list in 1.4.3 should be updated.
- 1.12.14 Environmental Analysis Not required for a DMF. Can include a statement that all sites comply with local environmental regulations.
- Other sections should be included as needed.

# 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

# 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 (AP) 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 not necessary in initial DMF but can be submitted in original DMF if there is a pre-assigned number.

# 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 and item referenced. Can be a link to 1.4.3
  - 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 IND/NDA/ANDA/BLA.
- 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 FDA's database (not the same as Submission Types in eCTD):
  - 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.
- All submissions after the initial submission undergo an Administrative Review to ensure that the Holder name, Subject, and DMF Type are the same as in FDA's database. If not the same, FDA will send an AFI Letter.

# Submissions to DMFs after Initial Submission -2

- Header of Cover 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 of the Cover Letter.
  - The description in the eCTD should be Multiple Submissions/Multiple Categories/Subcategories

# 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 3.2.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
- No requirement that the agent be in the U.S.
- Agent should be familiar with FDA regulations, guidances, and procedures in order to facilitate communication between the FDA and the DMF holder
- 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

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