



U.S. Food and Drug Administration

Generic Drug User Fee Amendments of 2012

DRUG MASTER FILES UNDER GDUFA: DMF Basics

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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 information 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., facilities, toxicological) may be filed in a DMF.

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: AskGDUFA@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 druginfo@fda.hhs.gov

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 Act (GDUFA) and Prescription Drug User Fee Act (PDUFA)
- Regulations: Section 21 of the Code of Federal Regulations (21 CFR) Required information
 - 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.

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

They contain RECOMMENDATIONS not 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)

Requirements for 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 (NDA or ANDA) 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 applicants

Clarification of some Terms

- Registration: In many parts of the world a company "Registers" an application or a "dossier." In the US, only manufacturing sites are "registered" in the Drug Registration and Listing System (DRLS)
- Active Pharmaceutical Ingredient (API) = "drug substance."
- Letter of Access: In some cases a DMF holder will call the permission to reference a DMF a "Letter of Access." (Phrase used in Europe). In the US, this is called a "Letter of Authorization" (LOA). An LOA does not permit anyone except FDA to "Access" i.e. "read" the DMF
- Transmittal Letter = Cover Letter
- Annual Report = Annual update

Initial Submission - Paper DMFs

- Holder sends the DMF in two copies to
Central Document Room
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266
- Use recommended binders
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>
- Fasteners must be obtained separately. 2 Piece Prong Fasteners, 8 1/2" Center to Center, 3 1/2" Capacity

Initial Submission – Electronic DMFs (EDMFs)

- Electronic Submission Gateway (ESG)

- Holder sends the DMF in Electronic Common Technical Document (eCTD) format through the ESG

- <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm>

- Choose "CDER" as the Center and "eCTD" as the "submission type"

- Physical Media (CD-ROM, DVD or USB drive)

- Holder sends the DMF on physical medium in eCTD format to the address on previous slide

- See the Transmitting Specifications website when transmitting via physical media (CD\DVD)

- <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163567.pdf>

- Acceptance of digital signatures the same as for any other submission to FDA

Initial Submission – (Cont.)

- Guidance

Follow the DMF Guidance and additional information on DMF Web site. (See Slide 3)

- Pre-assigned Number

A pre-assigned number is required for an EDMF. May also be obtained for paper DMF. 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 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.”)
 - NEW !! Not on Web site: List of Referenced applications e.g. DMF for intermediates
- Technical information

How the System Works

- DMF entered into FDA's database (DARRTS) and assigned a number
- Status = PENDING Not available for review
- Reviewed for administrative purposes ONLY by the Office of Pharmaceutical Science (OPS) staff. If incomplete, OPS sends an "Administrative Filing Issues" (AFI) letter.
- If administratively complete, OBI sends an acknowledgement letter
- Status = ACTIVE Available for review.
- Usual processing time is 2-3 weeks
- E-mail: dmfquestion@cder.fda.gov

Administratively Incomplete DMFs

- AFI letter details the missing information
- DMF Status remains PENDING and the DMF is unavailable for review.
- Response to AFI letter should be complete.
- If response is complete then Acknowledgment letter will be sent and DMF status changed to “Active.”

Acknowledgement Letter

- Notifies holder of DMF number and type. Includes Title (Subject) and Holder of DMF. Will appear on list posted on web site “SUBJECT OF DMF as manufactured in CITY, STATE or CITY, COUNTRY.”
- 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) for each item referenced for each customer to the DMF.

Confidentiality of Information in DMFs

- Confidentiality of info in DMF is covered by 21 CFR 314.430(g) and is the same as other type of submissions:

“The following data and information in an application or abbreviated application are not available for public disclosure ... (1) Manufacturing methods or processes, including quality control procedures.”

- This relates to information available upon submission of a Freedom of Information Act (FOIA) request
- FDA will not share information with a third party except through a FOIA request i.e. FDA will not tell Applicant anything about what is in the DMF.
- DMF holder and their customers can reach their own agreements about information sharing
- There are no “Open” and “Closed” part of a DMF in the US, as there are in Europe. All parts are considered “closed.”

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)
- Recommend that holder follow appropriate Guidances (see next slide)
- Facilities information (former Type I) not necessary. Address of facility is sufficient. Additional requirements under GDUFA.
- Recommend include statement of compliance with Current Good Manufacturing Practices (CGMPs)

Guidances for Technical Information

- Format: Common Technical Document (CTD)
- 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)
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073280.pdf>
- Drug Substance
 - [Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070632.pdf)
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070632.pdf>
 - ICH Quality Guidances: See next Slide

ICH Quality Guidances

General **FDA** Site

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065005.htm>

Q1 Stability Testing

Q2 Methods Validation

Q3 Impurities

Q4B Evaluation and Recommendation of Pharmacopoeial Texts

Q5 Biotechnology Products

Q6 Specifications

Q7 GMPs for Active Pharmaceutical Ingredients

Q11 Development and Manufacture of Drug Substances

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM261078.pdf>

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 (2 copies for paper) to the DMF
- THEN send a copy to the APPLICANT
- APPLICANT submits copy of LOA in their Application. ONLY mechanism to trigger complete technical review of the DMF.

LOA (cont.)

- LOA must contain a specific reference to a particular item in the DMF.
- Specify the item by its code 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)
Volume number not useful
- When the Authorized Party (AP) changes its name, the DMF holder should issue a new LOA and send a copy to new AP.
- When holder changes name the DMF holder should issue a new LOA 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: If a DMF holder withdraws authorization for a customer to reference the DMF this should be submitted as a “Withdrawal of Authorization” document.

Electronic DMF (EDMF)

- There is no requirement to submit ANY type of application in electronic format. This is projected to change under FDASIA two years after final guidance issued.
- Currently ALL electronic applications MUST follow the Electronic Common Technical Document (ECTD), unless a waiver is granted. No waivers granted for DMFs
- How to submit:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM149705>
- Can convert paper DMF to EDMF but once electronic, cannot submit paper, even for LOA.
- 17% of Type II DMFs submitted since 01/01/2001 are electronic 47% since Jan 2013

Annual Reports (ARs)

- Not required under any regulation
 - Regulations require that the DMF “...contain a complete list of each person currently authorized to incorporate by reference any information in the file...” See 21 CFR 314.420(d).
- Recommended in Guidance to permit DMF holders to fulfill this requirement on an annual basis, rather than submitting a new list whenever a new Authorized Party is added.
- Should contain
 - List of authorized Parties
 - 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 customers, 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.
- 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 (on the APPLICANT's clock) reviewing obsolete information.

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.

Closure and Reactivation 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 (90 days), FDA can change the status to “Closed.” Unavailable for review
- Reactivation of a Closed DMF
 - Holder submits a “Reactivation”
 - Should contain a complete copy of the DMF, containing any revisions since the last submission.
 - Contact DMFQuestion for a request for an exception to the recommendation to resubmit the entire DMF.
 - Entry of a Reactivation into DARRTS changes status to “Active” and the DMF is available for review.
- Status of DMF shows up on DMF Web site list

Submissions to DMFs after Initial Submission

- 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.
- Header of Cover Letter (Transmittal Letter) should identify all Submission Types and CSCs included in the Submission.
- Templates for different types of letters at DMF Web site.
- 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.
- All submissions in paper **MUST** be two copies, sent to same address as original submission (See slide 9).

Submissions to DMFs after Initial Submission (cont.)

- Amendment = A report of a change, deletion or addition of technical or administrative information. NOT a supplement (Supplements apply only to approved applications)
- All amendments should be paginated within the submission.
- Pages that replace an already-numbered page from a previous submission should also contain the page number in the current submission (e.g. a page replacing Page 10 in the original submission may be page 14 in the new submission)
- **NO PAGES ARE EVER PHYSICALLY REPLACED IN A DMF**

Submissions to DMFs after Initial Submission

Holder's Responsibility

- Header of cover letter should contain list of Submission Types and CSCs
- Cover letter should include a list of specific changes.
- Notify APPLICANT of types of changes
- Note - A new LOA specifying the date of the amendment is usually NOT necessary unless the amendment is for the addition of a new item to a multi-item DMF

Submissions to DMFs after Initial Submission: FDA's Role

- Information about the amendment entered into database
- Paper submission placed into binder in date order, most recent submission on top. When a binder is full, new volume created
- **NO REVIEWER ASSIGNMENT**, no review until submission of
 - New APPLICATION that references the DMFOr
 - Amendment to a pending application that references DMFOr
 - Supplement or annual report to an approved application that references DMF

Reporting Changes for Type II DMFs: Holder's Role

- Can implement the change when notification is submitted to the DMF
- Can ship “Post-Change Drug Substance” (PCDS) to customer
- Must notify the customer that a change has been made
- Should determine appropriate Reporting Category for the manufacturing change. See 21 CFR 314.70 and “Guidance for Industry: Changes to an Approved NDA or ANDA”
- <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm077097.pdf>
- Should notify the customer of the nature of the change
 - Provide sufficient detail to enable the customer to report change appropriately.
 - Level of detail determined by the contractual agreement

Reporting Changes for Type II DMFs (Applicant's Role)

- The APPLICANT has the responsibility of submitting the appropriate document to the FDA appropriately for an approved A/NDA.
- Drug product manufactured using PCDS can be marketed ONLY under the conditions spelled out in 21 CFR 314.70

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.

Review of the DMF

- When the reviewer receives an application that references a DMF, the reviewer triages the DMF to determine whether it requires review.
- If information has been reviewed previously and found acceptable and there has been no new information, the DMF does not need to be reviewed.
- Note that Type II DMFs submitted under GDUFA will undergo a Completeness Assessment when the User Fee is paid but a complete review occurs only when an application references the DMF

DMF Review and Communications Procedure

- DMF is reviewed using same regulatory and scientific criteria as review of an application
- If additional information is not needed for DMF
 - No letter to DMF holder except for “No Further Comments” letter specific for Type II DMFs under GDUFA.
 - Applicant not notified

Review of NDAs and ANDAs and the User Fee Clock

- PDUFA and GDUFA set specific timelines for FDA to take action on an application = User Fee Clock (UFC)
- Amendments to a pending application may or may not be reviewed, depending on when they are submitted relative to the goal date.
- If an application cannot be approved, FDA sends a “Complete Response” (CR) letter. This stops the UFC and no further review activity is done on the application.
- When the applicant submits a “Complete Response” the clock starts again, with a new goal date.

DMF Review and Communications Procedure (continued)

- If more information is needed to complete the review, a list of the information needed is communicated to the holder in an Information Request (IR) Letter
- If the information in the DMF cannot support approval of the application that references it, FDA sends a Deficiency Letter (DEF) or Complete Response (CR) Letter (specific for Type II DMFs under GDUFA)
- The APPLICANT is notified that information has been requested for the DMF
 - The letter to the APPLICANT is either an IR or CR Letter.
 - The nature of the information requested in the DMF letter is not communicated to the APPLICANT.

Amendment to the DMF in Response to Letter to Holder

- Holder submits amendment to DMF.
- Cover letter should contain:
 - Header stating:
 - Response to CR, Deficiency or Information request Letter
 - Specific technical CSCs.
 - Reference to date of Agency's letter to holder
 - A list of the specific questions and responses, with references to applicable amended sections of the body of the DMF, where appropriate.
- Holder notifies applicant that the DMF has been amended.
- Holder may notify reviewer or project manager, if that was requested in letter to holder
- No desk copy.
- Reviewer does NOT receive notification of receipt of amendment from document room. (contrast with amendment to APPLICATION)

Amendment to the DMF in Response to Letter to Holder: Applicant's Role

- If the Applicant was sent an IR Letter.
 - Applicant should submit an amendment to APPLICATION notifying FDA that DMF was amended. Reviewer receives assignment to review APPLICATION AMENDMENT. DMF amendment may be reviewed depending on timing relative to due date of A/NDA
- If the Applicant was sent a CR Letter.
 - The DMF amendment will be reviewed ONLY when the APPLICANT submits a Resubmission (Complete Response) to their CR letter. Rationale: CR letter may contain other deficiencies e.g.. Clinical issues. If these are not addressed then the DMF amendment does not need to be reviewed
 - The amendment to the DMF must be a Complete Response to DMF letter from FDA. Cannot be a notification that the DMF or sections thereof WILL be amended.
 - If amendment to DMF is not complete, then the Resubmission to the A/NDA is not a Complete Response.

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
- Do not include ANY changes in Annual Report.
- However may be reported at the same time as Annual Report.

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
- Do not use the word “authorize” in appointing an agent. This can be easily confused with a Letter of Authorization. Use the word is “appoint.”

Common Technical Document (CTD)

See ICH M4Q

<http://www.fda.gov/RegulatoryInformation/Guidances/ucm129901.htm>

Module 1 Administrative information that applies to DMFs There are no forms for DMFs.

- Section 1.2: Cover Letter, Statement of Commitment and Generic Drug User Fee Cover Sheet (3794), 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

- 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.

CTD (Continued)

- Module 2 = Quality Overall Summary (QOS)
Expected to be submitted.
- 3.2.S Body of Data for Drug Substance
- 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
 - Comparability Protocols: Not usually submitted for DMFs

DMFs for Intermediates

- If a chemical in the manufacturing pathway is defined as an “intermediate” rather than a starting material, it is expected to be manufactured under CGMPs. See ICH Q7. See Slide 18
- See also: ICH Q11
- Usually more information regarding the manufacturing is needed to ensure that the intermediate is acceptable for further processing to the drug substance.
- Therefore a DMF may be necessary if the intermediate comes from a third party.

Inspections

- Inspections of drug substance manufacturers are usually triggered when there is an application under review that references a DMF for the manufacture of that drug substance.

Summary

- The DMF system presents challenges for both the industry and the FDA
- Problems can be minimized if holders and applicants
 - Understand their responsibilities
 - Adhere to the regulations
 - Follow the recommendations in the Guidances
 - Communicate with each other