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 submission 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 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, most importantly, 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, 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 Harmonisation (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

- 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 Business Informatics (OBI) staff. If incomplete, OBI sends a request for additional information.
- 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

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

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
- 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
  - 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.
- However 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.
- ~12% of Type II DMFs submitted since 01/01/2001 are electronic
-

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 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. It is 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.

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
- 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 ASSIGNMENT, no review until submission of
  - New APPLICATION that references the DMF

  Or
  - Amendment to a pending application that references DMF

  Or
  - 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.
- See MAPP 5015.4: Chemistry Reviews of DMFs for Drug Substances/Intermediates (DSI) http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm079565.pdf
- Specifically applies to Type II DMFs
- 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 application
- 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.
- If no information needed for DMF
  - No letter to DMF holder except for “No Further Comments” letter specific for Type II DMFs under GDUFA.
  - Applicant not notified.

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)

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

CTD Module 1

- Section 1.12: 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

New DMF Requirements based on GDUFA

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Director DMF Review Staff/OGD

CDER Small Business Webinar on DMFs and GDUFA
January 28, 2013

Introduction to New GDUFA Requirements

- DMF fee – when and how to pay
- New DMF correspondences and meetings
  - DMF Complete Response letter
  - DMF Incomplete letter
  - DMF No Further Comments letter
  - DMF 10-day teleconference
  - Available for Reference List http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM332875.pdf

The DMF Fee under GDUFA

- Due for Type II DMFs for the API referenced by an initial letter of authorization by an ANDA submission on or after October 1, 2012
- Required upon the first reference on or after October 1, 2012
- Paid only once during the DMF lifecycle
- Is triggered when the DMF reference is included in the following ANDA submissions:
  - Original ANDA
  - An amendment to an ANDA
  - A Prior Approval Supplement (PAS)
  - An amendment to a PAS

When A DMF fee is not Required

- For ANDAs that are part of the backlog
- For submissions not part of GDUFA (INDs, NDAs, Changes Being Effected (CBE) 0 or 30 supplements)
- For any non-Type II DMF (Type IV DMF for an excipient)
- For any Type II DMF that is not referenced as the API
  - DMFs for API intermediates
  - DMFs for drug product manufacturing intermediates
  - DMFs for Drug Products
- For submissions reporting a change to the DMF that had established a relationship to the ANDA before GDUFA
- Issuing an updated Letter of Authorization that does not establish a new relationship to the ANDA submission

Fee Payment and the Filing of ANDAs

- Under GDUFA an important goal for the DMF holder is to get the DMF to "Available for Reference" status so referencing ANDAs can be filed
- Only ANDA submissions which reference DMFs for APIs that are "Available for Reference" can be received and filed by FDA
- Under GDUFA, an "Available for Reference" DMF must meet two requirements:
  - The DMF fee must be paid
  - The DMF must pass the Completeness Assessment
- Payment of the DMF fee is the trigger that automatically places the DMF in queue for the Completeness Assessment
- We strongly recommend paying the DMF fee at least three months in advance of submitting the referencing ANDA submission to allow sufficient time for the Completeness Assessment to occur.

Consequences for the ANDA when the DMF is not "Available for Reference"

- How fee Payment impacts filing:
  - Fee payment status check is performed by Office of Management (OM) within several days of the ANDA being submitted to FDA
  - ANDA sponsor will receive a notification from OM (Office of Management) that the DMF fee is due and ask that you pay within a 20-calendar day grace period.
  - Note that FDA does not care who pays the fee…ANDA sponsor or DMF holder is ok.
  - After 20 days, if the DMF fee is still NOT paid, the ANDA submission will be Refuse to Receive due to User Fee obligation not satisfied. The ANDA will not be processed further (i.e. sent to OGD for filing review) until the DMF payment is received. This will delay both the filing of the ANDA and the processing of the DMF for Completeness Assessment.
  - When all fees are paid (including the DMF fee) the ANDA is placed in queue at OGD for the comprehensive filing review and the DMF is automatically placed in queue for the Completeness Assessment.
  - Please note, that the date of the ANDAs submission receipt will be reset to the date all user fee obligations are satisfied.

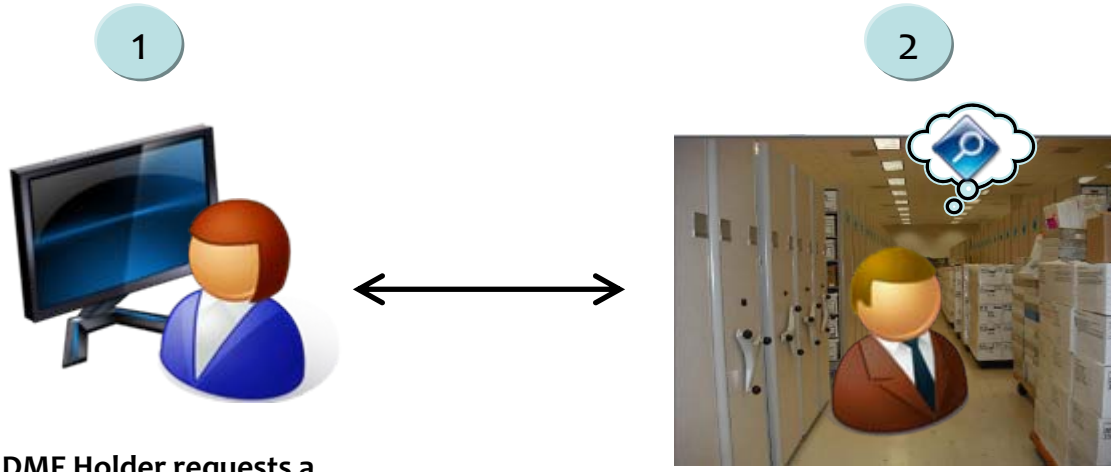
Consequences for the ANDA when the DMF is not "Available for Reference"

- How the Completeness Assessment impacts filing of the ANDA:
  - When the OGD filing review decision on the ANDA is ready to be made the DMF must be Available for Reference (i.e. the DMF must have passed the Completeness Assessment)
  - If the DMF is not Available for Reference, the ANDA will be Refuse to Receive by OGD for technical reasons and only a 75% refund of the ANDA submission fee can be granted.
  - OGD can not guarantee that the Completeness Assessment of the DMF will be finished during the filing window of the ANDA.
  - To reduce the risk of losing 25% ANDA submission fee due to DMF issues
    - Pay the DMF fee at least 3-months prior to ANDA submission (allow even more time for expedited ANDAs)

DMF Fee Payment Process

- Fee collection is processed in FDA for GDUFA by OFM (Office of Financial Management), who manage the payment infrastructure and OM (Office of Management) who manage and track the user fee obligations
- Two common cases for fee payment:
  - Paying DMF fees for DMFs which are not yet filed with FDA
  - Paying DMF fees for DMFs which are already filed with FDA
- Amount of the DMF fee for GDUFA year one is $21,340.

Case 1: Pay the DMF fee for a DMF that has not yet been filed (file and pay)



DMF Holder requests a pre-assigned DMF number from FDA*

FDA assigns a DMF# and communicates it to the holder

Case 2: Pay the DMF fee for a DMF that has already been filed (pay only): Skip this step since you already have a DMF#.

*For information on how to request a pre-assigned DMF#, see the DMF website at: *http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm114027.htm*

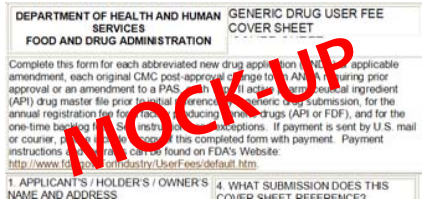
With Assigned DMF Number, DMF Holder Pays User Fee Through OFM User Fee System (i-Store)

1

DMF Holder Logs into OFM User Fee System (i-Store)

Generate User Fee Coversheet

2



User Fee Coversheet

Complete Payment

3

OFM User Fee System

1. DMF Holder logs into iStore at: https://userfees.fda.gov/OA_HTML/gdufaCAcdLogin.jsp and provides the requested information (including the DMF#)
2. System generates the appropriate user fee cover sheet with the required fee.
3. DMF Holder pays the required fee using the cover sheet (Note that partial payment is not acceptable).

With DMF User Fee Paid, DMF Holder Submits the DMF Document (Case 1 only)

1

DMF Document

DMF User Fee Coversheet (Form 3794)

Holder submits DMF to FDA's Central Document Room

Submits DMF

2

FDA Central Document Room

Document Room Receives DMF

Submitting Documentation

- Note the following for Case 1 (pay then file):
  - DMF User Fee Coversheet (Form 3794) must be included in the submission.
  - File in Section 1.2 under FDA Regional Information

- Note the following for Case 2 (pay only):
  - Submit DMF User Fee Coversheet (Form 3794) separately to the DMF as a stand-alone amendment (not within an annual update or other amendment)
  - Clearly indicate on the cover letter that the submission is the User Fee Cover Sheet.

Case 1: FDA Performs Administrative Review of DMF Application (Not to be confused with the completeness assessment)

1

DMF Application

FDA performs Administrative Review of submitted DMF

2a

If DMF is administratively complete, FDA sends the Filing Acknowledgement to holder and DMF is Active

2b

If DMF is <u>not</u> administratively complete, FDA sends a letter to firm identifying issues. DMF is not Active until issues are resolved.

CDER/OM (Office of Management) confirms User Fee payment and sets the status for the DMF

OM sees that DMF has paid DMF fees

Set User Fee status

DMF record indicates the Fee has been paid

Once the user fee status is “Met” OGD can perform the completeness assessment.

New DMF Correspondences and Meetings

- DMF Complete Response (CR) letter
- DMF No Further Comments letter
- DMF Incomplete Letter
- 10-day teleconferences
- List of “Available for Reference” DMFs posted on FDA website

Basis for the DMF CR Letter

- The GDUFA Commitment Letter, which outlines the GDUFA Performance Goals and Procedures (link provided below) states:
  - "FDA will issue a letter detailing all identified deficiencies, rather than discipline specific letters, for all DMFs including those under review at the time of enactment of the implementing legislation.
  - The DMF deficiency letters will reflect full division-level deficiency review of deficiencies from all relevant review disciplines, including inspections, and address other matters relating to the DMF review such as consults with other agency components (these will be subsumed into the DMF metrics)."
- http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf

Characteristics of the DMF CR Letter

- The DMF CR Template has been in use since mid-October 2012 and contains the following sections
  - Chemistry Deficiencies (if applicable)
  - Microbiology Deficiencies (if applicable)
  - Facilities information (if available)
    - Standard language approved by the Office of Compliance
    - No further questions if facilities acceptable
    - Inspections/evaluations pending
- We will not delay issuing DMF CR letters based on pending compliance evaluations or inspections.
- Letters will reflect the compliance status of facilities at the time the letter issues
- Deficiencies from any related consults are included under the discipline that requested the consult

Characteristics of the DMF CR Letter

- The DMF letters will issue before the ANDA CR letter for a given review cycle to comply with ANDA CR requirements.
- DMF CR letters will be referred to in the ANDA CR letter along with instructions to the applicant not to respond until the DMF holder has indicated that they have submitted a complete response to the DMF CR letter.
- DMF responses from the holder must address all issues raised in the Chemistry and Microbiology sections of the letter or they will not be reviewed.
- Note that statements in the DMF amendment deferring response to a future submission are not acceptable.
- DMF must notify the ANDA sponsor when they submit their response

DMF No Further Comments Letter

- The Commitment letter states:
  - "Once a DMF has undergone a complete review and the ANDA referencing same is either approved or tentatively approved – at such time there being no further outstanding deficiencies to the DMF – FDA will issue the DMF holder a letter to indicate that the DMF does not have any further open matters as part of the review associated with the referencing ANDA."
- Issued at approval of the ANDA, not when the DMF is first deemed adequate
- Not to be construed as an indication of any future status of the DMF (i.e. not equivalent to an approval letter)
- Applies only in the context of the referencing ANDA and not any other ANDA which may be referencing it
- Separate letters issued to the DMF holder for each referencing ANDA

DMF Incomplete Letter

- Issued to communicate issues discovered during the Completeness Assessment
- Comments in the letter will describe any issues and the additional information that is needed to address the issues
- DMF holders need to respond with an amendment as quickly as possible to avoid adversely impacting the filing of an ANDA
- Cover letter of the amendment should indicate that the submission is a “Response to DMF Incomplete”
- Notification instructions in the fax coversheet need to be followed to avoid delays in updating the Completeness Assessment

"10 day" Teleconferences

- Specific type of teleconference described in the commitment letter
- 30 minute t-con for first cycle deficiency letters limited to the contents of the letter
- To qualify, a written request must be received by FDA within 10 days of receiving the letter
- Contact information for requesting these teleconferences is included in the DMF CR letter
- Meeting timeframe is at the discretion of OGD and availability of involved parties
- There are limits of one teleconference per DMF holder per month

The Available for Reference List

- Required by the GDUFA legislation
- Comprehensive list of all Type II DMFs for APIs that have paid the DMF fee and passed a Completeness Assessment
- Updated list is posted on the FDA website on a weekly basis
- Once the DMF is on the list you remain on the list unless fee payment is withdrawn or the DMF has a status other than “active”
- All questions regarding the contents of the list should be sent to: DMFOGD@fda.hhs.gov

CDER Small Business Webinar on Drug Master Files (DMFs)
under Generic Drug User Fee Amendments (GDUFA)

Completeness Assessment for Type II Active Pharmaceutical Ingredient Drug Master Files to Be Referenced in ANDAs

Huyi Zhang, Ph.D.
DMF Review Staff / OGD

January 28, 2013 White Oak / Silver Spring, MD

Scope of Completeness Assessment (CA)

Five Defining Factors

- DMF
- Type II
- API
- ANDA, ANDA Amendment, ANDA PAS
- GDUFA

Completeness Assessment (CA) is specified in GDUFA

- Section 744B(a)(2)(D)(ii) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), which was added by GDUFA, states that a Type II API DMF will be deemed available for reference in an ANDA, ANDA amendment, or ANDA PAS, if the required fee has been paid and if the DMF has not failed an initial completeness assessment "in accordance with criteria to be published by" FDA.

  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM321884.pdf

- Section 744B(a)(2)(D)(iii) of the FD&C Act requires FDA to make publicly available on its website a list of DMF numbers that correspond to DMFs that have successfully undergone an initial completeness assessment, in accordance with criteria to be published by FDA, and that are available for reference.

  http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/default.htm
  http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/UCM2007046
  http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM332875.pdf

Completeness Assessment aims to improve submission quality and review efficiency

- New requirement in the GDUFA legislation
  - Drug substance (Type II) DMFs must be deemed *"available for reference"* by the HHS Secretary to be referenced by an ANDA
  - Two things must happen for the DMF to be considered "available for reference"
    1. DMF Fee must be paid
    2. DMF must pass a "completeness assessment"
  - ANDAs can only be filed by OGD if all DMFs for the drug substance(s) are "available for reference"
- Improve quality of the submission
- Improve the efficiency of the scientific review

Completeness Assessment focuses on "Complete"

- Criteria not specified in the legislation.
- A "complete" DMF contains all of the information necessary for a full scientific review.
- The scope of the review in a Completeness Assessment is higher than the administrative criteria used by Central Document Room.
- Similar in nature to the current ANDA filing review which served as the model for the Completeness Assessment

- *A "complete" DMF is not necessarily adequate to support approval of an ANDA*.

Completeness Assessment is performed by OGD/DMF Review Staff

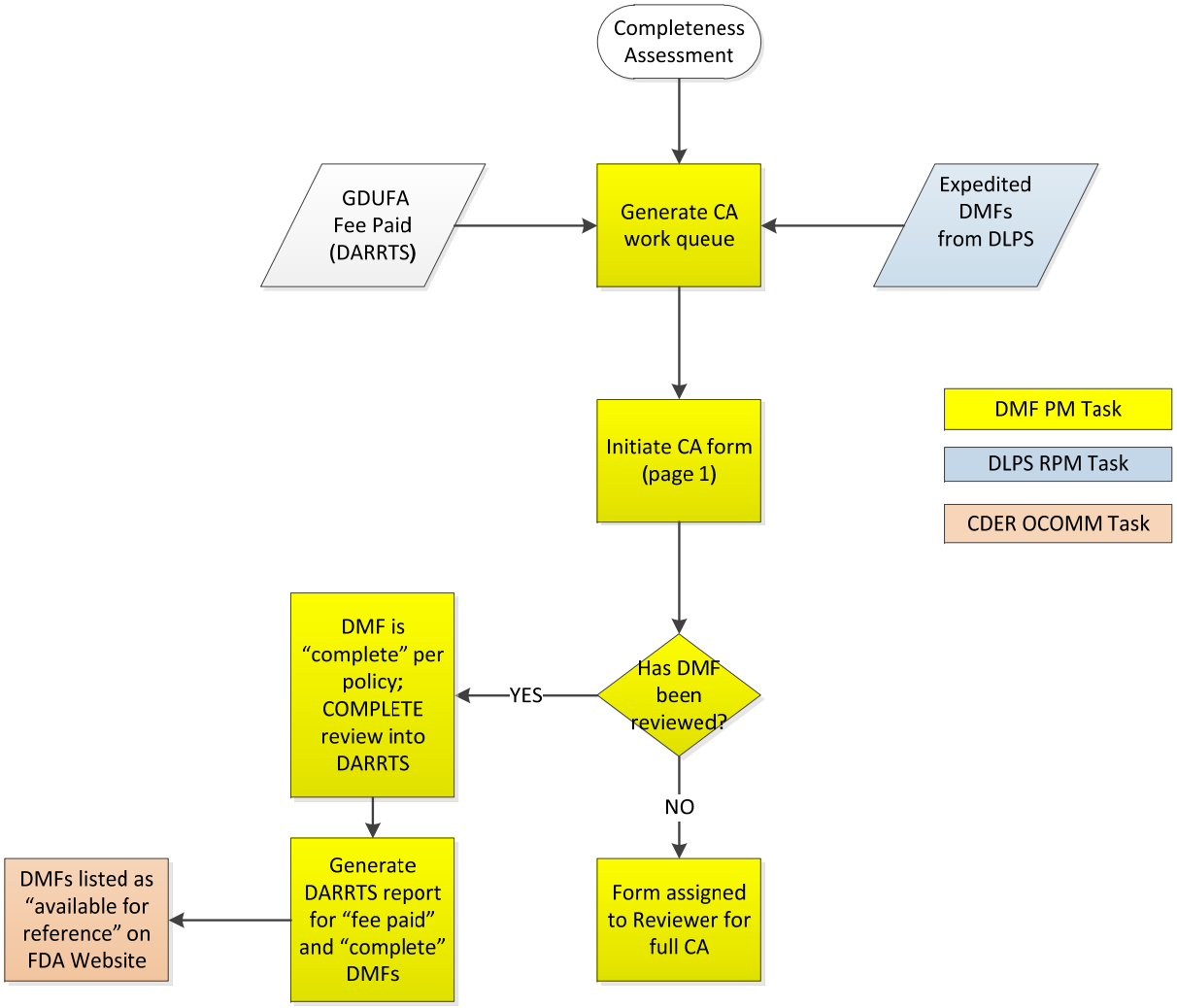
- Performed by OGD/DMF Review Staff
  - A review group dedicated to drug substance review (Type II DMFs) in support of original ANDAs
- Performed by a chemist
  - Leverage expertise
  - Enhance efficiency

DMF Fee payment triggers Completeness Assessment

- DMF Fee is a one-time fee
- Not to be confused with the facility fee related to the drug substance manufacturing facility
- Payment of the DMF fee triggers the Completeness Assessment process in OGD
- DMF Fee is required when the referencing ANDA is submitted
- DMF Fee may be paid independent of a referencing ANDA in order to get a completeness assessment and be to listed on the FDA's "Available for Reference" webpage.
- DMF Fee may be paid at the strategic timing according to the referencing ANDA submission
  - Requires proactive communication with ANDA applicant
  - risks of delaying the ANDA filling if DMF fee has not been paid

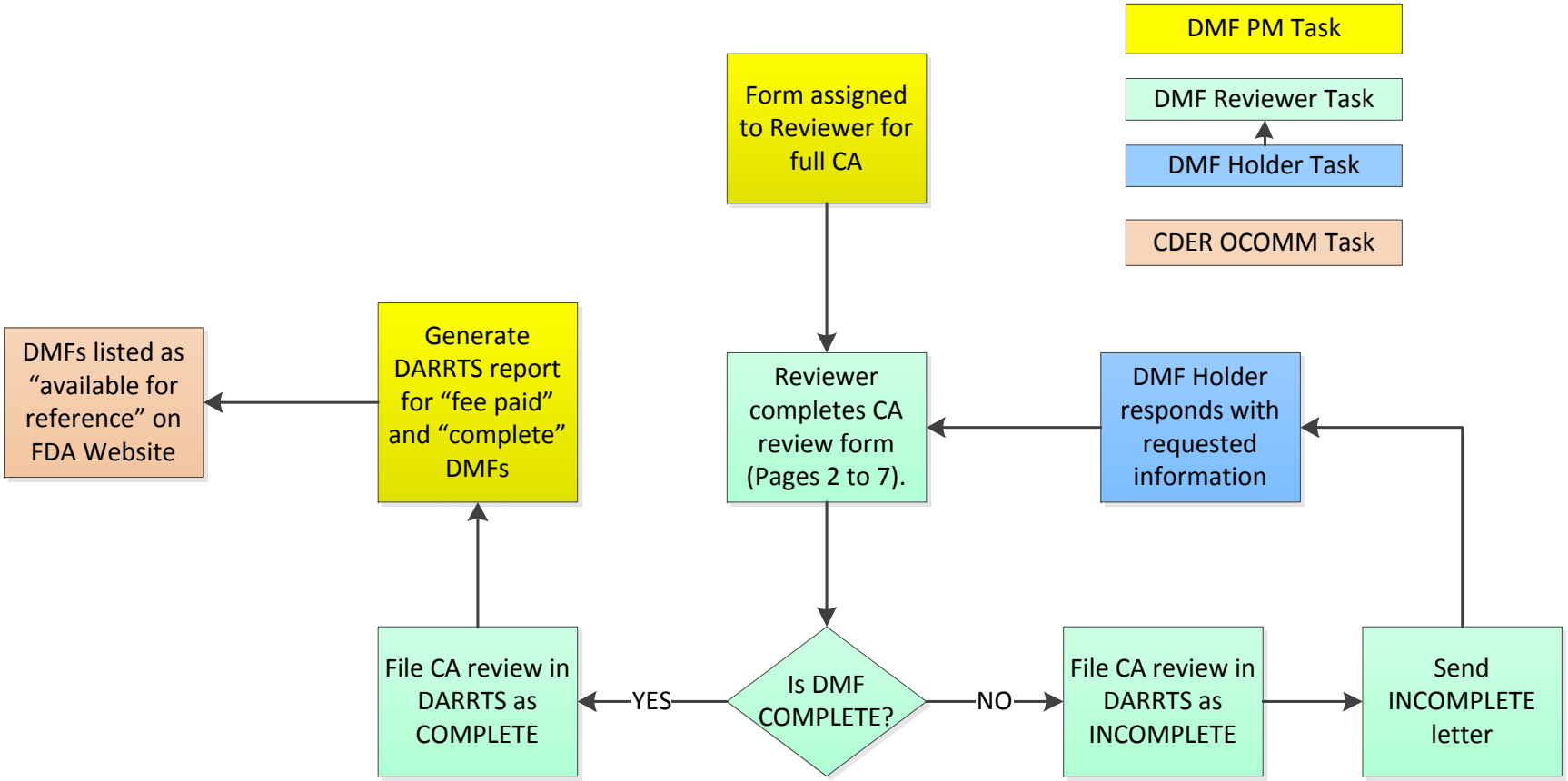
Process Flow of Completeness Assessment

Part 1: Queue generation and Project Manager (PM) processing



Process Flow of Completeness Assessment (2)

Part 2: Full Completeness Assessment review by the Chemist



Communication of "GDUFA DMF INCOMPLETE COMMENTS"

- OGD will issue a "GDUFA DMF INCOMPLETE COMMENTS" describing all issues causing the DMF to fail the completeness assessment
- Amendments must completely address all issues raised.
- Submit as an amendment using normal procedures for DMFs.
- Provide notification (email) to OGD/DMF Team when a response is submitted
  - Follow all instructions on the fax cover sheet

When you send in your DMF response please notify the review chemist by email using ***both*** *of the following email addresses:*

Attention: ~CHEM_REVIEWER~
Email address: firstname.lastname@fda.hhs.gov
Email address: DMFOGD@fda.hhs.gov

Please note that failure to provide notification as instructed may result in the delay of the completeness assessment process.

Draft Completeness Assessment Guidance

Guidance for Industry

Initial Completeness Assessments for Type II API DMFs Under GDUFA

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Division of Drug Information at 1-866-405-5367.

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/UCM2007046

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM321884.pdf

Completeness Assessment Checklist (Draft)

Administrative Section

APPENDIX 1: GDUFA INITIAL COMPLETENESS ASSESSMENT CHECKLIST FOR TYPE II API DMFs

DMF: (NAME/ NUMBER)
HOLDER:
DRUG NAME (Subject):

LETTER DATE:
RECEIVED DATE:
Electronic or Paper Submission:

DMF(s) referenced by the primary DMF being assessed, if applicable:

☐ EXPEDITED ASSESSMENT per REQUEST from FDA by: (requestor name here)

Primary Reviewer: Date:	Review Recommendation for Initial Completeness Assessment: ☐ **COMPLETE** ☐ **INCOMPLETE**

Completeness Assessment Checklist (Draft)

Administrative Section (2)

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

☐ Yes ☐ No

2. Is the DMF active?

☐ Yes ☐ No

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

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

☐ Yes ☐ No

If "yes," the DMF is COMPLETE per policy.
If "no," review DMF with checklist.

Completeness Assessment Checklist Is Arranged In Accordance to CTD Format

- Administrative/General Information
- 2.3.S QOS
- 3.2.S.1 General Information
- 3.2.S.2 Manufacture
- 3.2.S.3 Characterization
- 3.2.S.4 Control of Drug Substance
- 3.2.S.5 Reference Standards or Materials
- 3.2.S.6 Container Closure System
- 3.2.S.7 Stability
- 3.2.R. Regional Information

Each question has check boxes of “yes”, “no” or “not applicable”, If an item is marked “n/a,” it means the element may not apply to the DMF, and the element is treated the same as if it were marked “yes.” e.g

#61. Comparability protocols are provided if applicable. yes, no, ***n/a***

#1. Subject of the DMF is a single drug substance produced by one manufacturing process.

For purposes of facility self-identification and payment of fees, GDUFA defines API differently from the way this has been defined historically.

Sec. 744A. Definitions.
(2) The term ‘active pharmaceutical ingredient’ means—

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

- Limited to one drug substance while multiple manufacturing sites for a single drug substance is permitted when the same process is utilized in each of those sites.
- Limited to one manufacturing process while certain process alternatives/changes may be permissible with sufficient supportive information provided. e.g.:
  - Validated reprocess/rework procedures
  - Micronization leading to different particle sizes
  - Addition of a stabilizing antioxidant at various levels for stability purpose
  - Variation in final crystallization/purification step leading to different physical forms
  - Minor process variation that is the same chemical transformation with little risk to the impurity profile

- Separate DMF should be filed for:
  - Different salt form
  - Different synthetic route
  - Significant process alternation resulting in different impurity profile and requiring different control strategy

#2. For previously submitted DMFs, the DMF holder needs to submit a complete update

- The large number of amendments since the original submission or last complete update make it difficult to determine the current state of the information in the DMF.
- Five years since the DMF has received a complete update, or more than 5 amendments and annual reports to the DMF are the good guide to determine the necessity for submission of a complete update.
- The complete update should reflect the current status of the process and not require reference to any previous submission for information. The DMF holder is encouraged to submit the update in ECTD format which will convert this DMF to electronic format going forward.
- A complete update is not the same as the Annual Report.
- Clearly state “complete update” in the cover letter when a complete update is submitted.

#6. Contains Letters of Authorization for any DMFs referenced to support this DMF.

- If a DMF (primary DMF) has referenced another DMF (secondary DMF) for intermediates, the primary DMF holder will need to provide the Letter of Authorization from the secondary DMF holder which authorizes the primary DMF holder to reference the secondary DMF for information.
- Not to be confused with the LOA given to the ANDA applicants
- For all DMF submissions, even if the DMF holder is the same company as the authorized party, Letters of Authorization must be submitted in two copies to the DMF itself.
- The copy of LOA should be located in the section 1.4.2. For more information please refer to the following FDA DMF page: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/default.htm

#8. Contains label with storage conditions and retest date

- A specified temperature storage condition based on the stability studies
- Actual numerical temperature ranges are preferable although using a USP terminology associated with a defined temperature limit or range such as "USP Controlled Room Temperature" would be acceptable.
- Rest test date on both label and COA
- “Caution: for manufacturing, processing, or repacking”

.

#20-24 on the Controls of Starting Materials *if API is a fermentation product.*

Information required per #20-24 are common for a synthetic process.

For a fermentation process, information pertaining to the quality and control of the following should be provided:

- Microorganism
- Cell bank system
- Media components

#58. Stability Data is provided.

- Completeness Assessment does not specify how much stability data to be provided in the initial submission of a Type II API DMF
- Stability summary, conclusion, protocol, retest date and any available data should be provided to demonstrate a stability program is in place in order to meet the completeness assessment requirement
- Adequacy of the stability information will be evaluated during the scientific review when the DMF is referenced by other application with LOA

Summary

- Provide high quality submissions
- Plan ahead -- pay DMF Fees by due date (or earlier!)
- Increase communication between DMF holders and ANDA sponsors
- Use the resources available from FDA
- Respond to Information Requests in letters completely and promptly
- Submit DMFs in ECTD

Thank You