DRUG MASTER FILES

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Drug Master Files

- A Drug Master File (DMF) is a submission to the FDA of information, usually concerning the Chemistry, Manufacturing and Controls (CMC) of a component of a drug product, to permit the FDA to review this information in support of a third party's submission. Drug product information or other non-CMC information may be filed in a DMF.

Types of DMFs (Current)

- II Drug substance, drug product, intermediates and material used in their manufacture
- III Packaging
- IV Excipients
- V Other
  - Sterile manufacturing plants
  - biotech contract facilities
  - Non-CMC information e.g., clinical, tox

Requirements for a DMF

Who Must File a DMF?

NOBODY

There is no legal or regulatory requirement to file a DMF. A DMF may be filed to provide CMC information that the FDA reviews. Examples: drug substance, novel excipient

When is a DMF Usually Not Necessary

- Normally the CMC for a compendial excipient is not reviewed
- CMC for some drug substances used in some non-prescription drug products is not reviewed

Who's Who?

- The person or company who submits a DMF is the HOLDER
- The person or company who represents a DMF HOLDER is the AGENT
- The person or company who references the DMF is the APPLICANT or the CUSTOMER or the AUTHORIZED PARTY (AP)

What's What?

- Application means **any** of the following:
  - Investigational New Drug Application (IND)
  - New Drug Application (NDA)
  - Abbreviated New Drug Application (ANDA)
  - Biological License Application (BLA)
  - New Animal Drug Application (NADA)
  - Abbreviated New Animal Drug Application (ANADA)
- Supplement to an Application
  - A report of a change in an **approved Application**
- Amendment to an Application
  - Additional information to a **pending Application or Supplement**
- Amendment to a DMF
  - Additional information to an **existing 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

DMF or NDA?

Usually ALL CMC info for a drug substance is confidential

- For a “new drug”:
  - New Molecular Entity in an NDA:
    - Usually in the NDA
    - DMF can be used in this case but not preferred
  - Existing molecular entity in an NDA
    - previously approved drug in a new dosage form
    - Often in a DMF for a third party manufacturer
- For a generic drug (ANDA):
  - Often in a DMF for a third party manufacturer
  - Can be in ANDA if manufactured by the same company as the applicant

Confidentiality of DMFs

- Confidentiality of info in DMF 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."

- Pertinent to information available upon submission of a Freedom of Information Act (FOIA) request
- 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

Preparing a DMF

Follow the Guideline at
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073164.htm

- Binders recommended
- Strongly recommend including telephone and fax numbers and e-mail address for the responsible individual (contact person)

E-mail: dmfquestion@cder.fda.gov

FDA Receipt of DMF

- Holder sends the DMF to Central Document Room
  - Include 2 copies
  - No fee associated
- Central Document Room (CDR) staff enter DMF into database
- DMF reviewed for administrative purposes ONLY by Office of Business Informatics (OBI) staff.
  - If administratively incomplete, OBI will contact holder.
  - If administratively complete, OBI sends Acknowledgment letter (ACK). Entry of ACK into database changes DMF status to ACTIVE.
- Usual processing time is 2-3 weeks.
  - Most common delay: No statement of commitment, lack of COMPLETE ORIGINAL SIGNATURE

Acknowledgement Letter

- Includes Subject and Holder of DMF. Will appear on list posted on web site: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/default.htm

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
- SUBMIT ANNUAL UPDATE (Annual Report)
- Submit Letter of Authorization (LOA) for each item referenced for each customer
- Notify authorized parties of changes

Letter of Authorization (LOA)

- The DMF will be reviewed ONLY when it is referenced in an Application or another DMF
- An LOA does not permit anyone except FDA to “Access” i.e. “read” the DMF
- Term “Letter of Access” used in Europe

The Process:

(1)The holder submits an LOA (2 copies) specifying the DMF number to the DMF

DO NOT NEGLECT THIS!!!

(2) The holder sends a copy to the applicant

(3)The applicant includes copy of LOA in their Application.

- This is the ONLY mechanism to trigger review of the DMF

LOA (cont)

- LOA must contain a specific reference to a particular item in the DMF
- Specify the item by:
  - Code name
  - Page number and, most importantly
  - Date of submission as it appears on the cover letter of that submission (not an internal document date) **MOST IMPORTANT**
  - Volume number usually not helpful since volume numbers are generated in CDR

Example: Applicability of Green Chemistry to DMFs

- A company has a proprietary process (e.g., a novel catalyst that avoids heavy metals and can be used in many synthetic schemes)
- The company files the general scheme in a DMF
- Customer ships raw material to holder
- Holder runs proprietary step
- Holder ships finished material back to customer.
- Holder files this particular synthetic step in DMF.
- Can use a code to maintain confidentiality e.g., “Intermediate XYZ Manufactured in LOCATION.”
- Customer submits application, including synthesis of drug substance, referencing the DMF for the intermediate step
- Entire synthetic process reviewed by FDA, including step in the DMF

DMF Review Procedure

- The DMF is reviewed using same regulatory and scientific criteria as review of applicaiton
- If there are deficiencies
  - The detailed deficiencies are communicated to the holder
  - The APPLICANT is notified that deficiencies exist in either an Information Request (IR) or a Complete Response (CR) letter.
  - The nature of the deficiencies is not communicated to the applicant.
- If no deficiencies
  - No letter to DMF holder
  - Applicant not notified

Review of the DMF

- When the reviewer receives an application that references a DMF, the reviewer requests the DMF from the CDR.
- Contrast with application, where document is delivered automatically to reviewer.
- Delivery of DMF can take a couple of days. Reviewers are in three different buildings in Maryland near Washington DC.
- Highlights importance of specifying the date of the submission being referenced,especially for multivolume DMFs.

Changes to a DMF

- Amendment = A report of a change or addition of technical or administrative information. NOT a supplement (Supplements apply only to approved applications)
- Annual Update = Annual Report See slide below
- All amendments and annual update 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

Technical Amendments to the DMF Amendment in Response to Letter to Holder

- Holder submits amendment to DMF.
- Cover letter should specify “Quality/Response to Letter” in the header and should reference date of Agency’s letter to holder
- Holder MUST notify applicant that the DMF has been amended.
- Holder may notify reviewer, if that was requested in letter to holder
- No desk copies
- Will be reviewed only when APPLICANT whose application references DMF amends APPLICATION (See #2 on Slide 22) or another application references the DMF.

Spontaneous Amendments to the DMF: Holder Responsibility

- Cover letter should contain:
  - In the header: A list of the Categories/Subcategories (C/Sc) covered by the changes. Multiple C/Sc may be submitted in one amendment. List of C/Sc's available on DMF Web site. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/default.htm
  - In the body of the letter: A list of specific changes
- A new LOA specifying the date of the amendment is usually not necessary
- Notify APPLICANT of types of changes
- Do not report other personnel changes besides contact person at agent or holder

All Technical Amendments to the DMF: FDA Processing

- Amendment entered into database by CDR
- NO ASSIGNMENT, no review until submission of
  1. New application that references DMF

  or

  2. **Amendment to a pending application that references DMF**

  or

  3. Supplement or annual report to an approved application that references DMF

Annual Reports= Annual Updates

- Not required by regulation.
- RECOMMENDED in DMF Guideline (Section VII) Includes:
  - List of authorized parties, what they are authorized to reference, and the date of the LOA
  - List of changes reported during the past year. Note that this is NOT a list of changes MADE but a list of changes already REPORTED. If the anniversary date is missed FDA will not send a reminder (unlike applications) until three years pass. (See below "Retiring a DMF")
- If no changes, send update with a statement to that effect

Agents for DMFs

- Not required, although recommended to facilitate communication for foreign company
- Holder appoints agent
- Responsibilities of agent should be defined in Agent Appointment Letter
- Agent for DMF purposes NOT the same as agent for Drug Registration and Listing
- 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.”

Technical Information for Holders

- Holder must follow appropriate regulations
- Recommend that holder follow appropriate Guidances and Common Technical Document-Quality (CTD-Q)
- Facilities information (former Type I) not necessary. Address is sufficient. Statement of cGMP Compliance is required.
- Environmental Assessment (EA), MSDS's not necessary
- Completed batch records for Type II are expected

Important !!!
Applications and DMFs

The amount and level of detail of technical information in a DMF is the SAME as in an application

Common Technical Document (CTD)

- The CTD Guidance indicates an appropriate *format* for the data that have been acquired. See M4Q CTD-Q
- http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073280.pdf
- Module 1 Administrative information that applies to DMFs. (see next slide) There are no forms for DMFs.
- 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
  - 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

M1 in CTD

- Section 1.2: Cover Letter and Statement of Commitment
- Section 1.3: Administrative 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.
  - **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.
  - **1.4.3 - List of authorized persons to incorporate by reference**
    - Generally submitted in DMF annual reports.

Additional Issues of Concern for Drug Manufacturers

- Intermediates
- Reporting Changes
- Inspections
- Inactivation of DMFs
- Electronic DMFs
- Quality by Design

DMFs for Intermediates

- If a chemical in the synthetic pathway is defined as an “intermediate” rather than a starting material, it is expected to be manufactured under CGMP.
- 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 is “needed” if the intermediate comes from a third party.
- It is useful (within the limits of confidentiality) to have intermediate manufacturer submit LOA to applicant. Otherwise submit LOA to drug substance manufacturer.

Implications of Designation of a Material as an Intermediate

- Current definition in the Guidance for Post-approval Changes
- http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm077097.pdf
- Certain changes in manufacturing involving an intermediate should be reported in a supplement or AR for approved application supported by DMF.
- DMF holder's responsibility is to notify customer of the nature of the change.

Reporting Changes for Type II DMFs: Holder's Role

- Can implement the change when notification is submitted to the DMF and ship "Post-Change Drug Substance" (PCDS) to customer
- Holder must notify the customer that a change has been made
- Holder should determine the appropriate Reporting Category for the manufacturing change and notify the customer of the nature of the change. Provide:
  - Sufficient detail to enable the customer to report the change appropriately.
  - Level of detail in the notification to the customer is determined by the contractual agreement between the holder and the customer.

Reporting Changes for Type II DMFs (cont)

- The APPLICANT has the responsibility of submitting the appropriate document to the FDA as an Annual Report or Supplement.
- Drug product manufactured using PCDS can be marketed ONLY under the conditions spelled out in 21 CFR 314.70

Reporting Changes for Type II DMFs (cont)

- If there are multiple customers, notify the FDA before making change in order to coordinate reviews of supplements.
- A “Meeting Request” sent to the DMF will not be seen.
- Not the same as a “bundled” supplement, which cover the same change (e.g. change in resin supplier for a bottle) used in many A/NDAs held by the same applicant.

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.

Retiring DMFs

- If a DMF has had no annual report in three years FDA will send overdue notice to holder and/or agent using most recent address. Highlights the importance of keeping holder/agent name and address up-to-date.
- If no response in 90 days, one copy of DMF is sent to Federal Records Center (FRC) and the other is destroyed.
- Response: Close DMF or submit annual update to keep it open.

Electronic Filing of DMFs and CTD-Q

- CTD-Q not required for paper DMFs, although acceptable. Required for electronic DMFs
- Electronic DMFs are accepted http://www.fda.gov/cder/regulatory/ersr/ectd.htm
- DMFs originally submitted in paper can be resubmitted as electronic DMFs. Entire DMF must be resubmitted.
- Once a DMF has been submitted in electronic form NO paper documents (including LOAs) may be submitted.

Quality by Design

- FDA is working with industry on the Quality by Design (QbD) initiative
- Guidances:
  - ICH Q8, *Pharmaceutical Development*, http://www.ich.org/LOB/media/MEDIA1707.pdf
  - ICH Q9, *Quality Risk Management* *http://www.ich.org/LOB/media/MEDIA1957.pdf*
- The principles of QbD can be applied to drug substance manufacture.
- Process understanding links input variables (raw material attributes) and process parameters to Critical Quality Attributes (CQAs)/specifications and hence to the desired performance of the finished product
- Implementation of QbD, including establishment of design space and control strategy, by drug substance manufacturers in a DMF could lead to less need for reporting changes to DMF.

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