DRUG MASTER FILES

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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.

Current Types of DMFs

- II Drug substance, drug product, intermediates and material used in their manufacture
- III Packaging
- IV Excipients
- V Other

Type V DMFs

- Must first submit a letter of intent for "pre-clearance" by FDA to file
  - Clinical
  - Toxicology

- May be filed without submission of letter of intent
  - Sterile processing facilities
  - Biotech manufacturing facilities

- Information about these facilities can, like any other type of information, be submitted directly in an NDA or ANDA

Center for Drug Evaluation and Research (CDER)
Offices with Primary Review Responsibility

Office	Responsibility
New Drugs (OND)	Safety and efficacy review of •New Drug Applications (NDAs) •Investigational New Drug Applications (INDs)
Pharmaceutical Sciences (OPS)	•Chemistry, Manufacturing and Controls (CMC) review for new drugs •All reviews for generic drugs (ANDAs)

OPS

Office	Review Responsibility
New Drug Quality Assessment (ONDQA)	CMC for “new drugs” NDAs and INDs
Generic Drugs (OGD)	Abbreviated New Drug Applications (ANDAs), including CMC
Biotechnology Products (OBP)	CMC for protein and biotechnology products submitted to CDER

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**

Who's Who?

Name	Role
Holder	Submits DMF
Sponsor = CUSTOMER= AUTHORIZED PARTY (AP)	Submits IND, References DMF
Applicant =CUSTOMER=AP	Submits NDA, ANDA, BLA, NADA, ANADA, References DMF
Quality or Quality Microbiology Reviewer	Reviews DMF Reviews Quality and Quality Microbiology parts of Application
Regulatory Project Manager	Communicates with the HOLDER and the APPLICANT/SPONSOR

What's Where (all in Maryland)

Central Document Room (CDR)	Beltsville
White Oak (OND) Document Room	White Oak (WO), Silver Spring
OND	
ONDQA	
Office of Business Informatics (OBI)	
Office of Compliance (OC)	
OBP	WO, NIH Bethesda
OGD Review Staff and Document Room	Derwood (Gaithersburg)

Who Does What

CDR Contract Staff	Receives all incoming Documents. Processes and stores all incoming DMF documents. Mails DMF correspondence for ONDQA
OBI Staff	Manages all incoming Documents
White Oak Document Room Contract Staff	Processes and stores all INDs and NDAs Mails IND/NDA correspondence for ONDQA/OND
OGD Document Room Contract Staff	Processes and stores all ANDAs Mails DMF correspondence for OGD
Reviewer	Writes review of DMF and APPLICATION supported by DMF. Drafts DMF deficiencies and information requests
ONDQA, OGD, or OBP PM	Communicates DMF deficiencies and information requests to HOLDER
OND PM or OGD PM	Notifies APPLICANT/SPONSOR that information has been requested for 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)
- DMFQUESTION:
  - External: dmfquestion@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)
  - Prescription Drug User Fee Act (PDUFA)
- Regulations: Section 21 of the Code of Federal Regulations (21 CFR) Required information
  - 312 Investigational New Drug Application (IND)
  - 314 New Drug Application (NDA) and Abbreviated NDA (ANDA)
    - 314.50 Content and format of an application
    - 314.70 Changes to an Approved Application
    - 314.420 Drug Master Files

PDUFA and Time Clocks

- Under PDUFA, FDA has a specific time period to complete its review of an application (PDUFA clock).
- When FDA determines that the review period for a drug is complete and that the application is not yet ready for approval, it issues a "Complete Response" (CR) Letter. The letter describes specific deficiencies and, when possible, outlines recommended actions the applicant might take to get the application ready for approval i.e., what is required for the applicant to submit a "complete response."
- When a CR Letter is issued, the PDUFA clock stops.
- The PDUFA clock will be re-started ONLY when the applicant submit a "Resubmission" of the application that contains a "complete response" to ALL of the issues in the CR letter.

Guidances and MaPPs

- 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)

- A MaPP (Manual of Policies and Procedures) contains instructions for FDA personnel on performing administrative and review functions

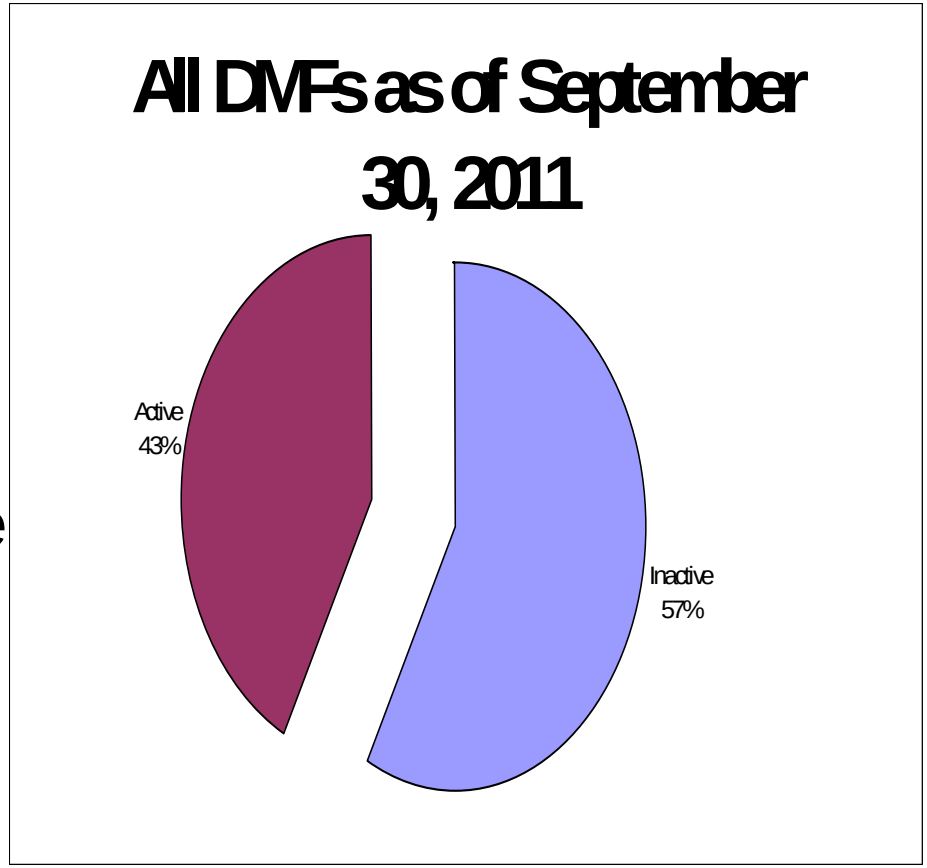
http://www.fda.gov/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/default.htm

DARRTS

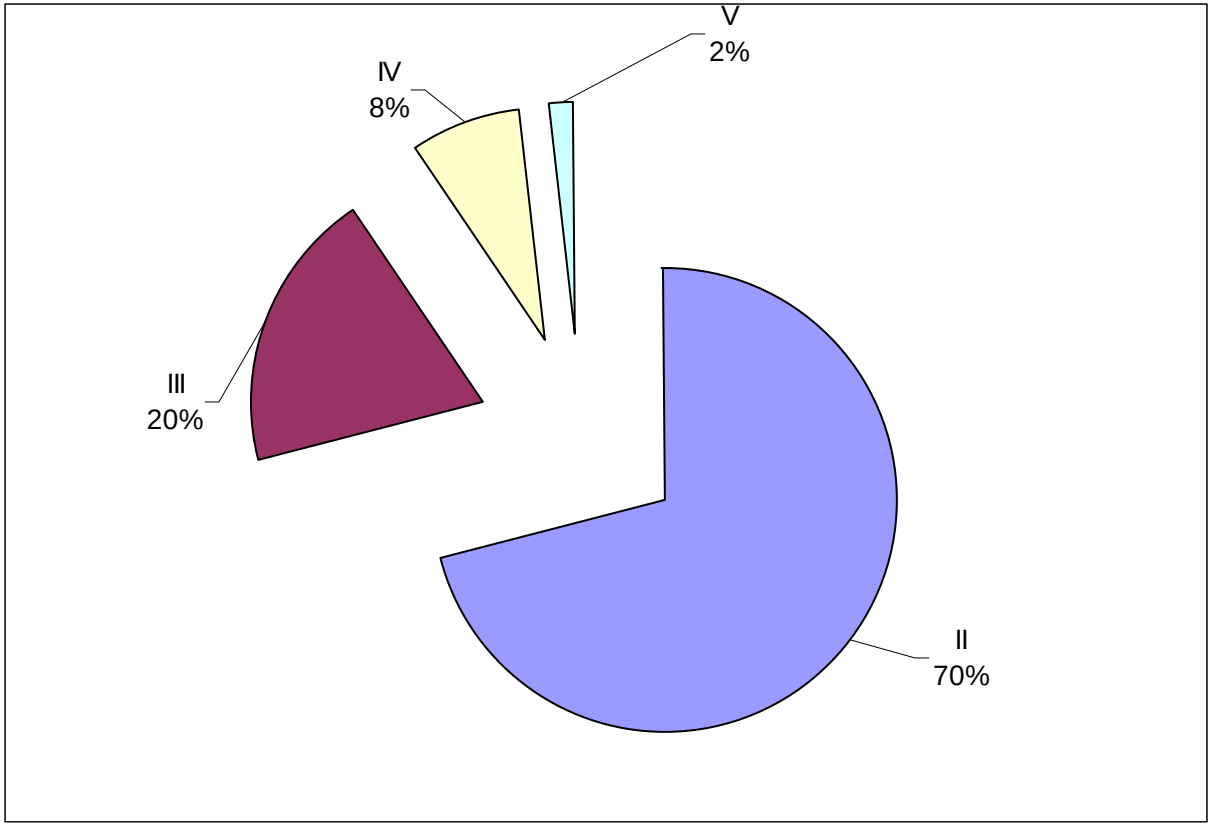
- Document Archiving, Reporting, and Regulatory Tracking System
- CDER's system for tracking:
  - Incoming Documents
  - Communications (Reviews, Correspondence, Forms)
- All Communications are entered electronically by CDER reviewers and PMs.
- Integrated with the Electronic Document Room (EDR)

Facts about DMFs

- As of September 30, 2011 there were 25219 DMFs (plus 125 pending)
- Percentage of active DMFs has remained within the range of 40% for a number of years



Types of Active DMFs



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 OR a DMF.
- A DMF may be filed to provide CMC information that the FDA reviews. Examples: drug substance, novel excipient
- Conversely, there is no need to file a DMF for information that FDA does not review

DMF or NDA?

- For a drug substance reviewed in ONDQA
  - New Molecular Entity: Usually in the NDA. Even if the drug substance is manufactured by a third party, FDA prefers the CMC info be in the NDA. However, a DMF can be used in this case. Not recommended
  - "Old" molecular entity e.g., previously approved drug in a new dosage form. If a third party manufacturer, usually in a DMF
- For a drug substance reviewed in OGD
  - If a third party manufacturer: In a DMF The usual case
  - If NOT a third party manufacturer (i.e., drug substance is manufactured by the same company as the applicant) CMC info can be in ANDA

When is a DMF Usually Not Necessary

- Normally the CMC for a compendial excipient (quality covered by USP or NF monograph) is not reviewed

- CMC for many packaging materials (See MaPP 5015.5 **CMC Reviews of Type III DMFs for Packaging Materials)**
  http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM205259.pdf

- CMC for drug substances used in some Over-the Counter (OTC) drug products is not reviewed (see next slide)

Non-prescription Drugs

- CMC Information is NOT reviewed for OTC drug products “marketed without prior approval by FDA” under the OTC monograph system. e.g. aspirin

- CMC information IS reviewed for non-prescription drug products (OTC) drug products which are marketed after approval of A/NDAs e.g. OTC Tagamet. CMC for drug substance reviewed - usually in 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) See slide 53
- Active Pharmaceutical Ingredient (API): This term is defined only in ICH Q7 (See slide 31). An API is the same as a “drug substance.” API does not appear anywhere in the CFR.
- 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). See Slide 32. An LOA does not permit anyone except FDA to “Access” i.e. “read” the DMF
- Transmittal Letter = Cover Letter
- Annual Report = Annual update

How the System Works

- Holder sends the DMF (No form, NO FEE, two copies) to
  Central Document Room
  Center for Drug Evaluation and Research
  5901-B Ammendale Road
  Beltsville, MD 20705-1266
  Containing:
  –Transmittal (cover) letter
  –Administrative information
    - Include telephone and fax numbers and e-mail address for the responsible individual (contact person)
  –Technical information
  –The “Subject” (title) of the DMF, which will appear on the Web site, can use whatever name the holder wishes e.g.. A code name rather than a chemical or established name
- All subsequent submissions (Amendments, Annual Reports, Letters of Authorization) are sent to the same address. Two copies

How the System Works (Cont)

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

Binders recommended
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

How the System Works (Cont)

- Statement of Commitment:
  - –The form for A/NDA contains a "Statement of Commitment"
  - –No form for DMFs
  - –Therefore the DMF Guideline recommends that the DMF contain:

"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."

How the System Works (cont)

- DMF entered into DARRTS and assigned a number, in PENDING status
- DMF reviewed for administrative purposes ONLY by the OBI staff. If incomplete, OBI sends a request for additional information. Most common reasons for delay:
  - No statement of commitment
  - Lack of COMPLETE ORIGINAL SIGNATURE
- Acceptance of digital signatures the same as for any other submission to FDA
- If administratively complete, OBI sends an acknowledgement letter which changes the status of the DMF to “Active.” Now 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 (see Slide 11)
- 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 (ANNUAL UPDATE) (See Slide 37)
  - Submit Letter of Authorization (LOA) (see Slide 32) for each item referenced for each customer

Submission of Technical Information

- Holder must follow appropriate regulations
- Recommend that holder follow appropriate Guidances (see next slide)
- Facilities information (former Type I) not necessary except for Type V DMFs for
  - Sterile Processing Facilities or
  - Contract Biotechnology Manufacturing Facilities.
- Address of facility for non-Type V DMFs is sufficient.
- Recommend include statement of compliance with Current Good Manufacturing Practices (CGMPs)

Guidances for Technical Information

- Format
  - 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
  - DRAFT ICH Guidance "Q11 Development and Manufacture of Drug Substances http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM261078.pdf
- Packaging
  - Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Documentation http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070551.pdf
  - Questions and Answers http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070553.pdf

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

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) to the DMF
- THEN send a copy to the APPLICANT
- APPLICANT submits copy of LOA in their Application. ONLY mechanism to trigger review of the DMF

LOA (cont)

- LOA must contain a specific reference to a particular item in the DMF.
- This is especially important for large Type III or IV DMFs that contain many products
- 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
- 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 (see Slide 37)
- 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.

Differences between Applications and DMFs

- Applications
  - Submitted to a particular review division
  - Each submission (including Supplement, Annual Reports and amendment) is entered into DARRTS, assigned and delivered to a reviewer and an acknowledgement letter sent
  - Each submission has a due date. REVIEW CLOCK
- DMFs
  - Submitted to Central Document Room (CDR)
  - Each submission is entered into DARRTS and **NO acknowledgement letter sent** for submissions after the initial original submission
  - Reviewed ONLY when referenced. No assignment to a reviewer, no due date REVIEW CLOCK for APPLICATION

Electronic DMF (EDMF)

- There is no requirement to submit ANY type of application in electronic format.
- However ALL electronic applications MUST follow the Electronic Common Technical Document (ECTD)
- Waivers from this requirement may be granted but not for DMFs.
- http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM149705

EDMFs (cont)

- ECTD is a structured format that permits life-cycle management, which is important for DMFs
- Can convert paper DMF to EDMF but once electronic, cannot submit paper, even for LOA.
- ~10% 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).
- Annual Report is recommended in DMF 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.
- 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 of this letter type into DARRTS changes the 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). Rationale:
    - DMF must be up-to-date when reviewed. Can be reviewed at any time.
    - Limited storage space in CDR.
  - 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.

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 to Cover Letter (Transmittal Letter) should identify all Submission Types and Categories/Subcategories (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.

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 (cont.)

- Holder
  - Header of cover letter should contain list of Submission Types and CSCs as described above
  - Include a list of specific changes.
  - 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
  - Notify APPLICANT of types of changes
- FDA
  - Information about the amendment entered into DARRTS by CDR
  - The actual paper submission is placed into the binder in date order, most recent submission on top. When a binder is full, CDR creates a new volume.
  - NO ASSIGNMENT, no review until submission of
    - 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 as an Annual Report or Supplement 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
- For a Type III DMF, MAPP 5015.5 tells reviewers to request that information to support safety of packaging materials used for solid oral dosage forms and other common packaging materials be provided directly to the A/NDA, rather than having that information in a DMF for review.
- Result: Information not needed for review does not need to be in a DMF.
- For any type of DMF: In general, if information has been reviewed previously and found acceptable and there has been no new information, the DMF does not need to be reviewed. Specifically applies to Type II DMFs
- See MAPP 5015.4: Chemistry Reviews of DMFs for Drug Substances/Intermediates (DSI) http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm079565.pdf

Review of the DMF (cont.)

- If the DMF is not electronic, the reviewer requests the DMF from the Central Document Room.
- 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.

DMF Review Procedure

- The 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
  - The APPLICANT is notified that information has been requested for the DMF
    - The letter to the APPLICANT is either an Information Request (IR) or a Complete Response (CR) letter.
    - The nature of the information requested is not communicated to the applicant.
- If no information needed for DMF
  - No letter to DMF holder
  - Applicant not notified.

IR and CR Letters to Applicant

- Not strictly a DMF issue but this affects how responses are dealt with
- IR Letter to applicant: Review clock for NDA is not stopped. Responses may be reviewed at reviewer's discretion depending on timing relative to the due date.
- CR Letter to applicant: Review Clock is stopped. Application (and supporting DMFs) will be reviewed only when all issues in CR Letter (including DMF deficiencies) have been addressed

Amendment to the DMF in Response to Letter to Holder

- Holder submits amendment to DMF.
- Cover letter should contain:
  - Header stating:
    - Response to 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, 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 (cont)

- 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 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 deficiency 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 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."

Agents as Holders

- The holder of a DMF is expected to be the manufacturer of the material described in a DMF. However

- If a manufacturer (Company A) of a MATERIAL wishes to have the DMF submitted by another company (Company B) and Company B wishes to act as the holder, the DMF should include statements from both companies that Company B
  - Takes full responsibility for
    - the accuracy and currency of all the information in the DMF
    - all the processes and testing performed by the manufacturer
  - Will submit all changes to the DMF as required under 21 CFR 314.420(c).

- The holder of the DMF will be Company B and the title of the DMF which will appear on the list of DMFs will be “MATERIAL manufactured in LOCATION OF COMPANY A for COMPANY B.”
- Note that Company A’s name will not appear on the Web site.

Environmental Assessment (EA)

- EA is necessary to support FDA's decision about whether FDA needs to prepare one of the following for FDA's ACTION in approving a drug
  - Finding of No Significant Impact
  - Environmental Impact Statement
- For most synthetic drugs an EA applies only to the environmental impact of USE of the drug by patients e.g., Amount in waste water following use of the drug.
- See Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070561.pdf
- DMFs are neither approved nor disapproved.
- Therefore there is no FDA action.
- Therefore no EA necessary.
- DMF holders should include a statement that their manufacturing facility complies with applicable environmental laws and regulations.

Common Technical Document (CTD)

Module 1 Administrative information that applies to DMFs

There are no forms for DMFs.

- Section 1.2: Cover Letter and Statement of Commitment
- 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.
  - 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 authorized persons to incorporate by reference: Submitted in DMF annual reports.
- Section 1.12.14 Environmental Analysis

CTD (Continued)

- See M4Q CTD-Q http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073280.pdf
- 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

Administrative and Technical Information for Applicants

- APPLICANTS should notify suppliers (DMF holders) of company name change. Will require new LOAs
- Submit amendment to application when DMF amended in response to letter requesting additional information
- Notify FDA via annual Report or supplement (where applicable) of technical changes in DMF reported by DMF holder.

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 CGMPs. See ICH Q7: Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073497.pdf
- See also: ICH Q11: DRAFT CONSENSUS GUIDELINE: DEVELOPMENT AND MANUFACTURE OF DRUG SUBSTANCES (CHEMICAL ENTITIES AND BIOTECHNOLOGICAL/BIOLOGICAL ENTITIES) (See Slide 30)
- 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 “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

- 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.

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
- 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."

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.

Quality by Design

- FDA is working with industry on the Quality by Design (QbD) initiative
- Guidances:
  - ICH Q8, Pharmaceutical Development http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073507.pdf
  - ICH Q9, Quality Risk Management http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073511.pdf
  - ICH Q11 See Slide 30
- 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