DRUG MASTER FILES

Arthur B. Shaw, Ph.D.

FDA DMF Expert

Adapted from DIA Webinar March 19, 2007
Revised November 7, 2008

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.

Type of DMFs

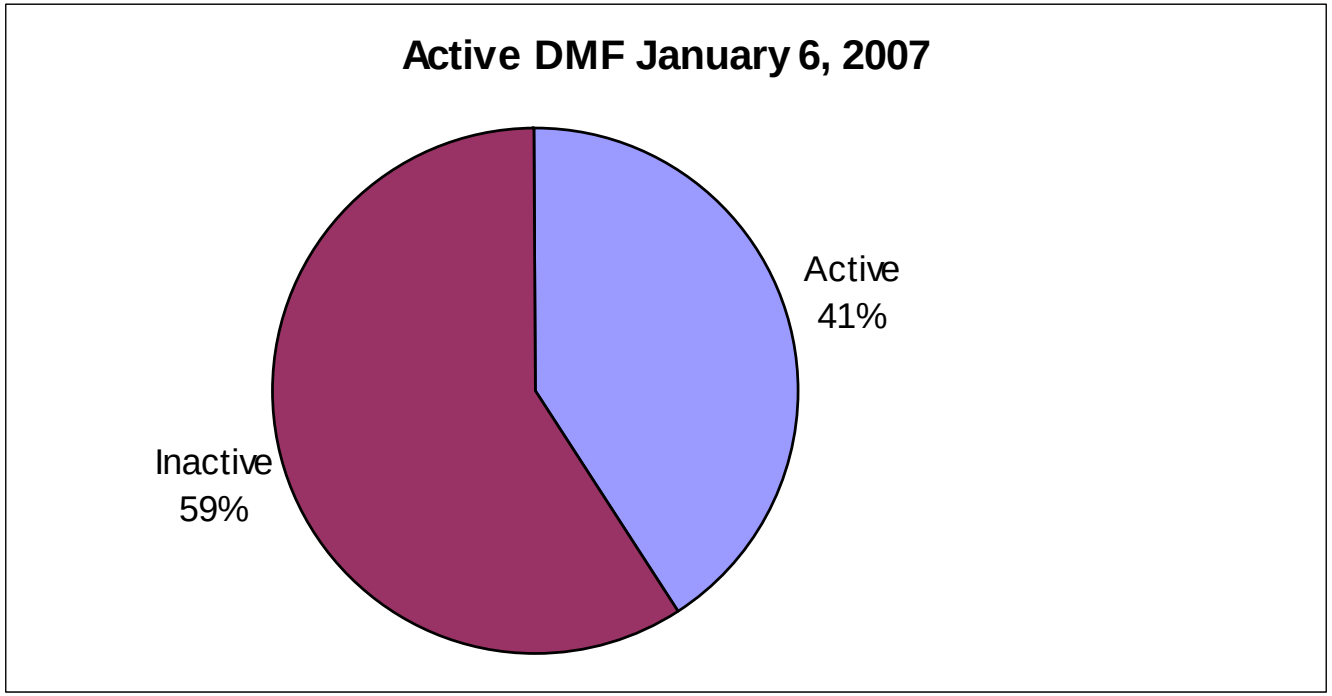
- Originally Five Types
- I Manufacturing plant information
- II Drug substance, drug product, intermediates and material used in their manufacture
- III Packaging
- IV Excipients
- V Other Usually clinical, tox

Current Types of DMFs

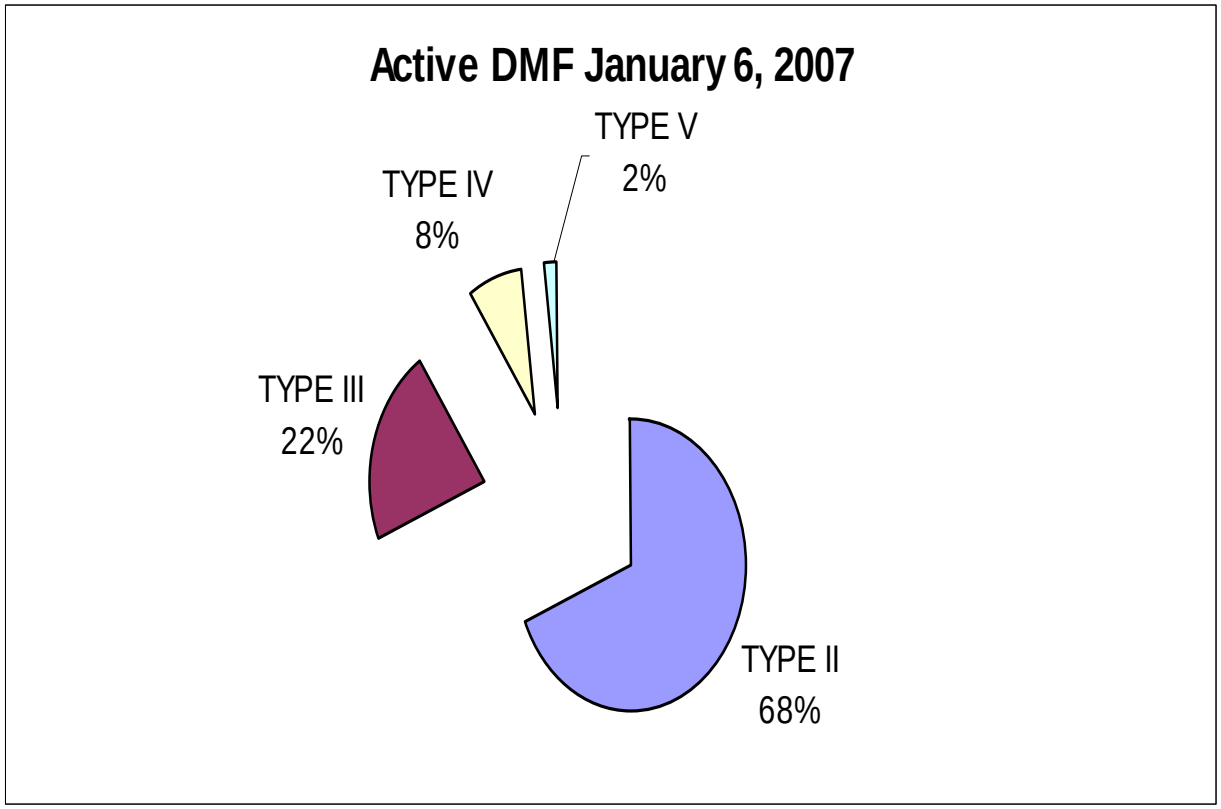
- Now Four Types (Numbering retained to avoid confusion)
- II Drug substance, drug product, intermediates and material used in their manufacture
- III Packaging
- IV Excipients
- V Other Sterile manufacturing plants, biotech contract facilities, clinical, tox

Facts about DMFs

- As of January 6, 2007, there were 19784 DMFs
- Percentage has remained constant over the past 3 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. A DMF may be filed to provide CMC information that the FDA reviews. Example: 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 Over-the Counter drug products is not reviewed (see Slide 11)

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 = Investigational New Drug Application (IND), New Drug Application (NDA), Abbreviated New Drug Application (ANDA)
- Supplement to an A/NDA = A report of a change in an approved A/NDA Since a DMF is not approved, there can be no supplements to a DMF, only amendments
- Amendment to an application = Additional information to an existing IND, a pending A/NDA or a pending A/NDA supplement

Non-prescription Drugs

- Some non-prescription drug products (Over-the-Counter = OTC) drug products are marketed after approval of NDAs e.g. OTC Tagamet. CMC information for such OTC products is reviewed by FDA
- Some OTC drug products are marketed without prior approval by FDA under the OTC monograph system. e.g. aspirin CMC information for such OTC products is NOT reviewed by FDA

Reasons for a DMF

- Maintain confidentiality of proprietary information (e.g., Manufacturing procedure) for the holder
- Permit review of information by reviewers in the Center for Drug Evaluation and Research (CDER) to support applications submitted by one or more applicants

How the System Works

Holder sends the DMF (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
–Technical information

All subsequent submissions (amendments, Annual Reports, Letters of Authorization) are sent to the same address. Two copies

Follow the Guideline at www.fda.gov/cder/guidance/dmf.htm

Binders recommended

http://www.fda.gov/cder/ddms/binders.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)

- Strongly recommend including telephone and fax numbers and e-mail address for the responsible individual (contact person)
- DMF reviewed for administrative purposes ONLY by Office of Business Process Support (OBPS) staff. Most common delay: No statement of commitment, lack of COMPLETE ORIGINAL SIGNATURE
- DMF entered into DMF database, assigned a number, and acknowledgement letter sent
- Usual processing time is 2-3 weeks
- E-mail: dmfquestion@cder.fda.gov

Acknowledgement Letter

- Assigns number and type. Includes Title (Subject) and Holder of DMF. Will appear on list posted on web site (see next slide)
- 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

DMF Web Site

- List of DMFs
- http://www.fda.gov/cder/dmf/index.htm
- Updated quarterly
- Contains additional information about DMFs

Letter of Authorization (LOA)

- The DMF will be reviewed ONLY when it is referenced in an Application or another DMF.
- The holder MUST submit an LOA (2 copies) to the DMF **DO NOT NEGLECT THIS**!!!
- THEN send a copy to the APPLICANT
- The applicant submits copy of LOA in their Application. This is the ONLY mechanism to trigger review of the DMF
- In some cases a DMF holder will call the permission to reference a DMF a “Letter of Access.” (Phrase used in Europe). An LOA does not permit anyone except FDA to “Access” i.e. “read” 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 usually not helpful since volume numbers are generated in CDR

Differences between Applications and DMFs

- Applications
  - Submitted to a particular review division
  - Each submission (including supplement) is entered into the application database and assigned to a reviewer and an acknowledgement letter sent
  - Each submission has a due date.
- DMFs
  - Submitted to CDR
  - Each submission is entered into a database (different from application database) and NO acknowledgement letter sent
  - Reviewed ONLY when referenced. No assignment to a reviewer, no due date

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.

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.

IR and CR Letters to Applicant

- Not strictly a DMF issue but this affects how responses are dealt with
- IR Letter: 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: Review Clock is stopped. Application (and supporting DMFs) will be reviewed only when all issues in CR Letter (including DMF deficiencies) have been addressed

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 with the DMF amendment should reference date of Agency's letter to holder
- Holder notifies applicant that the DMF has been amended.
- Holder may notify reviewer, if that was requested in letter to holder
- Desk copy
  - A copy of the amendment (desk copy) can be sent to the reviewer ONLY if requested.
  - If a desk copy is sent to a reviewer the cover letter should contain
    - a) a statement that the desk copy is an exact copy of the amendment submitted to the DMF and
    - b) a statement that the amendment was shipped to the DMF Central Document Room on the same day the desk copy was sent to the reviewer.

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

- If the Applicant was sent an IR Letter.
  - If the applicant did not submit an amendment to the NDA: DMF Amendment may be reviewed if the reviewer was notified by the holder that an amendment to the DMF had been submitted
  - If the applicant submitted an amendment to the NDA: DMF amendment will be reviewed.
- If the Applicant was sent a CR Letter.
  - The DMF amendment will be reviewed ONLY when the applicant submits a complete response to their letter CR letter. Rationale: Applicant's letter may contain other deficiencies e.g.. Clinical issues.
  - The amendment must be a COMPLETE RESPONSE to letter from FDA. It cannot be a notification that the DMF WILL be amended.

Technical Amendments to the DMF Spontaneous Amendment

- Holder
  - Cover letter should contain list of specific changes
  - A new LOA specifying the date of the amendment is usually not necessary
  - Notify APPLICANT of types of changes
- FDA
  - Amendment entered into database by CDR
  - NO ASSIGNMENT, no review until submission of
    - Amendment to a pending application

    Or
    - Supplement or annual report to an approved application

Administrative Amendments

- Administrative:
  - Change in holder name and/or address
  - Agent appointment or termination
  - Authorization termination
  - Request for closure
  - Not necessary to report personnel changes except for contact person or responsible official
- Recommend: Submit EACH change as a separate AMENDMENT. Do not include ANY changes in Annual Report

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. Stability updates should be reported as amendments.
- If the anniversary date is missed FDA will not send a reminder (unlike applications) (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

  http://www.fda.gov/cder/drls/registration_listing.htm
- 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.
- 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 (as well as the agent), the DMF must 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 title of the DMF which will appear on the list of DMFs will be “MATERIAL manufacture by COMPANY A in LOCATION OF COMPANY A for COMPANY B.”

Technical Information for Holders

- Holder must follow appropriate regulations
- Recommend that holder follow appropriate Guidances and CTD-Q
- Facilities information (former Type I) not necessary. Address is sufficient. Statement of cGMP Compliance is required.
- Environmental Assessment (EA) not necessary See slide below
- Completed batch records for Type II are expected

Common Technical Document (CTD)

- CTD documents are not intended to indicate what data or studies are required. “The text following the section titles is intended to be explanatory and illustrative only.” The CTD Guidance indicate an appropriate *format* for the data that have been acquired.

http://www.fda.gov/cder/guidance/4707dft.pdf

- Module 1 Administrative information that applies to DMFs. There are no forms for DMFs.
  - *Comprehensive table of contents*
  - *Administrative documents*
    - Addresses of DMF holder and manufacturing and testing facilities
    - Name and address of contact persons and/or agents
    - Agent Appointment letter (where applicable)
    - Letters of Authorization.
    - List of authorized parties (where applicable)
    - Statement of commitment
    - Environmental assessment or request for categorical exclusion

Common Technical Document (CTD) Continued

- See M4Q CTD-Q http://www.fda.gov/cder/guidance/4539Q.htm
- 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

Environmental Assessment (EA)

- The National Environmental Policy Act (NEPA) requires that all government agencies prepare an Environmental Impact Statement (EIS) or a Finding of No Significant Impact (FONSI) when they take an action e.g., approving a drug application. Companies submitting an application are required to submit an EA (or a waiver request) to permit FDA to determine whether an EIS or a FONSI is needed. See Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications http://www.fda.gov/cder/guidance/1730fnl.pdf
- Since DMFs are not approved, FDA does not take an action, therefore no EA needed.
- DMF should include a statement that holder will comply with all local environmental regulations

Environmental Assessment (continued)

- EA usually applies to impact of USE of the drug on the environment, not production.
- There are circumstances (e.g. use of an endangered species as a starting material) under which production of the drug requires an EA See EA Guidance
- DMF holder's responsibility is to provide sufficient information to customer to permit customer to file an EA.
- In general new drugs qualify for waiver. All generics qualify

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 deficiency letter
- Notify FDA of technical changes in DMF reported by DMF holder appropriately.

Issues of Concern for Drug Manufacturers

- Type V DMFs
- Confidentiality of Information in DMFs
- Intermediates
- Reporting Changes
- Additional Manufacturing Site
- Inspections
- Novel and Compendial Excipients
- Type III DMFs
- Inactivation of DMFs
- Electronic DMFs
- Quality by Design

Type V DMF

- Regulation 21 CFR 314.410(a)(5) states:

  "A person wishing to submit information and supporting data in a drug master file (DMF) that is not covered by Types II through IV DMF's must first submit a letter of intent to the Drug Master File Staff, Food and Drug Administration, 5901-B Ammendale Rd., Beltsville, MD 20705-1266.) FDA will then contact the person to discuss the proposed submission."

- This can be done via e-mail to dmfquestion@cder.fda.gov

Type V DMF (cont)

- When a request is submitted, the clinical review division affected by the proposed DMF will be contacted
- Safety and clinical data should be submitted to the NDA or IND not in a DMF.
- Types of information that are usually accepted:
  - Safety data for a novel excipient that may be used in a number of different products
  - CV’s for a large group of clinical investigators involved in a large clinical trial

Type V DMF (cont)

- Exception to the requirement to receive permission to submit a Type V DMF
- Information about manufacturing facilities that were formerly covered as “Type I” DMFs. Most Type I DMFs covered information that is not reviewed by CDER or CBER. However two types of facility require review by CDER and CBER
  - Facilities performing sterile processing
  - Facilities preparing biotech materials. See “Guidance for Industry: Submitting Type V Drug Master Files to the Center for Biologics Evaluation and Research (Draft**)** **http://www.fda.gov/cber/gdlns/dmfv.htm**

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. In general an intermediate is not accepted based on specifications alone. 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.

Confidentiality of Information in DMFs

- There are no “Open” and “Closed” parts of a DMF in the US
- 21 CFR 314.420(e) states:

  “The public availability of data and information in a drug master file, including the availability of data and information in the file to a person authorized to reference the file, is determined under part 20 and Sec. 314.430”
- Manufacturing information is covered under those parts of the CFR.
- Since DMFs usually cover manufacturing information they are not usually considered releasable via a Freedom of Information Act (FOIA) request
- Release of safety information e.g. toxicology studies, by the Freedom of Information Office is determined by current regulations.

Designation of an Intermediate as a Starting Material

- Definition of a Starting Material (SM) is in Drug Substance Guideline.
- Change from Intermediate to Starting Material is reported to the DMF like any other change and needs to be reported in applications supported by the DMF like any other post-approval change.
- Useful to meet with review division.
- ICH Q7A is a useful guide. However this applies to CGMP, which is the responsibility of the Office of Regulatory Affairs (inspectors). DMFs are reviewed by CDER.

Post-approval Changes

- Some post-approval changes (PAC) to an approved application must be reported. Some PAC's are not reportable but must be available in the manufacturing plant. Non-reportable changes are not reviewed by CDER.
- The category of reportable changes varies depending on their POTENTIAL (not actual) impact on Identity, Purity, Quality, Strength, and Potency (IPQSP) of the DRUG PRODUCT as they relate to Safety and Efficacy (S&E)
- Changes can be made to drug product (e.g. manufacture with changed drug substance) but it cannot be marketed until the appropriate filing and action has occurred

Post-approval Changes (continued)

- See regulations at 21 CFR 314.70 and Guidance for Industry: Changes to an Approved NDA or ANDA

http://www.fda.gov/cder/guidance/2766fnl.htm

Guidance specifies

  - Reporting Categories e.g. Annual Report

  for different

  - Categories of Manufacturing Changes that need to reported e.g., change in manufacturing site

- Note that Annual Reports (ARs) for approved applications are required by regulation. Not the same as Annual Updates to DMFs.

Post-approval Changes (continued)

Potential Impact on IPQSP as they relate to S&E	Reporting Category	Applicant Responsibility	Marketing status of drug product
Minor	Annual Report	Report change in AR	Market immediately without waiting for AR to be filed
Moderate	CBE-0	Submit a CBE supplement reporting change	Market when supplement submitted
	CBE-30	Submit a CBE supplement reporting change	Market only 30 days after submission of supplement
Major	PAS	Submit a Prior Approval Supplement reporting change	Market only after approval of supplement

Reporting Changes for Type II DMFs: Holder's Role

- Holder can implement the change when notification is submitted to the DMF.
- Holder can 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, providing sufficient detail to enable the customer to report the change appropriately. The 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 described in Slide 46

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.

Additional Manufacturing Site

	Same Process (minor differences)	Multiple Processes
Same Site	One DMF Identify differences	One DMF Identify differences
Multiple Sites	One DMF Identify differences	Separate DMFs

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.

Type IV DMFs

- CMC for a compendial excipient is usually not reviewed and therefore a DMF is not necessary.
- Exceptions: New route of administration or total dosing that may affect safety and efficacy, e.g. RESPITOSE, lactose for dry powder inhalation products

Type IV DMFs Novel Excipients

- IPEC has prepared a draft guideline for comment NOT OFFICIAL FDA policy
- CMC requirements for a novel excipient (one not used in an approved drug product) are the same as those for a new drug substance.
- Safety testing (submitted in a Type V) is the subject of an FDA Guidance.

http://www.fda.gov/cder/guidance/5544fnl.htm

Type III DMFs

- In general, a Type III DMF should contain sufficient CMC information to determine whether the components used in the manufacture of the item are safe e.g. HDPE for use in packaging solid oral dosage forms meets food contact regs
- Typically, provide chemical components with identification corresponding to appropriate CFR citation (i.e. not simply trade names)
- Information regarding packaging materials can be submitted directly to the applicant for inclusion in their NDA. DMF NOT required

Type III DMFs (cont'd)

- Can include extraction data in DMF but responsibility for compatibility and safety of packaging components in finished drug product is the responsibility of the CUSTOMER
- Assemblies (e.g. valve systems for pumps) can reference DMFs for components
- In general, all suppliers of components and or chemicals should provide LOAs directly to NDA (within limits of confidentiality)
- See Guidance for Container/Closure Systems http://www.fda.gov/cder/guidance/1714fnl.htm
- Guidance drafted in DMF Workshop (2002) is not official FDA guidance

Retiring DMFs

- If a DMF has had no activity (amendment or annual report) in three years FDA will initiate retirement procedure Note: LOA does not count for activity

DMF Retirement Procedure

- FDA sends 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.

Changes in the DMF System and Procedures

- Elimination of Type I DMFs
- Post-Approval Changes Guidance
- Creation of DMF List Website
- Creation of DMFQUESTION
- Establish Position of DMF Expert
- Transfer of BB-MFs to CDER when some review functions transferred to CDER

Unchanged

- Review only when referenced in application
- No Open and Closed parts
- DMFs are neither approved nor disapproved
- The holder must notify customer of changes

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