DRUG MASTER FILES

Arthur B. Shaw, Ph.D.
FDA DMF Expert
AAPS Short Course
October 26, 2003
Revised June 20, 2006 for Web Posting

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 drug product or a component of a drug product, to permit the FDA to review this information in support of a third party's submission. Other non-CMC information may be filed in a DMF.

Type of DMFs

- Originally Five Types
- I 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, clinical, tox

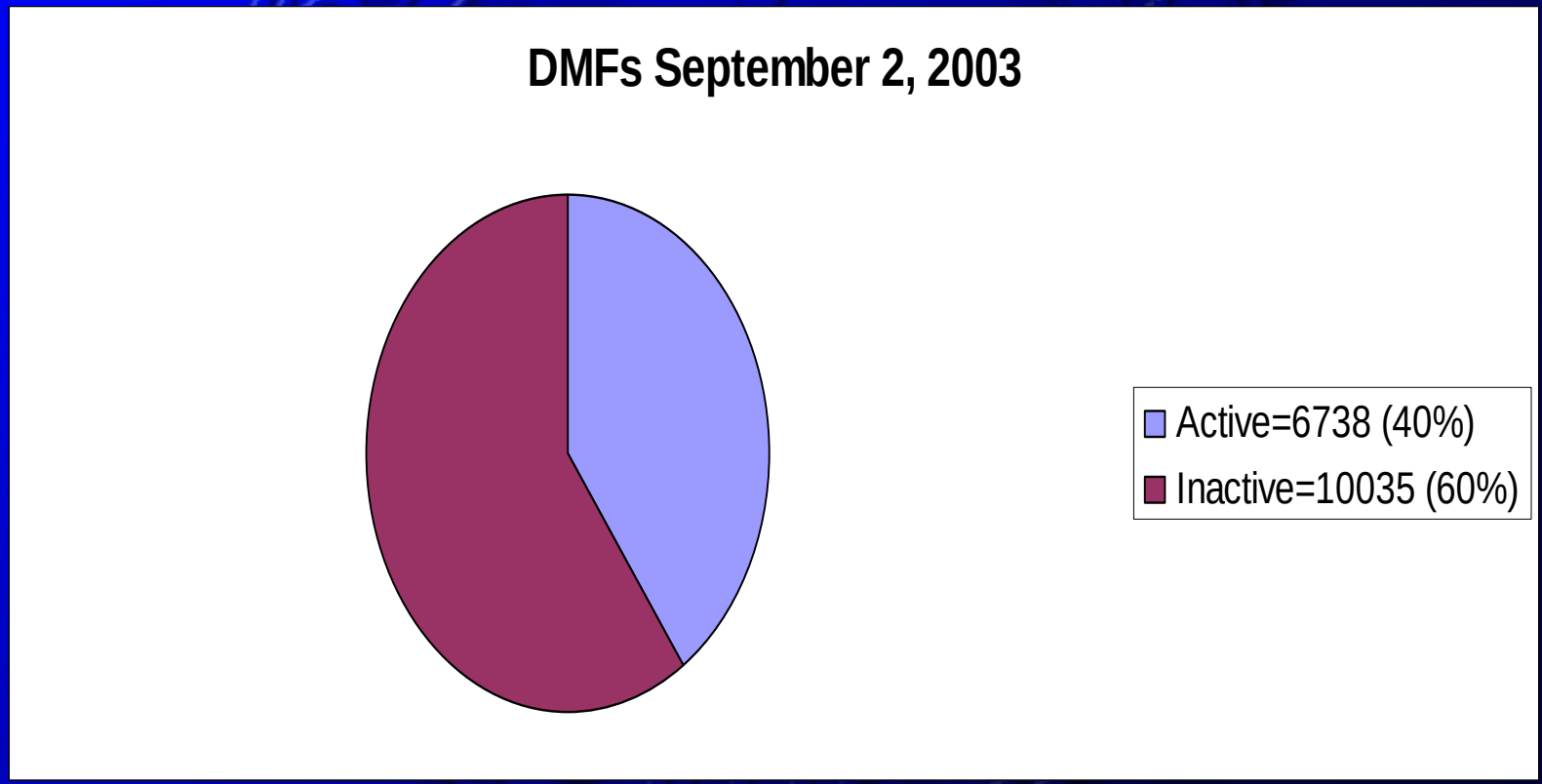
CU1

CU1 Type V DMfs require clearance from the FDA before submission except DMFs for sterile manufacturing plants

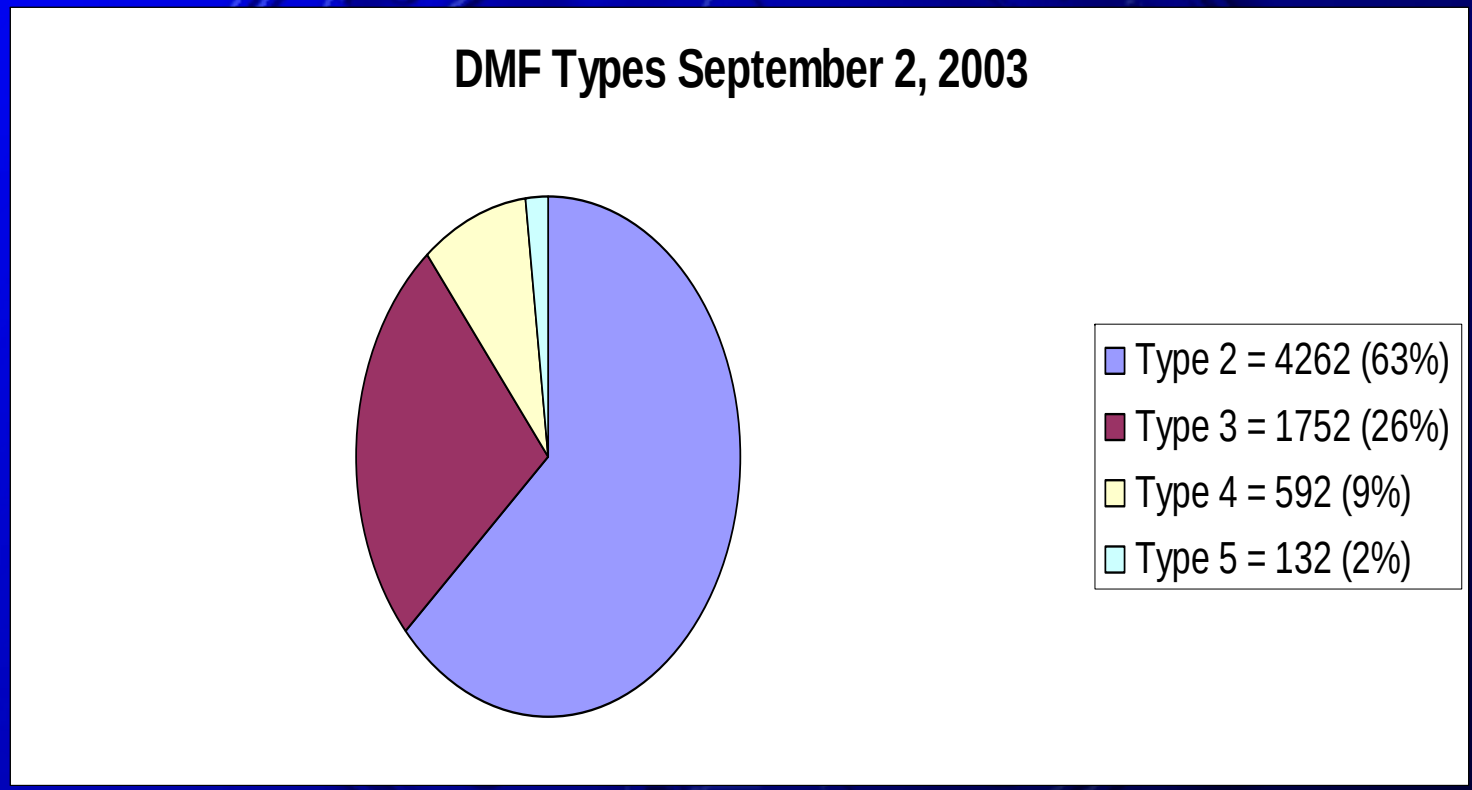
CDER User, 10/29/2003

Facts about DMFs

- As of September , 2003, there were 16773 DMFs



Types of Active DMFs



Rate of DMF Filing

	1999	2000	2001	2002	2003	Aver
All	604	536	563	548	699	590
Type II	384	360	340	342	353	356
Type III	174	120	165	155	185	160
Type IV	44	48	55	43	150	68
Type V	2	8	3	8	11	6.4

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

CU2

- Normally the CMC for a compendial excipient is not reviewed
- Many drug substance for OTCs (not NDA) not reviewed therefore CMC for drug substance not reviewed and therefore a DMF for drug substance will not be reviewed. However many drug substances used in non-NDA OTC products (e.g. aspirin) are also used in NDA OTC products. DMFs for these are reviewed.

CU2 A DMF may be submitted for information that is normally reviewed as part of the CMC review. If an item (e.g. manufacture of a compendial excepient, is not reviewed, then a DMf is not necessary

CDER User, 10/30/2003

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 CU3
- Amendment to an application = Additional information to an existing IND, a pending A/NDA or a pending A/NDA supplement

CU3 Since a DMF is not approved, there can be no supplements to a DMF only amendments

CDER User, 10/30/2003

Reasons for a DMF

- Maintain confidentiality of proprietary information (e.g., Manufacturing procedure) for the holder
- Permit review of information referenced by a number of applicants

How the System Works

NEW ADDRESS!!!!!

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

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

Binders recommended http://www.fda.gov/cder/ddms/binders.htm

How the System Works (cont)

- DMF reviewed for administrative purposes ONLY by Central Document Room (CDR) 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
- E-mail: dmfquestion@cder.fda.gov

Acknowledgement Letter

- Assigns number and Type
- 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.
- The holder MUST submit an LOA (2 copies) to the DMF and 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 Europe, the permission to reference a DMF is called a Letter of Access CU4

LOA (cont)

- LOA must contain a specific reference to a particular item in the DMF.
- This is especially important for large Type III DMFs that contain many products
- Specify the item by its code name, page number and most importantly DATE OF THE SUBMISSION on the cover letter (not an internal submission 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 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 CU5

CU5 No assignment to a reviewer, no due date

CDER User, 10/30/2003

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 many buildings all over Montgomery County, MD.
- Highlights importance of specifying the date of the submission being referenced,especially for multivolume DMFs.

DMF Review Procedure

- The DMF is reviewed when referenced
- If there are deficiencies the detailed deficiencies are communicated to the holder
- The APPLICANT is notified that deficiencies exist (usually in an IR, AE or NA letter) but the nature of the deficiencies is not communicated to the applicant. CU6
- If no deficiencies, no letter, applicant not notified.

CU6

IR= Information Request
AE = Approvable
NA = Not Approvable

CDER User, 10/30/2003

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. CU7

CU7 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)

CDER User, 10/30/2003

Technical Amendments to the DMF

- Amendment in response to letter to holder
  - Holder notifies the reviewer and applicant that the DMF has been amended. A copy of the amendment can be sent to the reviewer ONLY if requested. The cover letter of the copy sent to the reviewer must 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.
  - The amendment will be reviewed when the applicant submits a complete response to their letter (IR, AE, NA letter). Rationale: Applicant's letter may contain other deficiencies e.g.. Clinical issues
  - Cover letter with the DMF amendment should reference date of Agency's letter to holder

Technical Amendments to the DMF (cont)

- Spontaneous amendment
  - Holder
    - Cover letter should contain list of specific changes
    - Usually a good idea to include a new LOA specifying the date of the amendment
    - Notify APPLICANT of types of changes
  - FDA
    - Amendment entered into database by CDR
    - NO ASSIGNMENT, no review until application amended or supplement filed

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. Please do not include in Annual Report

Annual Updates

- List of authorized parties, what they are authorized to reference, and the date of the LOA
- List of changes reported during the past year. NOT a list of changes MADE 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
- An agent is not “authorized” in the US (unlike UK). An agent is “appointed” not “authorized”

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 next slide
- Include completed batch records for Type II

Environmental Assessment

- 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. Since DMFs are not approved, FDA does not take an action, therefore no EA needed.
- Expect a statement that holder will comply with all local environmental regulations
- EA usually applies to impact of USE of the drug on the environment.
- There are circumstances (e.g. use of an endangered species as a starting material) under which production of the drug requires an EA See 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 A/NDA or supplement when DMF amended in response to deficiency letter
- Notify FDA of technical changes in DMF appropriately.

Issues of Concern for Drug Manufacturers

- Intermediates
- Reporting Changes
- Additional Manufacturing Site
- Inspections
- Novel and Compendial Excipients
- Type III DMFs
- Inactivation of DMFs

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 gerneal 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.

Designation of an Intermediate as a Starting Material

- Definition of a Starting Material (SM) is in Drug Substance Guideline. Under discussion.
- This needs to be reported like any post-approval change.
- Useful to meet with review division.

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
- See Post-Approval Changes Guidance
- Guidances specify DATA to be reported and Reporting Category

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 only30 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

- Step 1: Holder should check Post-approval Changes Guidance for appropriate test documentation and reporting category

Reporting Changes for Type II DMFs (cont)

- Step 2.
  - If AR category, notify customer and implement change. Customer has responsibility to notify FDA in AR
  - If CBE Supplement, notify customer. DMF holder can implement change BUT drug product manufactured with post-change drug substance CANNOT be marketed until appropriate supplement has been submitted to FDA and appropriate waiting period (0 or 30 days) has passed from submission of supplement

Reporting Changes for Type II DMFs (cont)

- Step 2. (cont.)
  - If Prior Approval Supplement, notify customer. DMF holder can implement change BUT drug product manufactured with post-change drug substance CANNOT be marketed until appropriate supplement has been approved by FDA.

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. 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. CU9
- Safety testing (submitted in a Type V) is the subject of an FDA Guidance.

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

CU9 Draft DP Guidance defines a novel excipient as:

CDER User, 10/30/2003

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)

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, have all suppliers of components and or chemicals provide LOAs directly to NDA (within limits of confidentiality)

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
- Electronic DMFs may be filed as part of a pilot program http://www.fda.gov/cder/regulatory/ersr/ectd.htm

Changes in DMF System

Over the past decade, there have been some changes in the DMF system to help make it work better. However some things remain the same.

Changes in the DMF System and Procedures Internal

- Creation of Review Cover Form
- Creation of Type II Review Format
- Implementation of Re-review Policy
- Creation of Central Review File
- Revision of Database View

Changes in the DMF System and Procedures External

- Elimination of Type I DMFs
- Post-Approval Changes Guidance and BACPAC 1
- Creation of DMF List Website
- Creation of DMFQUESTION
- Establish Position of DMF Expert
- Elimination of AADAs for bulk antibiotics

Unchanged

- No review on receipt
- Review only when referenced in application
- All of the DMF is still confidential
- DMFs are neither approved nor disapproved
- The holder still has the responsibility to notify customer of changes

Summary

- The DMF system presents challenges for both the industry and the FDA
- Some of the changes have made the system smoother (hopefully for both industry and FDA)
- Problems can be minimized:
  - With full understanding of their responsibilities and adherence to Guidances on the part of holders and applicants
  - With adherence to policies and procedures on the part of reviewers.