Drug Master Files -

CBER Processes and Review

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OCBQ/CBER/FDA

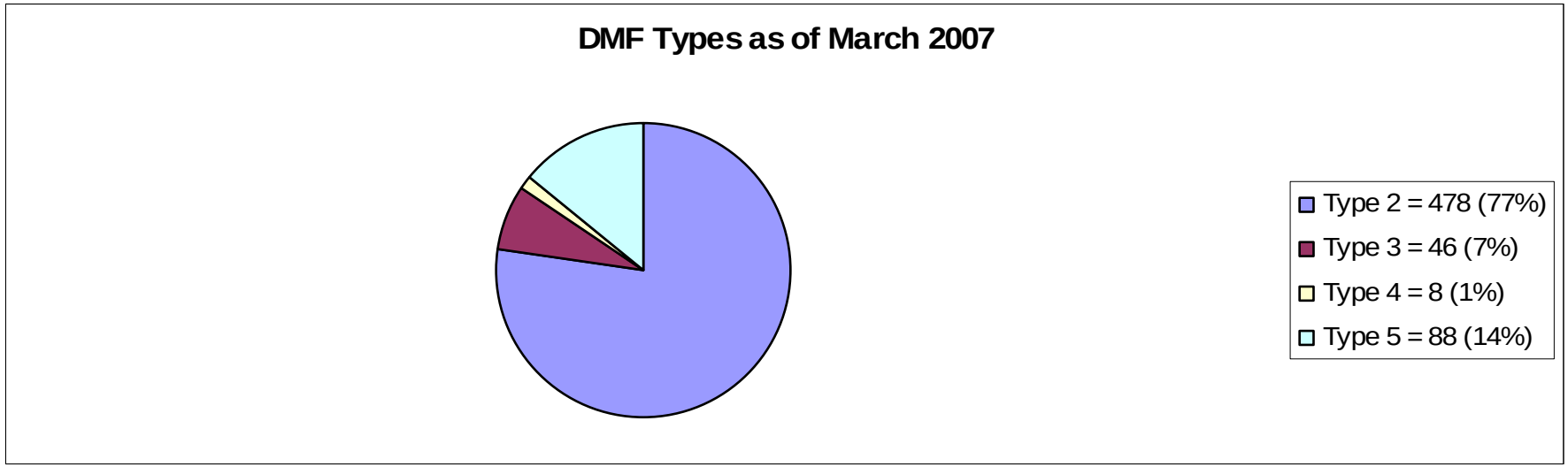
Items to be covered

- CBER Processes and relevant SOPPs
- Draft Guidance document
- Uses for Type V DMFs
- Problem areas and discussion items
- Summary

Regulatory Framework

- 21 CFR 314.420
- Jan. 12, 2000 FR notice – elimination of Type I DMFs by July 10, 2000
- Draft CBER Guideline for Submission of Type V DMFs to CBER
- CDER Guideline for DMFs (1989)
- Master Files submitted to CBER are “Biologics Master Files” (BB-MFs)

Active BB-MFs In CBER



CBER Receipt and Processing

- CBER SOPPs that include information for BB-MFs
- SOPP 8007 – DCC Binding Procedures for Regulatory Documents
- SOPP 8110 – Investigational and Marketing Applications: Submission of Regulatory Documents to CBER

CBER Receipt and Processing (SOPP 8110)

- All regulatory documents, including BB-MFs, should be submitted to the Document Control Center:

  Food and Drug Administration

  Center for Biologics Evaluation and Research

  Document Control Center, HFM-99, Suite 200N

  1401 Rockville Pike

  Rockville, MD 20852-1448

CBER Receipt and Processing (SOPP 8007)

- There are no regulations that cover the size of the paper used in the submission or type of binding
- Recommend:

  - 3 hole punched on left side of page
  - 2 copies should be sent (archive gray folder, red for duplicate
  - Identify with name, name of product, DMF number,date of submission

CBER Receipt and Processing

- All documents are logged and given receipt date
- In CBER, the same system/process used for BB-MFs and INDs – will get a “BB-MF” number
- BB-MFs sent to appropriate office/division for initial designation
- BB-MF routed for reviewer assignment
- Acknowledgment letter sent for new BB-MFs

CBER Receipt and Processing

- Review is normally conducted only when cross-referencing submission has been received and appropriate documentation submitted (cross-reference granted by DMF holder; copy of this letter in referencing submission)
- BB-MFs may be independently reviewed under some limited circumstances (facility review, patient data for example)

DMFs as Electronic Submissions

- Encourage submission of electronic DMFs – according to EIND guidance* or in eCTD format (*Guidance for Industry: Providing Regulatory Submissions to CBER in Electronic Format – Investigational New Drug Applications 3/26/2002)
- Can submit on multiple CDs or through gateway (account setup is necessary)
- eCTD
  - Administrative – Module 1
  - Summary section – Module 2
  - CMC information – Module 3

Master Files as Electronic Submissions

- **Guidance: Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications**
- FDA Electronic Submissions Gateway (ESG) – http://www.fda.gov.esq
- CBER – http://www.fda.gov/cber/esub/esubguid.htm

Format and Content Issues

- Suggest following CMC guidance or CTD format
- Information should be “compatible” with information in application
- Proprietary information or general information should be in Master File, but product-specific information should be submitted in market application

Timing of Submissions to BB-MF (Amendments vs Annual Report)

- In general, information to be submitted should be similar to what would be reported in application/supplement
- CBER: issues that may have immediate impact (major change) or additional authorized applicants should be amendments
- CBER: Annual reports may contain updates as well as list of authorize applicants as well as updates since last annual report

Problem Areas and Discussion Items

- Where do applicant's and MF holder's responsibilities begin and end with respect to information to be submitted?
- What is the best format for information submitted in MFs?
- Balance between complete information and proprietary issues (FDA can't be QA unit for applicant)

Problem Areas and Discussion Items

- Deficiency letters will go to MF holder, not applicant, so applicant will potentially not know the review issues
- GMP compliance issues will be discussed with MF holder (contract location), not applicant

Problem Areas and Discussion Items

- How do you ensure that information in MF is current when reviewed in context of an application? (cross-references, annual updates, etc)
- Concerns for contract facilities - how to ensure appropriate information is reviewed by applicant
- Concerns for multi-use facilities

Coordination of FDA Review

- When separate MFs are maintained at CBER and CDER, FDA will coordinate the review of the MFs between the Centers
- Recent examples of meetings between DMF holder and representatives of CBER and CDER

Type V DMFs

- FDA-accepted Reference Information
- Information and data inappropriate for Type II-IV DMFs
- Requires permission prior to submitting Type V DMFs* (exceptions in CBER draft guidance)
- Reviewed when cross-referenced by another submission (BLA, NDA, IND)

Samples of Type V BB-MFs on file at CBER

- Manufacturing facilities, especially for IND products
- Contract manufacturing facilities, contract test facilities, procedures
- Manufacture of diluents
- CVs for clinical investigators
- Cell lines and vectors
- Long-term patient monitoring

Type V DMFs

- CBER has found that MFs are particularly useful for facility, equipment, and other information in support of facilities being used to manufacture clinical products, especially gene therapy products, or where facilities will be cross-referenced by multiple INDs

Draft CBER Guidance

- In August 2001 CBER published the draft guidance “Submitting Type V Drug Master Files to the Center for Biologics Evaluation and Research”
- Certain information could be submitted without letter of intent and highlighted use in support of products under IND

Draft CBER Guidance

- Facilities for production of gene or cellular based therapies under clinical trials
- Contract facilities for manufacturing or testing
- Product-specific information is more appropriate under BLA

Expectations and Coordination of Files

- Recommend that the applicant be kept informed of all changes to the facility, process, and problems that may occur (deviations, complaints, adverse events, inspection issues)
- Regulatory filing should be harmonized between applicant and contractors

Multi-Use Facilities

- Contract facilities are often not dedicated to one product, hence there are concerns related to the other products that are being produced in the facility
- Dedicated equipment vs shared equipment will impact on the level of concern and data needed to support current processes
- Campaign vs concurrent?

Concerns for Multi-use facilities

- Responsibilities of both parties if problems are encountered; how effective will corrective actions be?
- Changes made to contract facility or processes; how will this information be conveyed to applicant?

Summary

- CBER uses the same regulatory framework as CDER, and CBER-specific processes highlighted
- Conveyed CBER references and policy issues regarding MFs
- Discussed some areas of concern
- Highlighted Type V MFs

Thanks to:

- Bob Yetter, Ph.D.
- Jules Meisler
- Michael Fauntleroy
- Arthur Shaw, Ph.D.

Contact and Reference Information

- Division of Manufacturing and Product Quality (HFM-670) 301 827-3031
- Draft CBER guideline: http://www.fda.gov/cber/gdlns/dmfv.htm
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