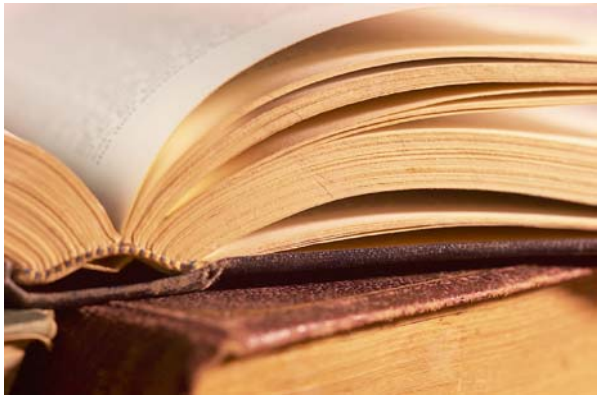
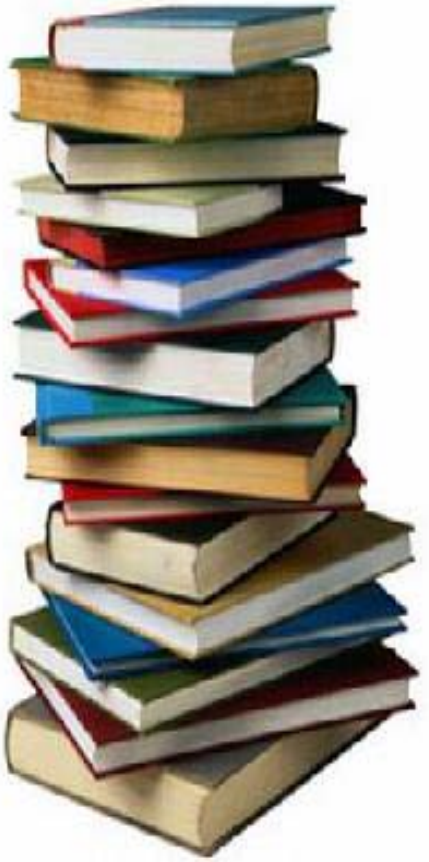
Facility Master Files





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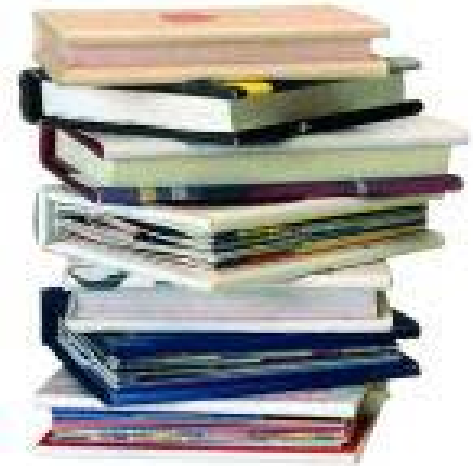
Baylor College of Medicine



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What are Master Files?

- Documents submitted to and held on file by the FDA
- Describe manufacturing processes, devices or facilities
- Are kept confidential from other parties
- May be cross-referenced by author and other parties (with written permission)

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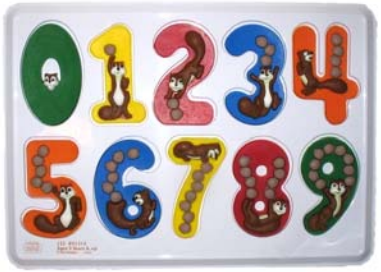

Types of Master Files

- ***Type I***: Manufacturing Site, Facilities, Operating Procedures, and Personnel
- ***Type II***: Drug Substance, Drug Substance Intermediate, and Material Used in Their Preparation, or Drug Product
- ***Type III***: Packaging Material
- ***Type IV***: Excipient, Colorant, Flavor, Essence, or Material Used in Their Preparation
- ***Type V***: FDA Accepted Reference Information

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Change of Categories

In the *Federal Register* of January 12, 2000 (65 FR 1776), FDA published the final rule "New Drug Applications; Drug Master Files." The final rule amended 21 CFR 314.420 by removing the provision for Type I DMFs. FDA amended the regulation to eliminate submission of information that was not necessary either to conduct inspections of manufacturing facilities or to review the chemistry, manufacturing, and controls sections of INDs, NDAs, and abbreviated applications. The regulation became effective on July 10, 2000, and the agency will no longer accept Type I DMFs as of that date.

Facility information is now submitted as a Type V Master File – and specific reference is made to Facilities for Production of Gene or Cell Based Therapies

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Guidance Document

August 2001

Guidance for Industry

Submitting Type V Drug Master Files to the Center for Biologics Evaluation and Research

DRAFT GUIDANCE

http://www.fda.gov/cber/gdlns/dmfv.pdf

No letter of Intent Required for this Type of File

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Type V Master File

Include information to assess the safety of the products used in clinical trials of gene or cell-based therapies

- Floor diagrams showing manufacturing areas
- List of products manufactured
- Equipment areas dedicated or shared
- Overview of production steps for all products manufactured

Type V Master File

- Description of containment features and contamination precautions
  - Specialized equipment
  - Air quality classification
  - Description of air handling units
  - Pressure differentials

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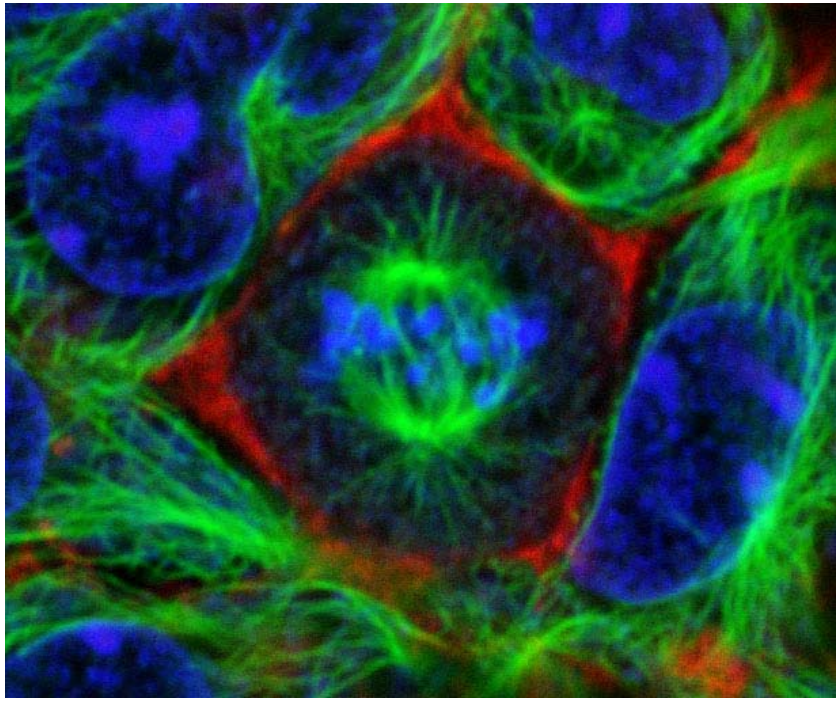
Type V Master File



- Screening & acceptance procedures for all cell lines brought into the Facility

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Advantages

- Since facilities are used to generate vectors or to transduce or manipulate cells used in a number of trials under IND, a Type V DMF eliminates the need to submit the same information numerous times & facilitates IND review
- Attractive to investigators wishing to use Facility

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Disadvantages

- Lot of up-front work to assemble
- Must be kept updated (yearly)
- If unacceptable to FDA then all related INDs can be put on hold

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Current Cell Processing Facility Master Files

- NIH Cell Processing Facility
- PACT Centers
  - University of Pittsburgh
  - University of Minnesota
  - Baylor College of Medicine
- ??

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Table of Contents
Baylor Master File

1. General Introduction
2. Other Manufacturing Activities within the CPF
3. Name and Address of Site, Contact Information
4. Types of Products Manufactured
5. Short Description of the Site
    a. Figure 1: Floor plan of Cell Processing Facility
    b. Figure 2: Traffic Patterns within the CPF
    c. Figure 3: Air Pressure Relationships in CPF
6. Employees
    Quality Assurance
    Quality Control
    Production
    Materials Handling
    Technical & Support Service
    Total Staff

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Table of Contents
Baylor Master File

7. Outside Scientific, Analytical and Technical Assistance
8. Quality Management System
    - Quality Policy
    - Quality Assurance Function
    - Elements of the Quality Assurance System
    - Process Validation
    - Documentation of Training
    - Tracking of Variances from SOPs and other Procedures
    - Accessioning of Cells and Tissues
    - Supply Release & Supply Release Specifications
    - Tracking of Supplies & Equipment during Manufacturing
    - Monitoring of the Facility, Equipment, Alarm System
    - Performance of QC Tests

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Table of Contents
Baylor Master File

8. Quality Management System
   - Coordination of Testing by External Laboratories
   - Maintaining the QA/QC Database
   - Label Control
   - Product Release
   - Audits – Internal & External
   - Quality Meetings
   - Patient Monitoring/Complaints File
9. Personnel
   - Responsibilities of Key Staff
   - Training of Manufacturing Staff
   - Health & Hygiene Requirements

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Table of Contents
Baylor Master File

10. Facilities
    - Construction and Finishes
    - HVAC System
    - Emergency Power System
    - Structural Repairs &Facility Maintenance
    - Cleaning
    - Equipment handling
11. Documentation
    - Standard Operating Procedures
    - Manufacturing Records
    - Batch Record & Worksheets
    - Testing & QA/QC Documentation
    - Error Detection
13. Production – generic major steps

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Table of Contents
Baylor Master File

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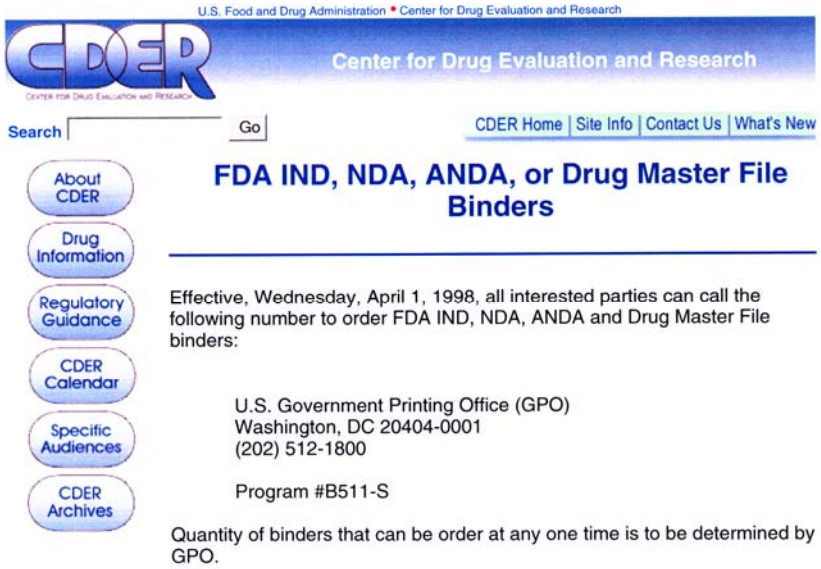
Submission of Master File

No electronic submissions
Must submit in special binders (1 original & 2 archive)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FDA IND, NDA, ANDA, or Drug Master File Binders

Effective, Wednesday, April 1, 1998, all interested parties can call the following number to order FDA IND, NDA, ANDA and Drug Master File binders:

U.S. Government Printing Office (GPO)
Washington, DC 20404-0001
(202) 512-1800

Program #B511-S

Quantity of binders that can be order at any one time is to be determined by GPO.

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

Center for Biologics Evaluation and Research
Document Control Center, HFM-99, Suite 200N
1401 Rockville Pike
Attn: OCTGT/RMS

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Review

- Review took about one year
- Minor comments related to
  - Vendor audits
  - Air handling
  - Qualification of Facility
  - Microbial species detected
  - Cleaning Validation

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Cross-Reference Letters

Center for CAGT Cell and Gene Therapy

September 30, 2005

FDA/CBER
Attn: Office of Compliance & Biologics Quality
HFM99 Room 200N
1401 Rockville Pike
Rockville, Maryland 20852

Dear Mr. Obiri:

This is to authorize Dr. Helen Heslop, Center for Cell and Gene Therapy, Baylor College of Medicine, to cross-reference our Drug Master File (BBMF 11232) for the Cell Processing Facility at the Baylor College of Medicine Center for Cell and Gene Therapy, in connection with their study, "Administration Of TGF-b Resistant LMP2a-Specific Cytotoxic T-Lymphocytes To Patients With Relapsed EBV-Positive Lymphoma."

Should you require any additional information, please do not hesitate to contact me.

Sincerely,

Adrian P. Gee, M.I.Biol, PhD.
Director, Clinical Applications Laboratory
Center for Cell and Gene Therapy
Professor, Department of Pediatrics and Medicine

cc: Bambi Grilley, RPH, CCRA, CCRP, CIP, Director Regulatory Affairs, CAGT.
Malcolm Brenner, MB. PhD, FRCP, FRCPath, Director, Center for Cell and Gene Therapy.

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Take Home Messages

- Master Files eliminate the need for repetitive submission of facility information to the FDA
- Preparation and updating are tedious and time-consuming
- Rejection by FDA places related INDs on hold

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