Common Challenges in Development of Cell and Gene Therapy Products

Mike Havert, Ph.D.

mike.havert@fda.hhs.gov

US Food and Drug Administration

Center for Biologics Evaluation and Research

Office of Cellular, Tissue, and Gene Therapies

Overview

- Types of cell and gene therapy products
- Regulatory expectations for product characterization and consistency
- New analytical technology for characterizing emerging therapeutics

Overview

- Types of cell and gene therapy products
- Regulatory expectations for product characterization and consistency
- New analytical technology for characterizing emerging therapeutics

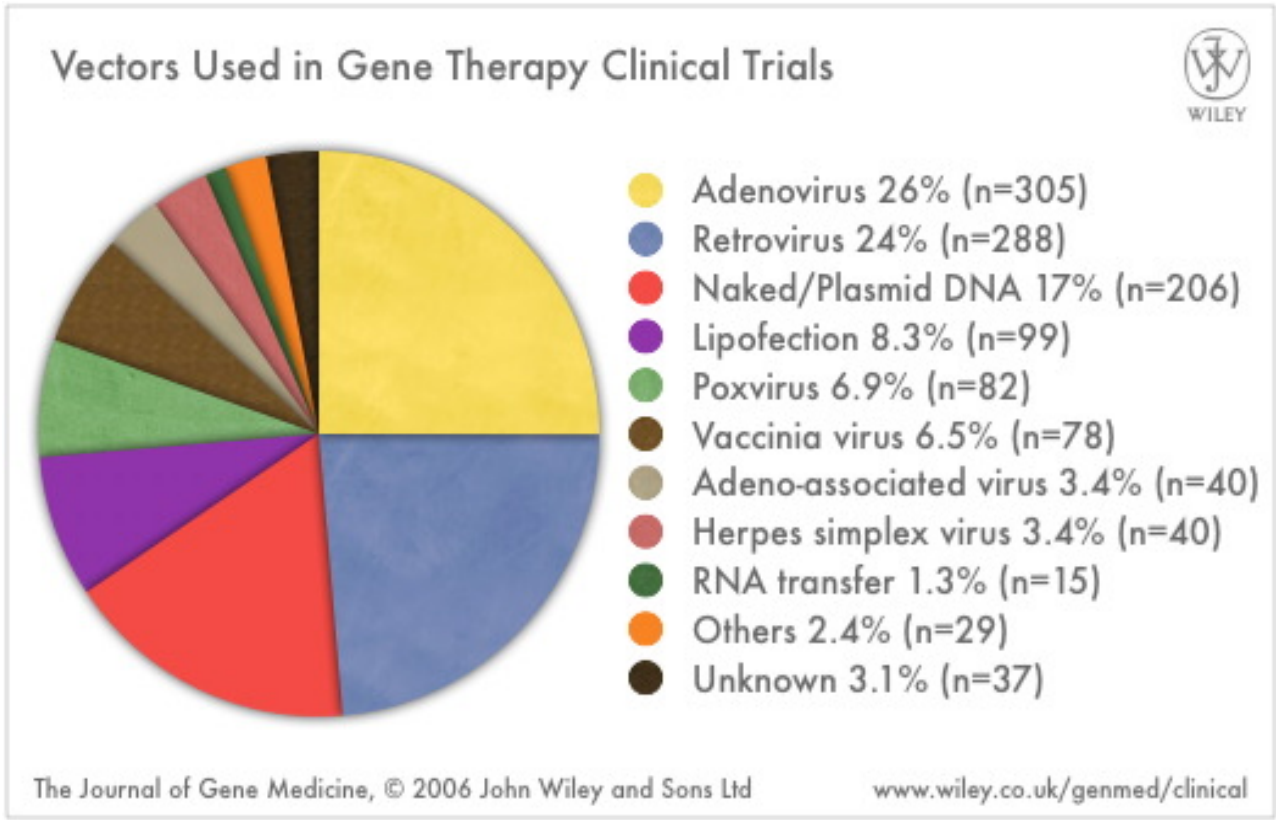
Products Regulated in OCTGT

- Somatic cell therapies
- Tumor Vaccines
- Gene therapies
- Xenotransplantation
- Combination products
- Devices used for cell/tissues
- Unique assisted reproduction (ooplasm transfer)
- Anti-idiotype antibodies
- Tissue and tissue based products

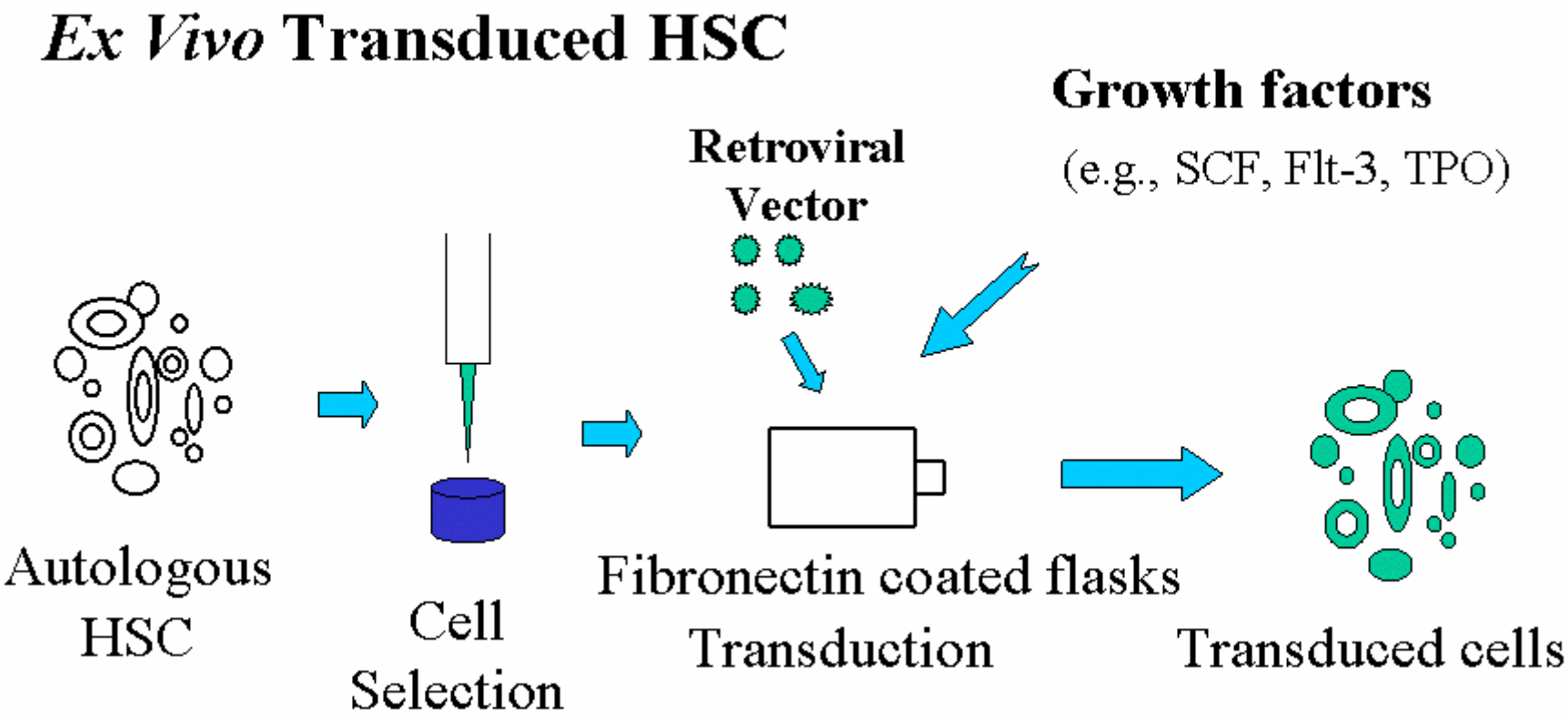
Gene therapy products designed for…

- **Inherited disease**
- **Acquired disease**
  - Cancer
    - cytokines, immune modulators, tumor suppressor genes, suicide genes, oncolytic viruses
  - Wound healing / new vasculature / improve cell survival or function
    - growth factors, extracellular matrix, cell cycle regulators, signal transduction or anti-apoptotic molecules
  - Chronic infection
    - antisense or siRNA targeting virus

Vectors for delivery



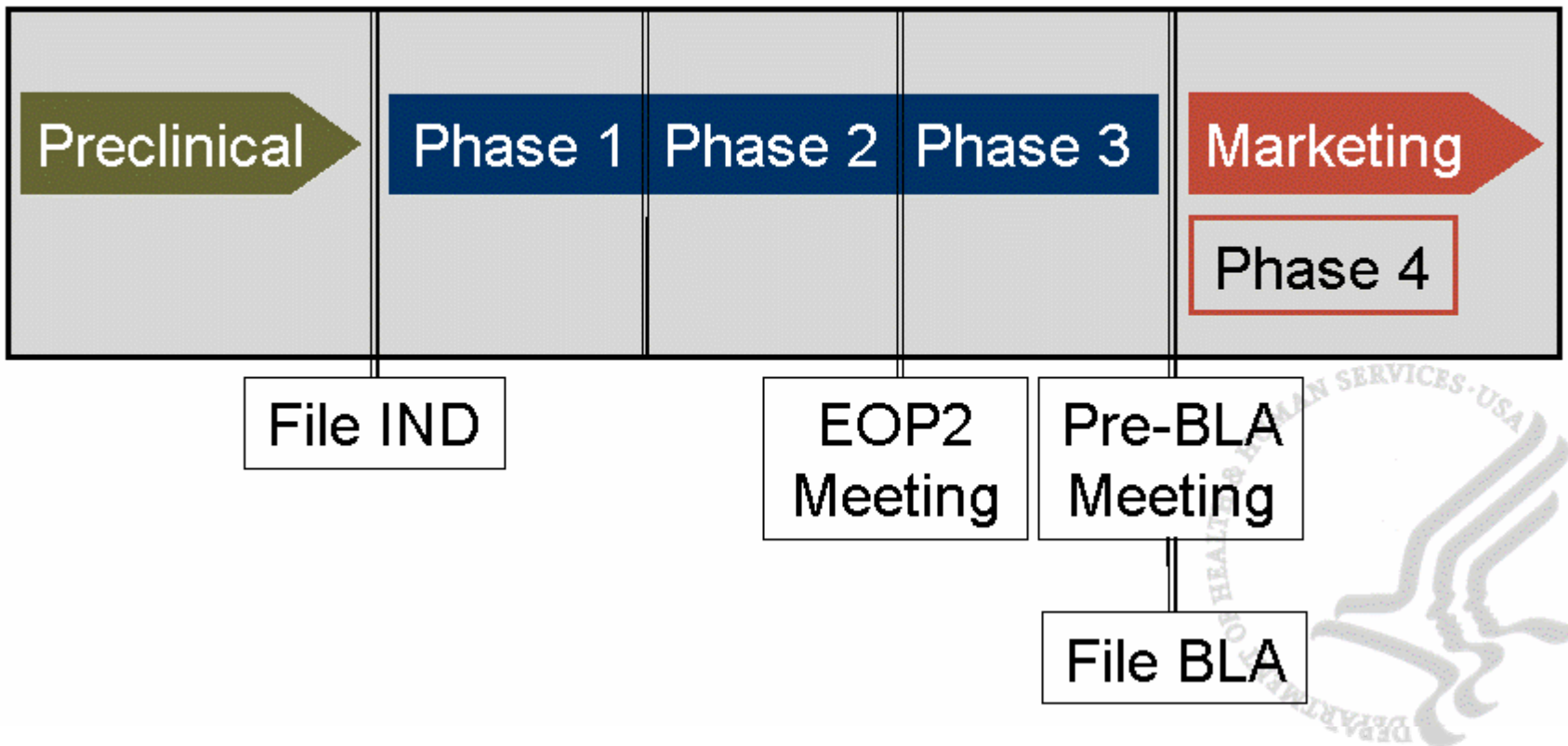
Autologous cells transduced with vector



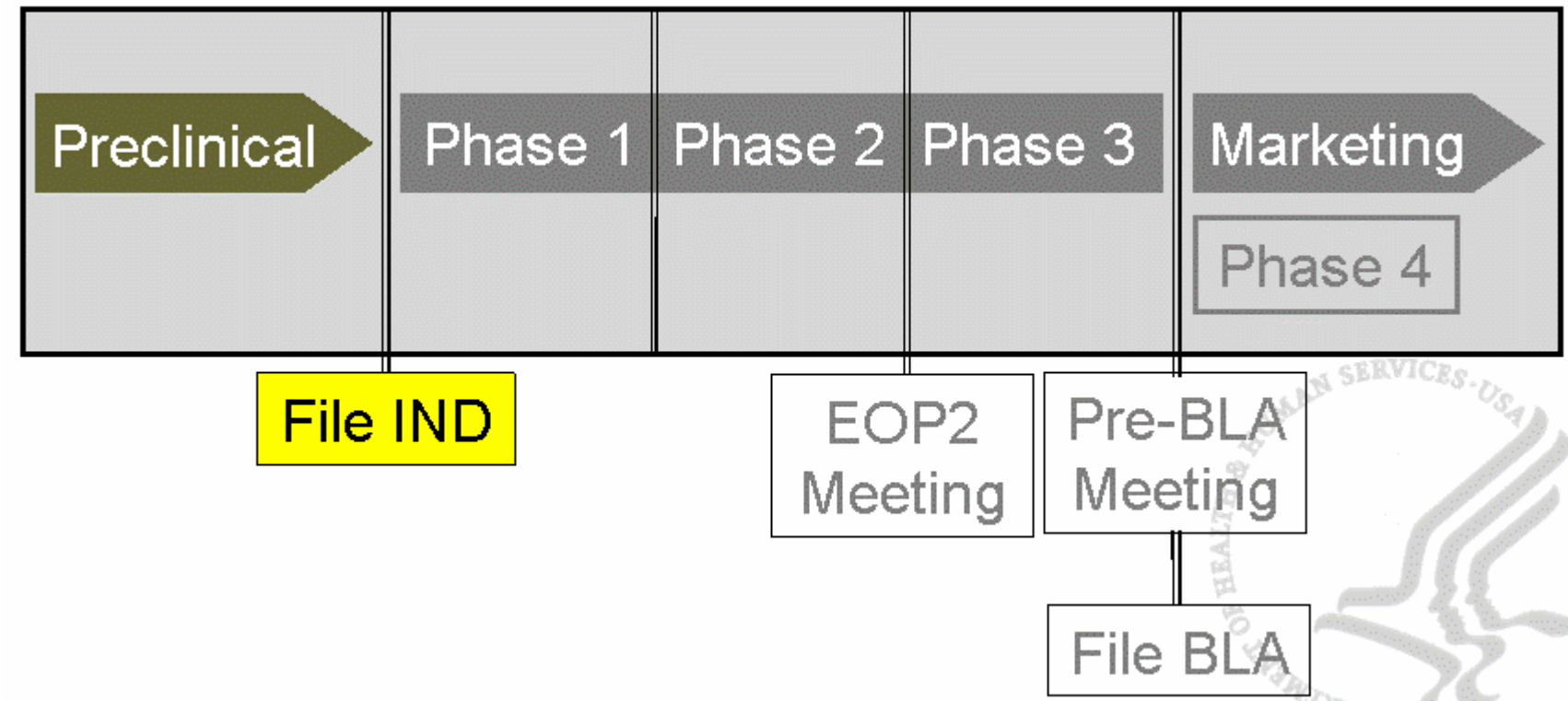
Overview

- Types of cell and gene therapy products
- **Regulatory expectations for product characterization and consistency**
- New analytical technology for characterizing emerging therapeutics

Regulatory timeline



Preparing to submit an IND



How does a manufacturer know what test to use for their product?

- **Sponsor is free to use any scientifically valid test for** in-process **testing of product**
- **For** final product **testing, if test method is not specified by biological product standards, sponsor can use any scientifically valid test** (21 CFR 610)
- **It is also possible to use alternative tests to those prescribed by biological product standards**
  - 21 CFR 610.9
- **Information on generally acceptable types of testing:**
  - FDA Guidance documents
  - ICH Guidance documents
  - United States Pharmacopeia (USP)
  - Scientific literature, etc..

General Biological Products Standards

CFR	Test
610.9	**Alternative Methods**
610.10	**Potency**
610.11	***General Safety**
610.12	**Sterility**
610.13	**Purity**
610.14	**Identity**
610.15	**Constituent Materials**
610.30	****Mycoplasma**
610.40	**Communicable diseases**

*Cellular Therapies are exempt
**Only required for cells that are cultured

Biologics Standards

Required Test	Test Method	Test Timing	Specification
Sterility	**Specified**	**Final Product**	**Negative**
Mycoplasma	**Specified**	**Final Product**	**Negative**
Purity (pyrogenicity)	**Specified**	**Final Product**	**Pass**
Identity	**Not Specified**	**Final Product**	**Product Specific**
Potency	**Not specified**	**Final Product**	**Product Specific**
Other tests	**Viability, Phenotype, etc.**		**Ensure safety and consistency**

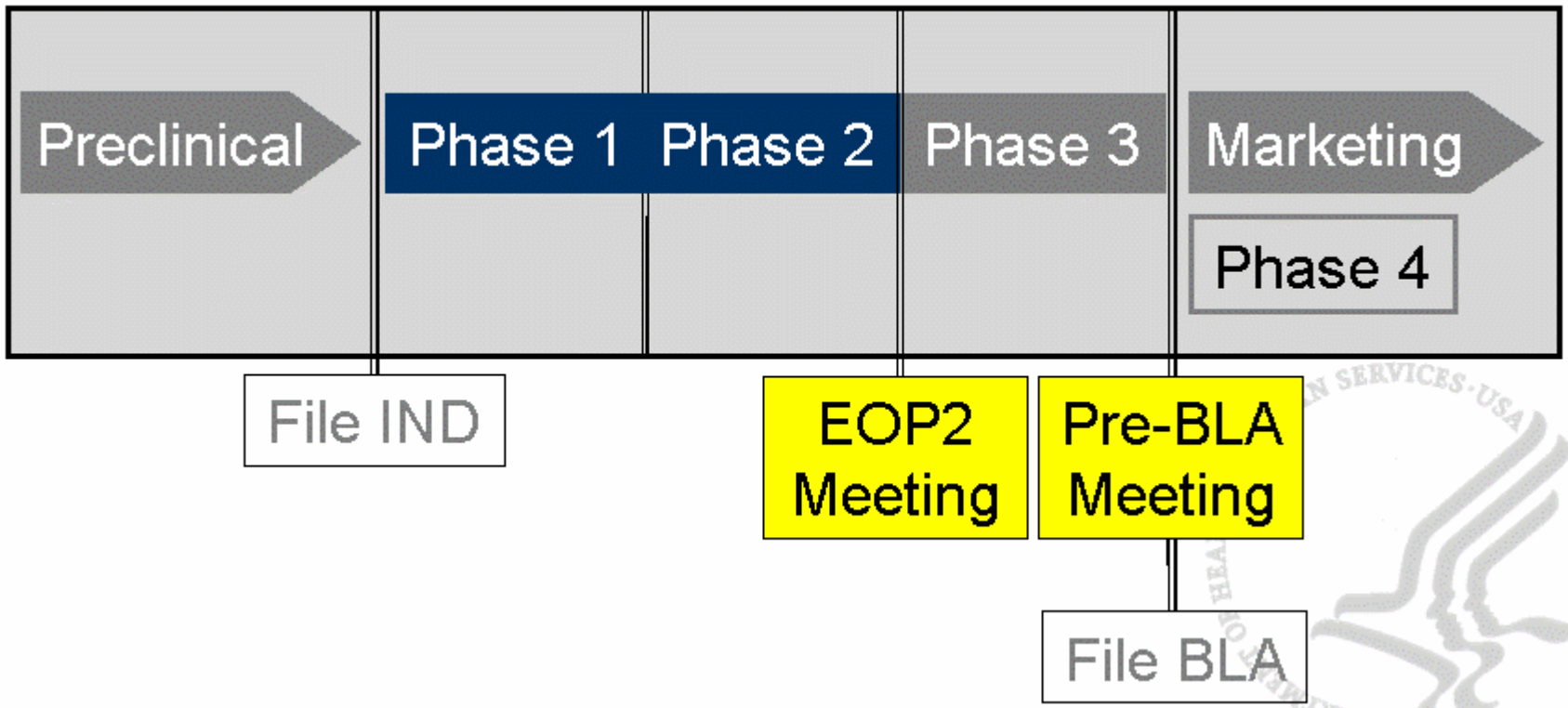
Identity

- **Verification that vial contents match the label**
  - Develop identity assay specific for the product
  - Multiple active components in product?
    - The test methods should identify all of them
  - Distinguish the final product from other products made in the same facility

Potency Assay Wish List

- Available for release
- Consistent/validatable
- Demonstrate product activity
- Quantitative
- Stability indicating
- Demonstrate product consistency

Preparing for pivotal studies



Common challenges for Pivotal Studies

- **Product characterization**
  - Lack of understanding of the product
  - Inability to ensure product consistency
- **Potency**
  - Assay(s) is insufficient to determine biological activity
  - Assay(s) is not quantitative
  - Acceptance criteria are inadequate

Solution lies in preparation

- **Determine critical product characteristics and how they will be controlled**
  - Identify and characterize therapeutic and inactive components
  - Identify and measure impurities and inactive components
- **Establish a meaningful potency assay**
- **Refine procedures and acceptance criteria based on development experience**
- **Make plans for potential comparability studies for new sites and unexpected process changes**

Overview

- Types of cell and gene therapy products
- Regulatory expectations for product characterization and consistency
- **New analytical technology for characterizing emerging therapeutics**

Identifying critical attributes may involve new technology

- **New Technologies**
  - Microarray, proteomics and others
- **May be useful for**
  - Product development
    - Characterize complex products
    - Identify markers predictive of behavior
  - Lot release
    - Potency
    - Identity

Contact Information

Cell and Gene therapy product manufacturing questions

Mike Havert
mike.havert@fda.hhs.gov
301-827-5102

General CBER Issues

Office of Communication, Training & Manufacturers Assistance
Manufacturers Assistance and Technical Training Branch

Telephone: 800-835-4709 or 301-827-1800
E-mail: matt@cber.fda.gov
Internet: http://www.fda.gov/cber/manufacturer.htm