Embryonic Stem Cell-based Therapies: US-FDA Regulatory Expectations

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Challenges on the Horizon

Recent Examples from the Scientific Literature:

- **The therapeutic potential of embryonic stem cells: A focus on stem cell stability. *Curr Opin Mol Ther.*** 2006 Aug; Vol 8(4), pg. 338-344 (Zeng and Rao).
- **Sources, derivation and culture of human embryonic stem cells. *Semin Reprod Med*** 2006; Vol 24, pg. 298-303 (Amit M and Itskovitz-Eldor J).
- ***In vitro* culture conditions favoring selection of chromosomal abnormalities in human ES cells. *J Cell Biochem.*** 2006 Oct 1; Vol 99(2), pg. 508-516 (Imreh and Ahrlund-Richter, et al.).
- **An *in vitro* model of human dopaminergic neurons derived from embryonic stem cells: MPP(+) Toxicity and GDNF Neuroprotection. *Neuropsychopharm.*** 2006; Vol 31, pg. 2708-2715 (Zeng X and Freed WJ, et al.).
- **Clinical hurdles for the transplantation of cardiomyocytes derived from human embryonic stem cells: role of molecular imaging. *Curr Opin Biotechnol.* 2006** (Epub Ahead of Print) (Swijnenburg RJ and Wu JC et al.).

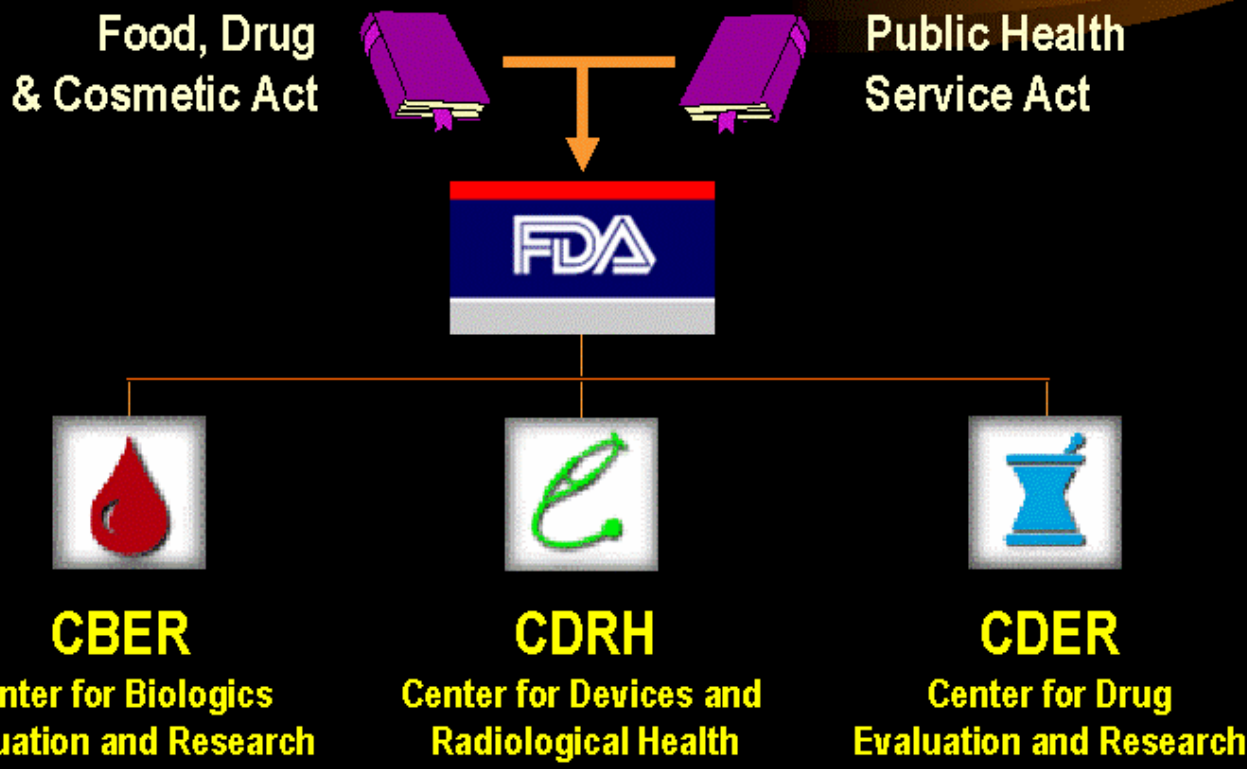
Topics to be Covered

PARADIGM: Regulation of Embryonic Stem Cell-Based Cellular Therapies

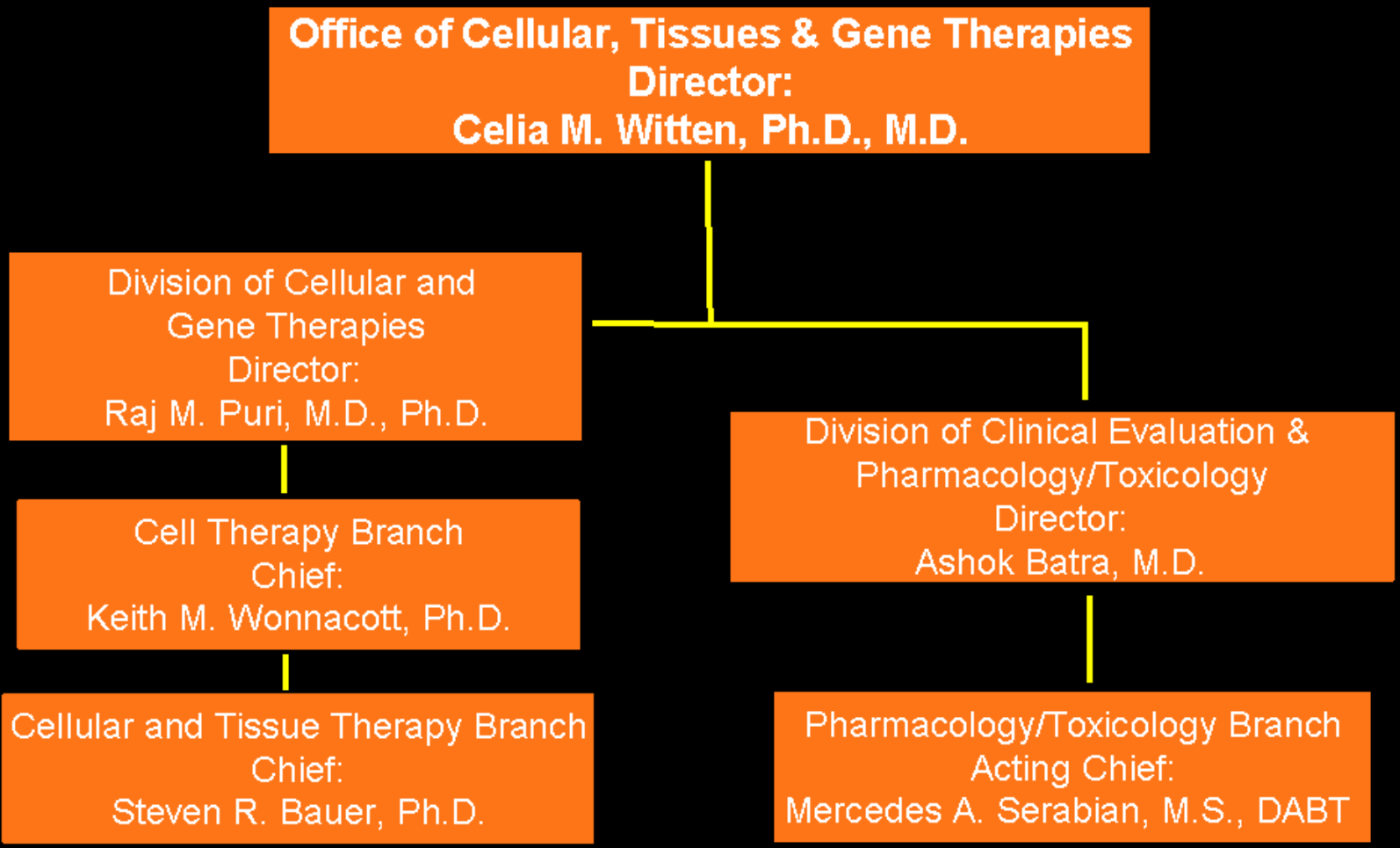
- **Responsibility for Product Review**
- **Important Tools/Resources that Support the Regulatory Review Process**
- **Regulatory Framework**
- **Issues Critical to the Regulation of Stem Cell-Based Therapies**
- **Helpful Hints**
- **Roadmap to a Phase 1 Clinical Trial**

Application of FDA Authority Through Product-Centric Centers

Application of FDA Authority Through Product-Centric Centers



CBER Unit Responsible for Review of Embryonic Stem Cell-Based Products



Resources Important to the Regulatory Review Process

- **Memorandum of Understanding:**
- ***CBER/NINDS Interagency Working Group: 5th Year***
  - **PURPOSE: Provides an infrastructure to support information sharing between FDA/CBER and NIH/NINDS**
  - **GOAL: To expedite translation of basic research involving promising biological therapies to well-designed clinical studies for the treatment of neurological disorders through enhanced information exchange.**
  - **FORMAT: CBER and NINDS staff conduct monthly meetings to discuss regulations, policies, and statutory responsibilities, as well as address difficult questions and issues that confront development of new therapies.**
- **Laboratory-based, Research/Reviewer Model**
- ***Conduct research that supports FDA's Critical Path Initiative***

Resources Important to the Regulatory Review Process

Cellular, Tissue and Gene Therapies Advisory Committee (CTGTAC)

http://www.fda.gov/oc/advisory/acbiologics.html

- The Committee reviews and evaluates available data relating to the safety, effectiveness, and appropriate use of biological response modifiers which are intended for use in the prevention and treatment of a broad spectrum of human diseases.
  - **Human Stem Cells as Cellular Replacement Therapies for Neurological Disorders: July 13-14, 2000**
  - **Purpose:** To provide the FDA with current, reliable scientific and medical guidance to facilitate regulatory decisions relating to cellular replacement therapies in neurological disorders.

Regulation of Cellular and Tissue-Based Products: Tissue Action Plan

- Provides a unified regulatory framework
- Provides greater flexibility intended to encourage innovation in the field of cellular therapies
- Provides a tiered regulatory approach with the level of regulation proportional to the degree of risk
- Risk determines level of regulation
  - **Lower Risk** – Tissue Regulations Suffice: Section 361, PHS Act, 21 CFR Part 1271- *Human Cells, Tissue and Cellular and Tissue-Based Products*
  - **Higher Risk** – Preapproval Required: Section 351, PHS Act (Biologic); Section 505 Food, Drug and Cosmetic Act (Drug), Investigational New Drug Requirements – 21 CFR Part 312.

Regulation of Stem Cell Therapies Under the Tissue Action Plan Framework

- Novel biologic therapies comprised of, or derived from, stem cells will be regulated as human cells, tissues or cellular or tissue-based products: HCT/P's

- 21 CFR 1271.3(d)- (HCTP) means articles con-taining or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.

Regulatory Framework Goals

- Prevent unwitting use of contaminated tissues with the potential for transmitting infectious disease
- Prevent improper handling or processing that might contaminate or damage tissues
- Ensure that clinical safety and effectiveness is demonstrated for cells and tissues that are highly processed, used for purposes other than re-placement, combined with non-tissue compon-ents, or that have systemic effects

Obtaining a Biologics License for a Stem Cell-Based Product

Code of Federal Regulations for Food and Drugs (21 CFR 600 - BIOLOGICS)

Demonstrate through analytical and clinical testing:

- Sterility
- Purity
- Potency
- Identity
- Stability
- Safety
- Efficacy

NOTE: Complete understanding of the mechanism of action is not a regulatory requirement.

Stem Cells: Biological Characteristics Convey Both Therapeutic Promise and Regulatory Challenges

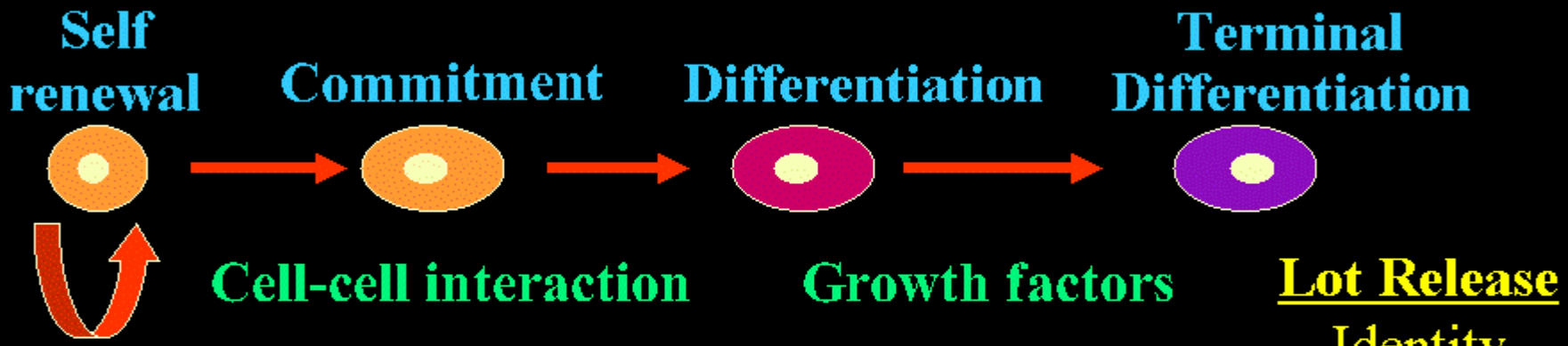
- Capacity for self-renewal, robust proliferative potential.
- Capable of differentiating into varied, disparate tissue phenotypes in response to appropriate biologic cues.
- Putative Plasticity / Transdifferentiation

ALL OF THE ABOVE!!!

Characterization

Gene expression profile,
Antibodies, Enzymes,
In vitro differentiation

Developmental Stages
Exogenous Influences
Manufacturing Concerns



Lot Release

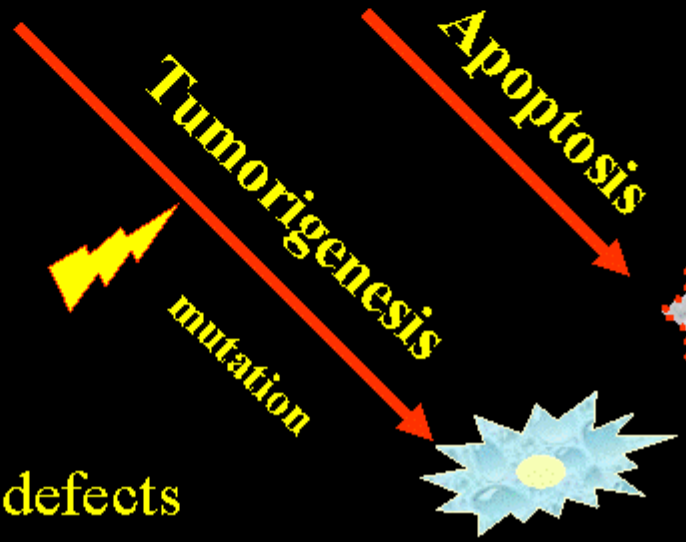
Identity
Potency
Safety
Viability
Purity

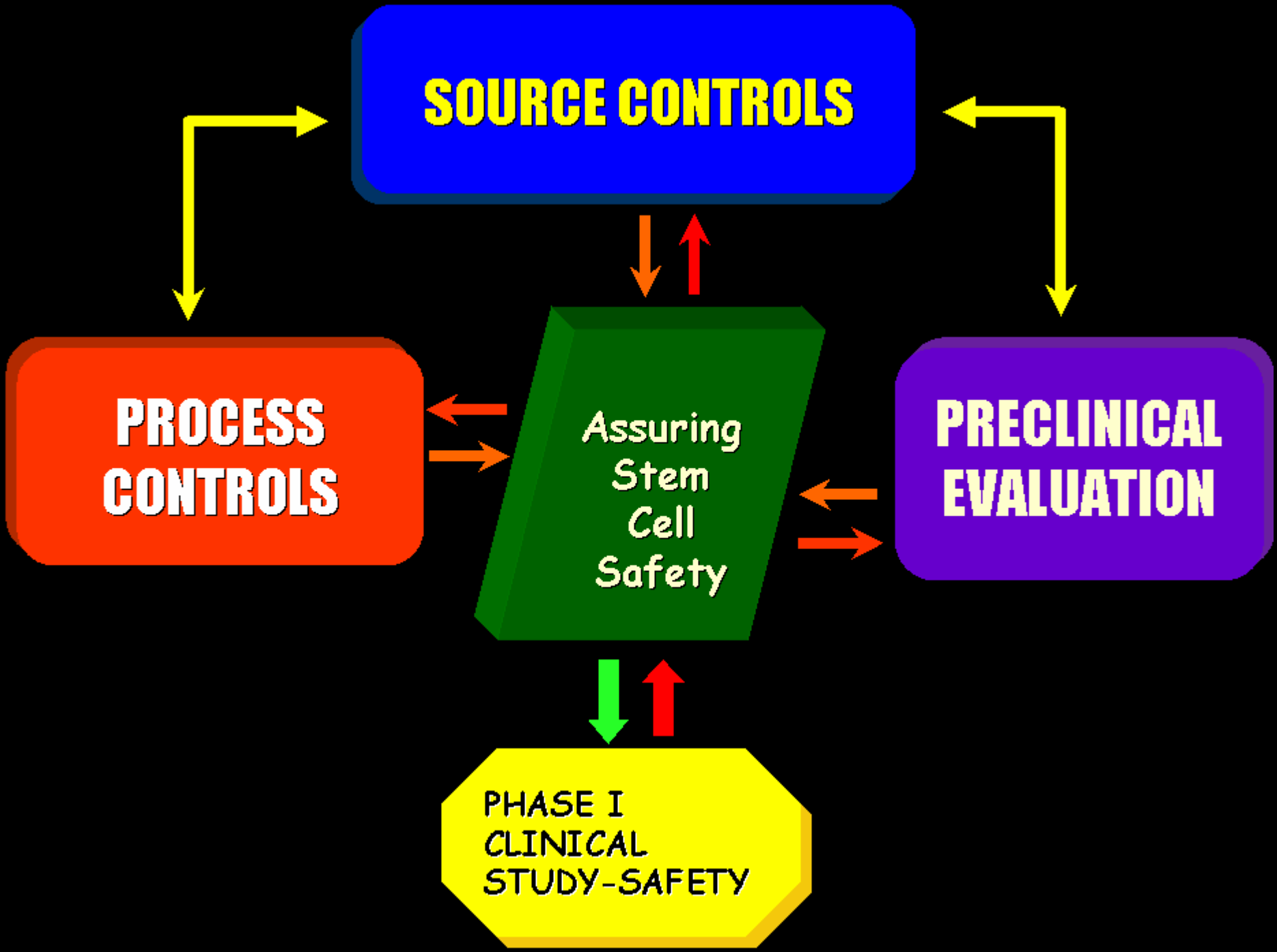
Manufacturing

Cell Banks
Feeder Layers
Growth Factors
Cell Characterization

Screening

Donors, Viruses, Genetic defects




SOURCE CONTROLS
PROCESS CONTROLS
Assuring Stem Cell Safety
PRECLINICAL EVALUATION
PHASE I CLINICAL STUDY-SAFETY

Human Embryonic Stem Cell Lines

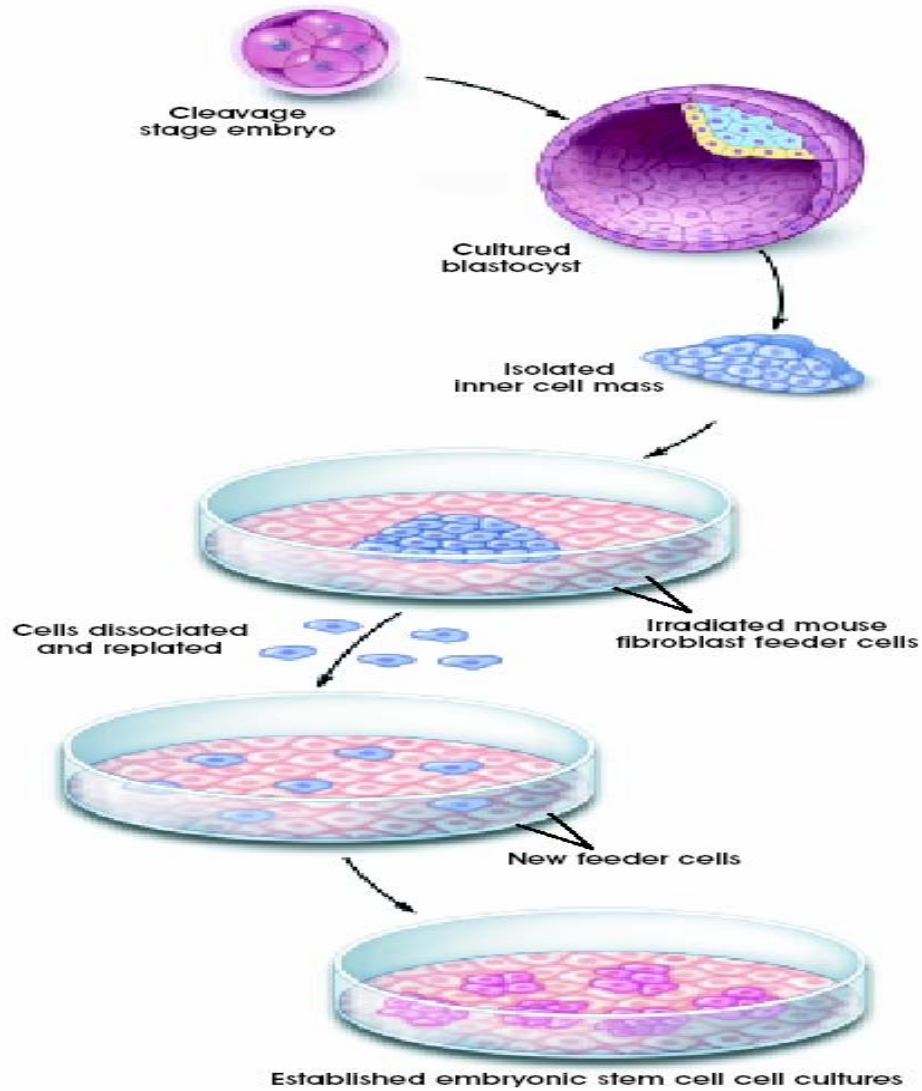


Figure C.1. Techniques for Generating Embryonic Stem Cell Cultures.

Developing a Stem Cell-Based Product: Source Controls

- Evaluating Human Stem Cell Sources
  - Appropriate screening / testing of donor tissue for communicable disease is essential- 21 CFR 1271, Subpart C: Donor Eligibility Final Rule
  - Consider implications of molecular genetic analysis
  - Determine whether intrinsic safety concerns exist based on cell source (adult, fetal, embryonic)
  - Develop and standardize criteria for accepting donor source materials to initiate production of a stem cell-based investigational product.

Developing a Stem Cell-Based Product: Process Controls

- Critical Manufacturing Process Controls
  - Standardization and optimization of reagents and processing procedures
  - Product characterization and development of acceptance criteria.
    - Controlling purity and impurities profiles of the final cellular product.
    - Establish specific characteristics to ensure product integrity.
    - Identify product parameters that anticipate adverse events.
    - Develop analytical approaches for evaluating proposed acceptance criteria for in-process intermediates and final cellular product.

Human Embryonic Stem Cell Lines: Establishing Undifferentiated Cell Cultures: Process Controls

- **Characterization of undifferentiated cell line continued:**
  - Do your cell lines express molecular markers indicative of undifferentiated hES cells?
  - Have you assessed the stability of your undifferentiated hES cell line? How long are you able to maintain your hES cells in culture (number of passages/ doublings over time) without loss of their undifferentiated properties?
  - Have you evaluated your cell lines grown on mouse feeder layers for the presence of murine viruses and endogenous murine retrovirus?
  - Are your hES cultures free of microbial (bacterial/fungal) and mycoplasma contamination?

Developing a Stem Cell-Based Product: Detailed Characterization

- Detailed characterization of stem cell-based products involves multi-parametric analytical testing:
  - Morphologic evaluation
  - Detection of phenotype-specific cell surface antigens
  - Unique biochemical markers
  - Gene and protein expression analysis (microarray and proteomics)
  - Cellular impurities profile assessment
  - Biologic activity assay ≈potency
  - MHC/HLA expression- predicting immunologic compatibility /anticipating immunogenicity

Developing a Stem Cell-Based Therapy: Preclinical Assessment

- **Demonstrating Proof-of-Concept**
  - Perform studies in animal transplant models of human disease – results serve to support a rationale for conducting a clinical trial
  - Proof-of-Concept Studies performed to:
    - Provide information concerning feasibility, establish rationale
    - Permit concurrent measurement of bioactivity/safety endpoints
    - Explore dose-response relationship between product and an activity/safety outcome
    - Facilitate route of administration optimization

Developing a Stem Cell-Based Product: Preclinical Evaluation

- **Animal Testing: Toxicological Assessment**
  - Comprehensive histological examination-evidence for:
    - Implant site reaction
    - Any inflammatory response in target/non-target tissue
    - Host immune response
    - Cellular fate-plasticity: differentiation/phenotype expression, transdifferentiation, fusion
    - Morphologic alterations in either target/non-target tissues.

Developing a Stem Cell-Based Product: Preclinical Evaluation

- **Animal Testing: Toxicological Assessment**
  - Comprehensive histological examination- evidence for:
    - Cell survival post transplantation
    - Cell migration
    - Cellular fate-plasticity: differentiation, trans-differentiation, fusion
    - Tissue integration
    - Tumorigenicity (hyperplastic or unregulated growth.

Human Embryonic Stem Cell Lines

- Issues Receiving Attention:
  - **Media used for culturing hES cells is routinely supplemented with bovine serum (concern over BSE/TSE, vCJD) as well as other animal-derived ancillary products.**
  - **Characterization of therapies derived from hES cells as xenotransplantation products: use of irradiated murine embryonic fibroblast feeder layers.**
  - **Published technical report in *Nature Medicine:* Human embryonic stem cells express a nonhuman immunogenic sialic acid (Neu5Gc).**
  - **Karyotypic / genetic stability of long-term hES cell cultures**

Human Embryonic Stem Cell Lines

Culturing hES Cells in Serum-Containing Medium

- Use of bovine serum is acceptable provided demonstration that source of serum is from herds reared for the entirety of their lives in certified, BSE-free countries. *(Additional information about herd demographics, health monitoring and product collection methods may be requested)*
- Use clinical-grade serum sourced from humans.
- May elect to develop a serum-free, chemically defined medium that obviates risks associated with serum supplementation (bovine or human sources).

Human Embryonic Stem Cell Lines

Human ES Cell Lines Established on Non-Human Feeder Cell Layers

- **Fit the definition of xenotransplantation as defined in CBER Guidance for Industry issued April 2003.**
- **FDA DOES NOT intend xenotransplantation requirements to preclude use of hES cell lines in human clinical trials.**
- **For stem cell products derived from hES cell lines raised on non-human feeder layers it may be necessary to demonstrate that the hES cell line is free from infectious agents that may pose a risk for transmission to recipients. *(Adventitious agent testing is equally important when feeder layers are comprised of human cells)***

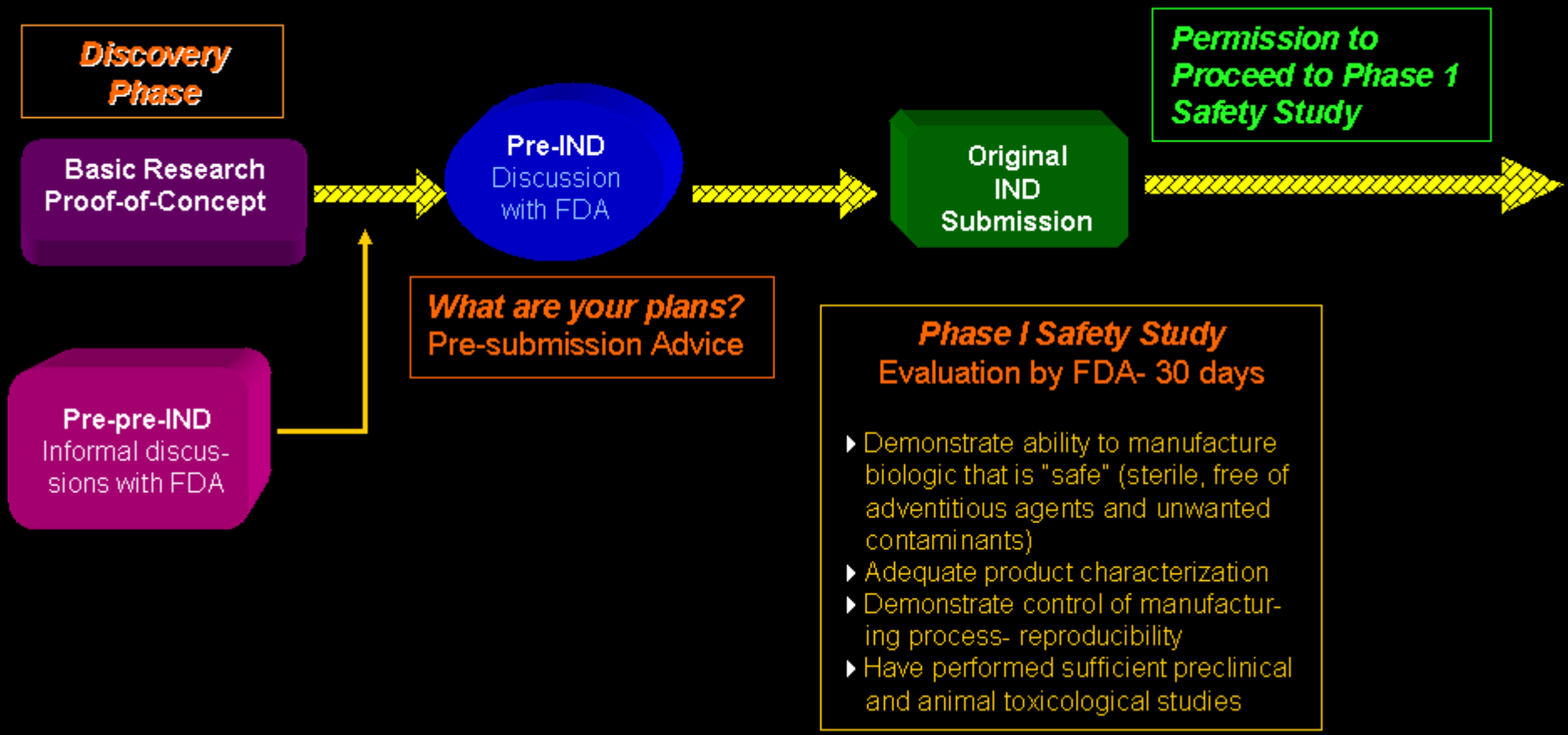
Regulatory Approach to Evaluating Human Stem Cell Therapies

- The review of Investigative New Drug Applications (INDs) that involve human stem cell products will be based on the best available science.
- When appropriate, CBER will seek input from its relevant advisory committees.
- CBER encourages early interactions between itself and sponsors as necessary in order to facilitate an efficient and effective product review process.

Helpful Hints

- When in doubt or unsure about an issue, seek Agency advice.
- For novel investigational products or the uninitiated sponsor, take advantage of the pre-IND meeting opportunity to seek Agency guidance and advice that reflects “current thinking”.
- Don’t delay addressing critical tasks until the 11th-hour.
- Consider your interaction with the Agency to be a partnership that will assist you in meeting regulatory requirements for demonstrating safety and efficacy.

Regulatory Roadmap: Phase 1 Clinical Trial



References for the Regulatory Process for the Office of Cellular, Tissue and Gene Therapies (OCTGT)

References for the Regulatory Process

GENERAL INFORMATION AND REFERENCES

OCTGT organization, mailing address, and contact numbers:

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Cellular Tissue, and Gene Therapies
Document Control Center, HFM-99, Suite 200N
1401 Rockville Pike Rockville, MD 20852-1448
Phone Number: 301-827-5102
Fax Number: 301-827-9796

http://www.fda.gov/cber/genadmin/octgtprocess.htm

Selected Relevant Guidance Documents Supporting Regulatory Review of Stem Cell-Based Therapies

- TISSUE ACTION PLAN: FDA Approach to the Regulation of Cellular and Tissue-Based Products- http://www.fda.gov/cber/tissue
  - Guidance for Industry: INDs – Approaches to Complying with cGMP During Phase 1 **– January 2006** http://www.fda.gov/cber/gdlns/indcgmp.pdf
  - Draft Guidance for Reviewers: Instructions and Template for Chemistry, Manufacturing, and Control (CMC) Reviewers of Human Somatic Cell Therapy Investigational New Drug Applications (INDs) - **8/15/2003** http://www.fda.gov/cber/gdlns/cmcsomcell.pdf
  - Final Rule: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) - **5/20/2004** http://www.fda.gov/cber/gdlns/tissdonor.pdf
  - Final Rule: Current Good Tissue Practice for Human Cell, Tissue and Cell and Tissue-Based Product Establishments; Inspection and Enforcement **11/24/2004** http://www.fda.gov/cber/rules/gtp.pdf
  - Guidance for Human Somatic Cell Therapy and Gene Therapy- **3/30/1998** http://www.fda.gov/cber/gdlns/somgene.pdf

Selected Relevant Guidance Documents Supporting Regulatory Review of Stem Cell-Based Therapies

- TISSUE ACTION PLAN: FDA Approach to the Regulation of Cellular and Tissue-Based Products- http://www.fda.gov/cber/tissue (cont.)
  - ICH Guidance on Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin - **9/24/1998** http://www.fda.gov/cber/gdlns/virsafe.pdf
  - Draft Points to Consider in the Characterization of Cell Lines Used to Produce Biologicals (1993) - **7/12/1993** http://www.fda.gov/cber/gdlns/ptccell.pdf
  - Guidance for Human Somatic Cell Therapy and Gene Therapy- **3/30/1998** http://www.fda.gov/cber/gdlns/somgene.pdf
  - Guidance For the Submission of Chemistry, Manufacturing and Controls Information and Establishment Description for Autologous Somatic Cell Therapy Products - **1/10/1997** http://www.fda.gov/cber/gdlns/xvcmc.txt

Contacting the Center for Biologics

CBER Contact Information

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- 301-827-1800 (Local or Outside U.S.)
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  - Consumers – Health Care Professionals: OCTMA@CBER.FDA.GOV
  - Manufacturers – Regulated Industry: MATT@CBER.FDA.GOV
- CBER Regulatory and Guidance Documents on the Internet at: http://www.fda.gov/cber/guidelines.htm