



Stem Cell-based Therapies: FDA Regulatory Perspectives

Deborah A. Hursh, Ph.D.

**Office of Cellular, Tissue and Gene Therapies,
Division of Cellular and Gene Therapies / FDA**

Phone: (301) 827-0670

E-Mail: deborah.hursh@fda.hhs.gov

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Stem Cell Therapeutics
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CFR Regulation of Cell Therapy

- Federal Food, Drug and Cosmetic Act
- Public Health Service Act, Section 351
 - Premarket approval
- Public Health Service Act, Section 361
 - Control of infectious disease
 - 21 CFR Part 1271-FDA Human Tissue Regulations
- Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products, Oct. 14, 1993

Regulation of Cell Therapy is not new to CFR

CBER Public Interactions

● Advisory Committee Meetings

- July 2000-Stem cell-derived products for Neurological Disorders
- March 2008-Considerations for Safety Testing for Cellular Therapy Products Derived From Human Embryonic Stem Cells
 - Inappropriate Differentiation, Tumorigenicity
 - Preclinical safety assessment
 - Product Characterization
 - Characteristics related to safety
 - Clinical Trial Design
 - Monitoring the fate of infused cells
 - <http://www.fda.gov/ohrms/dockets/ac/cber08.html#CellularTissueGeneTherapies>

● Interactions with Stakeholders

- Stem Cell and Regenerative Medicine Groups: NIH, ISSCR, CIRM
- AATB, ISCT, BIO
- Patient Groups

Stem Cell-based Products: Considerations for Safety Evaluation

- **Properties of stem cell products**

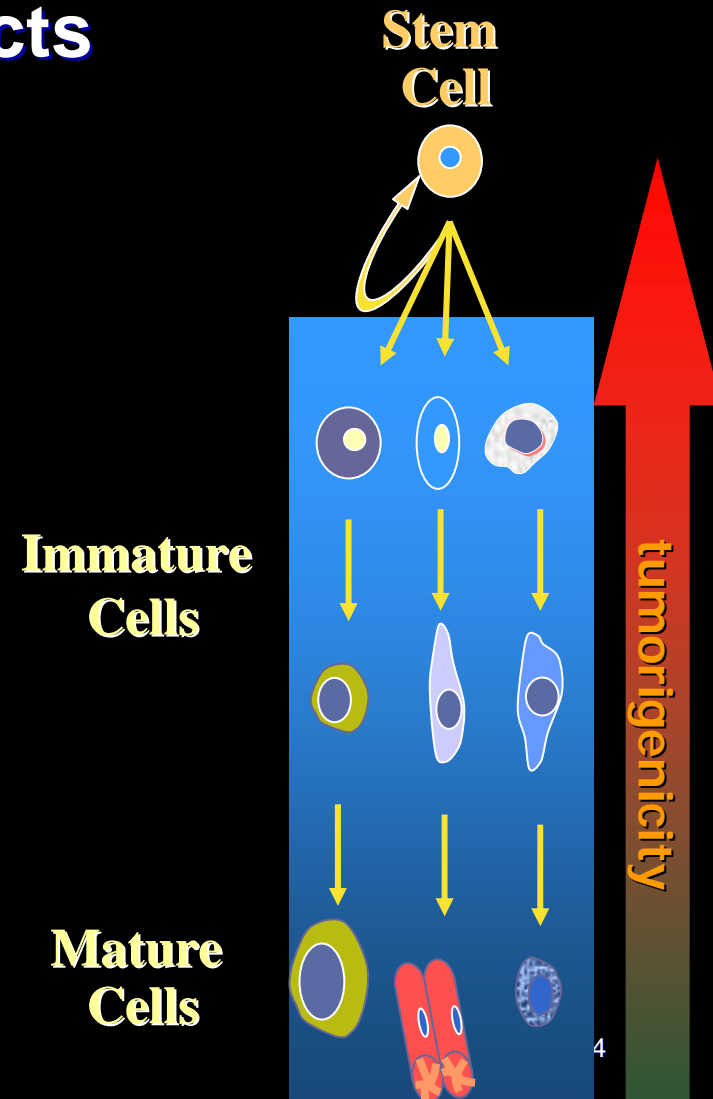
- Heterogeneous mixture
- Persistence
- Pluripotency

- **Safety Evaluation**

- Inappropriate differentiation
 - Tumorigenicity
 - Ectopic tissue formation
- Migration

- **Anatomic constraints**

- Enclosed space (eg IC vs. IV administration)



What about iPS cells?

- Same rules and recommendations apply, but...
- iPS cells reprogrammed using gene transfer via vectored delivery mechanisms (i.e. retrovirus, adenovirus, plasmid) would be considered gene therapy
 - --FDA review will include assessment of risks associated with gene delivery
 - --NIH/OBA/RAC review of scientific and ethical considerations of proposed clinical trial

Developing a Stem Cell-Based Product: Source Controls

- Evaluating Human Stem Cell Sources
 - Appropriate screening / testing of donor and/or tissue for communicable disease: **21 CFR 1271, Subpart C: Donor Eligibility Final Rule**
 - Testing of Master Cell bank/Working Cell bank for adventitious agents
 - Intrinsic safety concerns, based on cell source or cell history
 - **Molecular genetic analysis for selected disorders**

Control of infectious agents

- **Screening/Testing the donor of a manipulated cell product will not control transmission of all infectious agents**
 - Diseases with lag times (HIV)
 - Infectious agents not predicted
 - Infectious agents introduced in manufacturing/processing
 - Animal-derived ancillary products
 - Infectious material from personnel, cross contamination
 - Intermediate manufacturing steps (Cell Banks)

Requirements for cell bank testing: 21CFR 610.18

- Cytogenetic characteristics and tumorigenicity
- Growth characteristics and life potential
- Presence of detectable microbial agents

Product Characterization

- Detect cells with undesired characteristics
 - Minimize undifferentiated stem cells
- Identify characteristics that predict safety and clinical effectiveness
 - in-process assays and lot release
- Ensure that products administered to patients are as safe as possible
 - current limitations in scientific knowledge

Preclinical Studies: Proof of Concept

- Perform studies in animal models of human disease
 - Results serve to support a rationale for conducting a clinical trial
 - Reflect the proposed clinical indication as closely as possible
 - Provide information concerning feasibility
 - Facilitate route of administration optimization
 - Permit measurements of bioactivity/safety endpoints
 - Analyze dose-response relationship between cells and an activity or safety outcome

Preclinical Studies: Toxicological Assessment

Animal Testing: Comprehensive examination

- Implant site reaction
- Inflammatory response in target/non-target tissue
- Host immune response
- Morphologic alterations in either target/non-target tissues

Preclinical Studies: Toxicological Assessment

Animal Testing: Comprehensive examination

- Cell survival post transplantation
- Cell migration/cell homing
- Cellular fate-plasticity: differentiation, trans-differentiation, fusion
- Host tissue integration
- Tumorigenicity or ectopic tissue
 - Hyperplastic or unregulated growth

Preclinical Studies: Design

- POC studies in animal model of disease
- Toxicology studies in healthy animals
- Hybrid POC-toxicology study design: i.e. if pathophysiological conditions may exert effects on cells
 - Incorporate activity & toxicity endpoints in an animal model of disease
 - Morphological vs. functional comparison/ correlation
 - Understand abilities & limitations of model(s) used

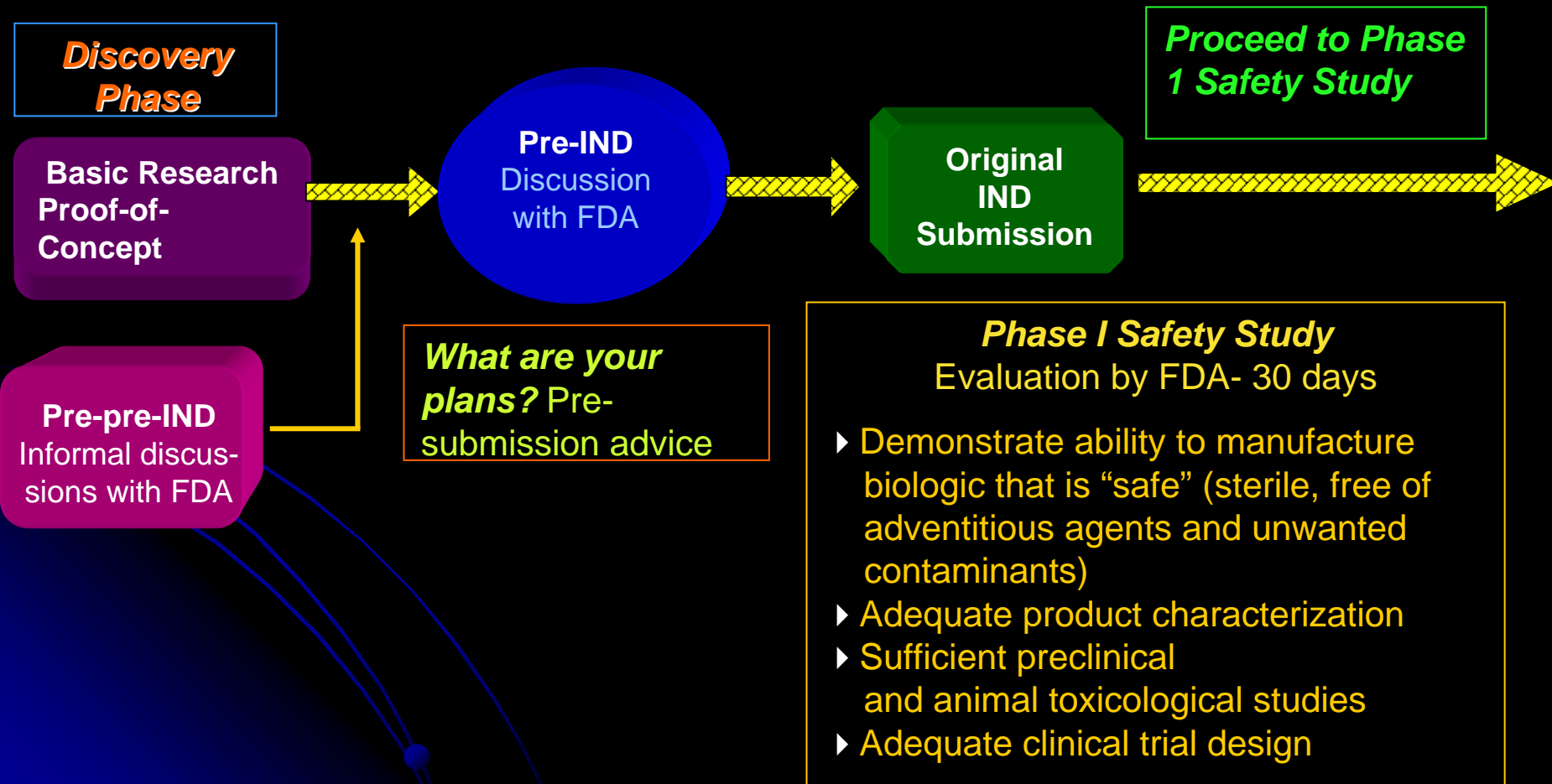
Animal model considerations:

- Pathophysiology and allometric scaling
 - Comparative to human
- Immune status
 - Immune tolerance to human cells...or use of analogous cells from animals
- Site/route of administration
- Absolute number of undesired cells, vs. percentage in the final product
- Number of animals for statistically valid evaluation of potentially rare adverse events
- Duration of study
- Appropriate monitoring
 - Clinical chemistry
 - Biopsy
 - Imaging
 - Other non-invasive studies

Clinical Trial Design

- Rationale
 - Risk (teratoma) vs. benefit (little experience)
 - Justified by particularly strong preclinical proof-of concept
- Case-by-case consideration of proposed therapeutic trials
 - Adequate product characterization, preclinical safety and proof-of-concept testing
 - Appropriate trial design
 - Doses/dose escalation
 - Patient monitoring

Regulatory Roadmap: Investigational New Drug (IND) Application-Phase 1 Clinical Trial



Team Approach to Regulation of Cell Therapy Products

- **Review Team**

- Product
- Clinical
- Pharm-tox
- Statistician
- Project Manager

- **CDER Research/Review Model**

- Scientists / Clinicians: researcher-reviewers and full-time review staff

Our Thinking Process

Guidance for Industry: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs)
(April 2008)

<http://www.fda.gov/cber/gdlns/cmcsomcell.htm>

Goals of research and FDA do not conflict

- Know how to reproducibly make your progenitor cells
- Know what other cell types exist in your preparation
- Know your cells are stable in genotype and phenotype
- Know your cells have an activity in your model system
- Design therapies to help patients

Contacting the Center for Biologics

CBER CONTACT INFORMATION

- ▶ **PHONE:** 1-800-835-4709 (Within U.S.)
301-827-1800 (Local or Outside U.S.)
- ▶ **INTERNET:** <http://www.fda.gov/cber>
- ▶ **Send e-mail to:**
 - Consumers – Health Care Professionals: OCTMA@CBER.FDA.GOV
 - Manufacturers – Regulated Industry: MATT@CBER.FDA.GOV
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