FDA Oversight of Cell Therapy Clinical Trials

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FDA Organization

- Office of the Commissioner
  - Office of Combination Products
- CBER (Center for Biologics Evaluation and Research): vaccines, blood and blood products, human tissue/tissue products for transplantation, cell therapy, gene therapy, donor screening tests for blood and tissue safety, devices
- CDRH (Center for Devices and Radiological Health): devices for treatment, implants, diagnostic devices
- CDER (Center for Drug Evaluation and Research): drugs, monoclonal antibodies, therapeutic proteins
- CVM
- CFSAN
- NCTR
OCTGT Products

- Cellular therapies
- Tumor vaccines and immunotherapy
- Gene therapies
- Tissue and tissue based products
- Xenotransplantation products
- Combination products
- Devices used for cells/tissues
- Donor screening tests (for use with cadaveric blood samples)
The “Tissue Rules”  
(21 CFR 1271, Effective May 25, 2005)

<table>
<thead>
<tr>
<th>Tissue Rule</th>
<th>Issues Addressed</th>
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<td>Establishment Registration and Listing</td>
<td>Applicability: types and uses of products that will be regulated by these rules; requirements for registering and listing products</td>
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<tr>
<td>Donor Eligibility</td>
<td>Requirements for donor screening and testing for “relevant communicable disease agents and diseases”</td>
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<tr>
<td>Current Good Tissue Practice (CGTP)</td>
<td>Manufacturing to ensure that HCT/Ps do not contain communicable disease agents; reporting; inspections</td>
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These three rules form the platform for regulation of all human cells, tissues, and cellular and tissue-based products (HCT/Ps).

For certain HCT/Ps ("361 HCT/Ps"), these regulations comprise the sole regulatory requirements.

For HCT/Ps regulated as drugs, devices, and/or biological products, the new tissue regulations supplement other requirements (GMP, QSR).
Stem Cell-Based Products

Fit regulatory definitions of the following:

- Human cells, tissues, or cellular and tissue based products (HCT/P) (21 CFR 1271.3(d))
- Biologics (PHS Act)
- Drugs (FDC Act)
- Cell therapy
- Gene therapy- when genetic material is transferred to cells ex vivo
Evolution of Stem Cell Field

- Cell therapy and gene therapy products—and therefore stem cell products—do not lend themselves to a “one size fits all” concept of product development and regulation.

- Regulations set framework of criteria that must be fulfilled: safety, identity, purity, potency, and clinical efficacy.

- Flexibility in how to fulfill the criteria.
Examples of Safety Concerns for Stem Cells

- Defining the intended mode of action
- Characterization of the product, including potency
- Cell differentiation to undesired cell types
- Cell migration/trafficking to nontarget site(s)
- Potential uncontrolled cell proliferation or tumorigenicity
- Immunogenicity
- Graft-vs-host effects
- Interactions with devices, other tissues or drugs in vivo
- For gene-modified cells
  - Potential uncontrolled biological activity of the transgene
  - Alteration of expression of the nontransgenes
  - Insertional mutagenesis
# FDA Review Team

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<thead>
<tr>
<th>REVIEW OFFICE</th>
<th>CBER</th>
<th>FDA</th>
<th>OUTSIDE CONSULTANT</th>
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<tr>
<td>Project Manager</td>
<td>Product Quality</td>
<td>Scientific Expert</td>
<td>Patient Advocate</td>
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<tr>
<td>Pharm/Tox</td>
<td>Epidemiology</td>
<td>Product expert</td>
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<tr>
<td>Clinical</td>
<td>Statistics</td>
<td>Clinical specialist</td>
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<tr>
<td>CMC</td>
<td>Compliance</td>
<td>Methodology expert</td>
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- **Basic Review Team**
- **Extended Review Team**

- **Potential Consults or Collaborators**
  - Policy Expert
  - Scientific Expert (SGE)
  - Orphan products
  - Ethicist
  - Animal rule

- **Potential Consults**
  - Advisory Committee

- **FDA**
  - Scientific Expert
  - Product expert
  - Clinical specialist
  - Methodology expert
Examples of CMC Issues

- Controls to prevent transmission of infection from the donor or introduction of infectious agents during cell processing
  - Donor Testing and screening for relevant communicable diseases
    - Autologous donors recommended but not required
    - Allogeneic donors must comply with 21 CFR 1271 Subpart C
      - HCT/P donor screening is medical history interview, physical assessment and medical record review
      - HCT/P donors are tested using FDA approved or cleared donor screening tests
  - Cell banks- adventitious agent testing & characterization
  - If mouse feeder layers used- test for the presence of murine viruses (and is a xenotransplantation product)
  - Components, reagents, materials qualification
Examples of CMC Issues- 2

- Account for and control donor to donor variability
- Intrinsic safety concerns, based on cell source or history
- Adequate characterization of the product
  - Identity, purity, potency
  - Additional characterization
- System for product tracking and labeling
  - critical for patient specific products
- Stability of product and or cell line
  - number of passages/ doublings over time
  - maintain desired differentiation properties
  - karyotypic alterations
- Product comparability for manufacturing changes
Examples of Preclinical Issues

- Scientific basis for conducting clinical trial
- Data to recommend initial safe dose & dose escalation scheme in humans
- Proof of Concept Studies in relevant animal models
- Toxicology Studies in relevant animal species
  - Identify, characterize, quantify the potential local and systemic toxicities
Examples of Clinical Issues

- Collection procedure
  - Standard medical practice? Special instrument or kit?
- Optimal dose and administration
  - Starting dose level/dose escalation scheme
  - Route of administration
  - Dose schedule
- Define appropriate patient population
- If immunosuppression will be used:
  - Is the dose-schedule justified?
  - Long-term vs short term
  - Single drug vs a combination regimen
- Safety Monitoring plans
- Safety Reporting requirements
- Pediatric issues
Administration of Stem Cell Products

- Delivery of stem cells to certain anatomic locations may require novel procedures and/or novel delivery devices
  - This needs to be considered early
- Cells delivered by certain devices (i.e. catheter) will be a Combination Product
  - Cells under Biologics/Drug regulations and Device under Device regulations (see 21 CFR 3.2(e))
  - Early consultation with FDA, and Device manufacturer, about regulatory aspects
- Compatibility of cells with the device
- Preclinical testing of cells and device
- Delivery procedure used during clinical trial and beyond
  - Training of clinical investigators
Outstanding Needs for the Field

- Standardized reporting/publication of results
- Technology to enable validated assays for enhanced product characterization and testing
- Biologically relevant animal species/models that will provide useful information about safety of the product
- Technology to assess biodistribution and fate of the product in patients
- Data regarding optimal timing and methods for stem cell delivery
Scientific Advice from the FDA

- Provide advice in response to specific queries
- In person or by teleconference
- Written minutes for formal meetings
- No fee
CBER Outreach to Stakeholders

- Advisory Committees
- Regulations
- Guidance Documents
- Standards Activities
- Workshops
- Liaison Meetings
- International Harmonization
Public Discussions of the Issues

- Nov 9 2009 NIH/JDRF/FDA Workshop: Next Generation Beta-Cell Transplantation
- Oct 27 2009 FDA/NCI Workshop: Therapeutic Cancer Vaccines Considerations for Early Phase Clinical Trials Based on Lessons Learned from Phase III
- May 14 2009 CTGTAC: Animal Models for Porcine Xenotransplantation Products Intended to Treat Type 1 Diabetes or Acute Liver Failure
- May 15 2009 CTGTAC: Products Intended to Repair or Replace Knee Cartilage
- Mar 13 2009 FDA/NIH/CIBMTR/ASBMT Workshop: Clinical Trials Endpoints for Acute Graft-Versus-Host Disease After Allogeneic Hematopoietic Stem Cell Transplantation
- April 10 2008 CTGTAC: Safety of Cell Therapies Derived from Human Embryonic Stem Cells
- Topics prior to 2008:
  - Cellular Replacement Therapies for Neurological Disorders
  - Placental/Umbilical Cord Blood For Hematopoietic Reconstitution
  - Allogeneic Pancreatic Islets for Type 1 Diabetes
  - Cellular Products for the Treatment of Cardiac Disease
  - Cellular Products for Joint Surface Repair
  - In Vitro Analyses of Cell/Scaffold Products
  - Insertional Mutagenesis by Retroviral Vectors
Use of Consensus Standards by Federal Agencies

- Codified in the National Technology Transfer and Advancement Act of 1995
  - Implementation defined by FDA Policy
- Standards may be referred to in FDA Guidance and Regulation
Potential Benefits of Standards Use

- Facilitate the development and maintenance of guidance
- Address issues not covered by FDA Guidance
- Facilitate product design
- Improve time to market
- Leverage industry efforts
- May lead to international harmonization
Standards Examples:

- ASTM F2386 Standard Guide for the Preservation of Tissue Engineered Products
- ASTM F2315 Standard Guide for Immobilization or Encapsulation of Living Cells or Tissue in Alginate Gels
- ATCC ASN-0002 Authentication of Human Cell Lines: Standardization of STR Profiling*
- AMII/ISO 13022 Tissue Safety*
- ISO 11238 Identification of Medicinal Products Structures and Controlled Vocabularies for Substances and Ingredients*
As an emerging product area, cell and gene therapies are prime area for prospective harmonization and convergence of regulatory approaches

- International Conference on Harmonisation (ICH)
- FDA-EMA ATMP “Cluster”
- Regulatory exchanges
ICH Gene Therapy Discussion Group (GTDG)

- Monitor emerging scientific issues
- Proactively set out principles that may have a beneficial impact on harmonization
- Ensure that the outcomes of the GTDG are well understood and widely disseminated
  - Public ICH web page
  - Public communications papers
  - Public press statements from the ICH SC
  - Public ICH workshops
Published ICH Considerations

- General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors, 10/2006
- Oncolytic Viruses, 11/2008
- Viral/Vector Shedding, 6/2009
FDA-EMA ATMP “Cluster”

- Formal cooperation and confidentiality arrangement between FDA and European Medicines Agency (EMA) for pharmaceuticals initiated 9/03; extended 9/05 to 9/2010
- Over time, “clusters” of specific areas of interest were developed for more targeted information exchanges
- With EMA product scope enlargement to include tissue engineering with cell and gene therapies (“advanced therapeutic medicinal products” – ATMPs), ATMP “cluster” initiated 2008
FDA-EMA ATMP “Cluster”

☐ Regular teleconferences to share thinking on regulatory approaches, both general and specific issues
☐ Information sharing on draft documents
☐ Engage reciprocally in workshops and advisory committees, working parties
OCTGT has hosted on limited basis regulatory colleagues, Fall of 2009:
- EMA ATMP expert
- Japan Pharmaceutical and Medical Device Agency (PMDA) cell therapy expert
- Additional exchanges planned for Fall of 2010

OCTGT experts routinely respond to foreign regulatory inquiries, calls for assistance, both through written communication, face-to-face exchanges, presentations at international fora.
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