Stem Cell-based Therapies: FDA Regulatory Perspectives

Stem Cell Translation: Strategies, Best Practices, and Regulatory Considerations

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Outline

- Regulatory framework applicable to stem cells
- Challenges in product development
- Source control
- Manufacturing
- Lot release
- Potency
- Stability
- Comparability
- OCTGT resources and contact information
Regulatory Framework: 3-Tiered System

- **Statutes (Laws):**
  Passed by Congress and signed by the President
  - Food, Drug & Cosmetic Act (FD&C Act)
  - Public Health Service Act (PHS Act)

- **Regulations (details of the law):**
  Written by FDA and approved by the Executive Branch
  - 21 CFR (Code of Federal Regulations)
    - 300 series = new drugs, 600 series = biologics, 800 series = devices
    - 1271 series = tissues

- **Guidance (the FDA’s interpretation of the Regulations):**
  Written and approved within FDA
  - Advice non-binding on FDA or sponsor
Stem Cell Products

• Fit regulatory definitions of the following:
  - Human cells, tissues, or cellular and tissue based products (HCT/P) (21 CFR 1271.3(d))
    • Section 361 Public Health Service Act, infectious disease
  - Biologics (21 CFR 600)
    • Section 351 Public Health Service Act, premarket approval, safety and effectiveness
  - Drugs (21 CFR 200)
    • Food Drug and Cosmetic Act
  - Cell therapy
  - Gene therapy- when genetic material is transferred to cells ex vivo
iPS Cells Fit Within Existing Regulatory Framework

• Reprogrammed using gene transfer via vectored delivery mechanisms (i.e. retrovirus, adenovirus, plasmid)
  – Would be considered a gene therapy product
  – FDA review will include assessment of risks associated with gene delivery
  – NIH/OBA/RAC review of scientific and ethical considerations of proposed clinical trial
Cell-based Products: Considerations for Safety Evaluation

- Properties of stem cell products
  - Heterogeneous mixture
  - Persistence
- Safety Evaluation
  - Pluripotency
  - Inappropriate differentiation
    - Tumorigenicity
    - Ectopic tissue formation
  - Migration
- Anatomic constraints
  - Enclosed space (eg IC vs. IV administration)
Trends in Cell Therapy

- Novel sources of adult stem cells
  - Placental and amniotic membrane, adipose derived
- New Methods of iPS induction
  - Episomal plasmids
  - Chemical reprogramming
- Cell products to induce immune tolerance
- Cells encapsulated in a biomaterial
- Tissue engineering constructs
- Cells administered using a Device
OCTGT Approach

• 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, needed for diverse and novel products in evolving fields.
FDA Review of Safety and Effectiveness

- FDA review is **product-based**
  - Parallels prudent product development
  - Early interactions with sponsors facilitate effective product development
  - Detailed manufacturing information is needed during product development
  - Preclinical studies designed to support the use of specific products
  - Clinical trial design supported by manufacturing, preclinical data
Developing a Stem Cell-Based Product: Chemistry, Manufacturing & Controls

- Source Control: All Components Used for Product Manufacture
  - Potential for adventitious agents
    - Cells
    - Reagents used in manufacture
- Manufacturing Process (in vitro culture)
  - In-Process Testing
- Product Testing
  - Specifications and lot release
  - Tests robust enough to monitor product stability, manufacturing changes
Source Control: Donor Testing

• 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
    – RCDAD: relevant communicable diseases agents or diseases
      » All donors: HIV 1 & 2, HBV, HCV, Treponema pallidum
      » Viable Leucocyte-rich cells: additional tests for HTLV 1 & 2, CMV
  • Applies to all tissue recovered after 5-25-05
Source Control-Cell Banks

- **Cell banks-**
  - Master Cell Banks
    - Adventitious agent testing: HIV 1&2, HTLV 1 &2, CMV, EBV, B19, HCV, and HBV, in vivo, in vitro virus testing (inapparent virus testing). Other adventitious agents based on reagents (e.g. fetal calf serum: bovine viruses, porcine trypsin:porcine viruses)
    - Sterility (bacteria, mycoplasma, fungus)
    - Characterization-viability, identity by molecular markers that define cells (e.g. cell surface markers), purity
    - Stability of cell line
      - number of passages/ doublings over time
      - maintain intrinsic properties
      - karyotypic alterations
    - Retroviral testing, when required
    - Tumorigenicity, when required
  - Working Cell Bank
    - in vitro virus testing (inapparent virus testing)
    - viability, purity, sterility, mycoplasma and endotoxin
Source Control: Materials Qualification

Qualify your reagents

• Ensure that reagents will perform as desired in the manufacturing process
• Document reagent quality (in-house testing or COA)
• Ensure clinical quality reagents (safety, purity, potency)
  What about when it says “For research purposes only, not for human use” - you need to establish that these are safe, which may mean additional testing (sterility, endotoxin, etc.)

Of particular concern:

• Human serum or serum proteins - use a licensed source
• Affinity purified proteins – adventitious agents in antibodies
• Cell or tissue extracts – possible viral contaminants

Availability

– What is your plan if sole vendor of a critical reagent or equipment ends production?
Cell Culture = Manufacturing

• Control of the Manufacturing Process
  – Applies to both the manufacturing process and the facilities
  – Control of both product & process
• Standardization of processing procedures
• Establishing critical manufacturing process controls
  • In-process controls
• Reproducibility/Consistency of Product Lots
  – lot to lot reproducibility – in-process and lot release specifications
  – Important in addressing issues of proper dosing needed to achieve efficacy
Special considerations for manufacturing

- How tissue/cells are collected and processed
- Autologous/patient-specific products raise importance of tracking and labeling throughout
- Open versus closed system
- Lengthy culture periods
- How you manipulate the cells (FACS, immuno-magnetic separation, adherence, etc.)
- Cell feeder layers
- Final formulation
- Terminally differentiated vs progenitor population
- Shelf life may affect manufacturing logistics, including how the therapy is given to the patient
- Product quality issues may affect clinical safety and effectiveness of the therapy
Product Specifications: what they do for you

• Demonstrate Product Consistency
• Control purity and impurity profiles of the final product.
  – Identify characteristics that predict safety and clinical effectiveness
  – Detect cells with undesired characteristics
• Demonstrate control of the Manufacturing Process.
• Ensure product integrity and stability.
• Identify undesirable product parameters that anticipate adverse events.
Biologic Product Specifications: Codified in Regulation (CFR Specifications)

Product should be characterized with reference to its:

- Safety (610.11, 610.12, 610.30, 610.40)
  - Sterility (bacterial and fungal sterility)
  - Endotoxin
  - Mycoplasma
  - Tests for opportunistic viruses
- Purity (610.13)
  - Free of extraneous materials
- Identity (610.14)
  - Specific test to distinguish it from others
- Constituent Materials (610.15)
  - Ingredients, Preservatives, Diluents, Adjuvants, Excipients
- Potency (610.10)
  - Assay for biological function
Product Quality Testing

• In-process testing
  – Should provide meaningful insight into process and product quality
  – Should contribute to the safety and quality of the final product

• Final product testing (Lot release)
  – Needs to be performed on the final product, not intermediate
  – Establish proper specifications
    • Should be based on experience and may change with new data
Who decides on lot release specifications used to define a product?

Some lot release specifications are dictated by regulations:
• Sterility – 14 days by either CFR or USP method, or equivalent test method

Some are based on recommendations in guidance documents:
• Viability of at least 70% for cell therapies

However, most lot release specifications are established by the sponsor and justified based on their manufacturing experience and clinical need—sponsor is responsible.
• Identity/product characterization
• Potency
• Dose/volume/concentration
• Purity/level of contaminants
Identity testing: in-process and final product lot release considerations

How many markers should you use?
• Recommend more than one to define your cell type of interest
• If multiple cell types, or cells at different stages of differentiation are expected to be present, we suggest you include markers that will identify the major contributing populations (for identity or purity)

What kind of measures can be used for identity?
• Morphology (best if quantitative)
• Cell surface markers (FACS or ICC)
• Gene or protein arrays
• Other technologies
Challenges for testing cell therapy products

• Small lot size/limited sample volume
• Limited shelf life (due to cell viability)
• Limited availability of starting material for process, product, and test method development
• Lack of reference standards
• Patient to patient variability and cellular heterogeneity
• Multiple potential mechanisms of action
Special Challenges: Potency

21 CFR 600.3(s), 21 CFR 610.10, ICH Q6B

• Measured bio-activity: ability or capacity to achieve intended effect
  – **Direct measure of biological activity**
    • In vivo or in vitro assay
  – **Indirect measure of biological activity**
    • Analytical assay methods: non-bioassay method directly correlated to a unique and specific activity of the product
  – **Multiple Assay Approach (Assay Matrix)**
    • May not be possible or feasible to develop a single assay that encompasses all elements of an acceptable potency assay
• A well-qualified potency assay is required by Phase III
• Relate data to appropriate Reference Standard
• A US regulatory requirement for biologics
Purpose of Potency Testing

- Demonstrate that each product “lot” manufactured has biological activity within established limits
- Demonstrate product consistency
  - Lot to lot, patient to patient
- Demonstrate product stability
- Aid interpretation of clinical data

➢ Don’t wait till the end of Phase II to think about this!
Special Challenges: Stability Determination

21 CFR 312.23(a)(7)(ii), ICH Q5C

• Stability testing required in all phases of the IND
• Recommend a stability protocol and data for both:
  • In-process material
  • Final product
• Stability protocol should measure:
  – Product sterility
  – Identity
  – Purity
  – Potency
• Expiration dating should be based on real-time/real-temperature data
Stability and shipping studies in preparation for phase I

**Stability issues** - concerned mostly with viability, identity, sterility at this stage
- Does the product maintain its characteristics from end of manufacturing to patient administration?
- Proposed shelf life of cryopreserved intermediates and final product
- Expect a limited study, looking for stability indicating parameters

**Shipping** – concerned mostly with sterility, segregation and tracking, and viability.
- From collection site, or from one manufacturing site to another
- From manufacturing site to clinical site, or held for administration
- Expect limited study- demonstrate that the product is not adversely affected by the process of shipping/holding from one place to another.
Special Challenges: Comparability

- **Comparable**: a conclusion that products have highly similar quality attributes before and after a manufacturing change and that no adverse impact on the quality, safety or efficacy of the drug product occurred.
  - Not necessarily identical products

*From ICH Q5E Comparability Guidance*
Comparability: why change is not good

- Preclinical and clinical products need to be comparable
  - If your preclinical studies use analogous animal cells, what test methods can you use to show comparability of animal and human product?
- Manufacturing changes may affect product safety, purity, potency, clinical effectiveness
- The need to make changes may be unexpected
  - starting materials: reagents, cell bank
  - manufacturing site
- Products used to generate safety and efficacy data in clinical trials need to be comparable to licensed product

Need appropriate tests with capacity to detect and assess effects of changes
Summary

• Manufacturing, pre-clinical testing, and clinical trial design are all inter-related
• Safety is the primary concern, including reagents, cell banks, and devices
• Source control has stood the test of time to ensure safety
• Your process defines your product-make sure it is well developed and controlled
• Knowledge is power- know your product characteristics
• Potency, stability and comparability present special problems- address them early
• Call us if you have a question- it may save you time and money
OCTGT Resources & Contact Information

- **References for the Regulatory Process for OCTGT:**

- **Guidance Documents for Cell and Gene Therapies:**

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