Development of Regenerative Medicine Products: FDA Perspectives

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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)

- **Guidance (the FDA’s interpretation of the Regulations):**
  Written and approved within FDA
  - Advice non-binding on FDA or sponsor
What is and is not an HCT/P

**Regulated as HCT/Ps**
- Musculoskeletal tissue
- Skin
- Ocular tissue
- Human heart valves; vascular graft
- Dura mater
- Reproductive tissue/cells
- Hematopoietic stem/progenitor cells; other cellular therapies
- Combination products (e.g., cells or tissue + device)

**Not regulated as HCT/P’s**
- Vascularized human organs
- Minimally manipulated unrelated donor bone marrow
- Xenografts - separate regulatory pathway
- Blood and blood products - separate regulatory pathway
- Blood vessels recovered with organs and used for organ transplantation only
- Autologous cells recovered and used in same surgical procedure
HCT/Ps – Two Regulatory Tiers

Risk determines the level of regulation:

- **Tissue (“361 HCT/P”) – lower risk**
  - Section 361 of PHS Act
  - Premarket review and approval not required; Product regulated solely under Tissue Regulations to control communicable disease (21 CRF 1271)
  - The Establishment Registration, Donor Eligibility and Good Tissue Practice (GTP) final rules comprise 21 CFR Part 1271

- **Therapeutic (“351 HCT/P”) – higher risk**
  - Sections 351 & 361 of PHS Act, FD&C Act
  - Product regulated under Tissue Regulations and premarket review requirements (21 CFR Parts 1271, 600, 200, 312, 812)
  - Regulatory path: **Biologic** (IND/BLA) or **Device** (IDE/PMA)
Cellular Therapies

- Regulated as HCT/P and subject to 1271 regulations
- Regulated as drugs and biologics and subject to premarket review requirements
- Clinical trials require an Investigational New Drug Application (IND)
  - A formal document with defined structure and content
  - Purpose is to request exemption from premarketing requirements and to allow lawful shipment of drug for clinical investigation.
  - Regulations (21 CFR 312) outline requirements for:
    - Use of investigational drug
    - Submission of application to FDA
    - Review by FDA
Regulation of Cell Therapies Under the 1271 Tissue Rules

HCT/P’s regulated solely under section 361 of the PHS Act and 21 CFR Part 1271 ONLY IF ALL FOUR of the following are met:

- Minimally Manipulated: Relevant biologic characteristic(s) are not altered by processing.
- Homologous Use Only: The HCT/P performs the same basic function in the recipient as in the donor.
- Production of the HCT/P does not involve combination of cells with another article (with limited exceptions and on the condition that addition of the excepted article does not raise new clinical safety concerns).
- Does not have a systemic effect, is not dependent upon the metabolic activity of living cells for primary function: exceptions for (a) autologous use, (b) first- or second-degree blood relatives, or (c) reproductive use.
More than Minimal Manipulation

• Risk of adventitious virus introduction during manufacturing
  – Reagents
  – Operators
  – Environment

• Risk of alteration of biological properties
  – Manufacturing is a novel, non physiological microenvironment
Risk/Benefit Considerations

• Protect patients from unreasonable risk

• Case-by-case
  – Patient population
    • Age
    • Medical condition
    • Availability of other treatment
    • Previous experience with similar products
  – Clinical Trial Design
  – Preclinical Information
  – Product Characteristics and Characterization
Team Approach to Regulation of Regenerative Medicine Products

• Review Team
  – Product
  – Clinical
  – Pharm/Tox
  – Statistician
  – Regulatory Project Manager
  – Consult reviewer(s)

• CBER Research/Reviewer Model
  – Scientists/Clinicians: research-reviewers and full time review staff
Reviewer Expertise

• Training
  – Education/Experience
  – On-the job
    • Scientific and regulatory meetings
    • Mentoring
    • Internal working group
    • Career development
      – clinical service, laboratory and clinical research
• Research/Review model
  – Laboratory based review staff
  » ~ 50% review, 50% research
Phases of Investigational Studies
(21 CFR 312.21)

• Phase I Investigational Studies
  – Designed to evaluate safety and side effects
• Phase 2 Investigational Studies
  – Expanded safety; evaluates efficacy
• Phase 3 Investigational Studies
  – Emphasis efficacy, additional information on safety; expanded study
Interactions with FDA Throughout the Product Lifecycle

Product development is an iterative process, with frequent FDA and sponsor interaction.
Combination Product

• A product composed of different categories of regulated articles:
  – Device-biologic, biologic-drug, drug-device, biologic-drug-device (not biologic-biologic, etc)
• Both components are:
  – intended for use together
  – required to mediate the intended therapeutic effect
• Can be:
  – Physically or chemically combined
  – Co-packaged; or packaged separately but cross-labeled
• Guidance:
  – Early Development Considerations for Innovative Combination Products (2006):
    http://www.fda.gov/RegulatoryInformation/Guidances/ucm126050.htm
Determining Classification and Lead Review
Center for Combination Products

• Publically Available Resources
  – Meetings and workshops
  – Classification and Jurisdictional Information (FDA website):
    http://www.fda.gov/CombinationProducts/JurisdictionalInformation/default.htm

• Center Jurisdictional Officer
  – Informal jurisdictional inquiries

• Office of Combination Products (OCP)
  – OCP Jurisdictional Updates
  – Informal assignment requests
  – Request for Designation (RFD): classification and jurisdiction assignments made based on primary mode of action (PMOA) determination, inter-center agreements, most relevant expertise, and/or precedence
Cell-Device Combination Products Regulated by OCTGT

- Tissue-engineered and regenerative medicine products (TEMPs): Cell-scaffold constructs
  - Tissue repair and replacement:
  - Orthopedic, cardiovascular, wound healing, musculoskeletal, ophthalmologic, osteogenic ….. indications
  - Bioartificial metabolic support system:
    - Hepatic, urinary, renal ….. indications

- Cells (and other biologics) + delivery device (catheters, injection/spray devices, etc):
  - Cardiovascular, orthopedic, musculoskeletal, wound healing….. indications
Chemistry, Manufacturing, & Controls

- CMC= Product manufacturing and testing
- How do you make the product?
  - Processing and manufacturing
- What do you use to make the product?
  - Cell or tissue source
  - Vector or genetically modified cell if gene therapy
  - Reagents and components
  - Equipment
- Product Safety and Quality testing
- Product Stability
- Other controls- product container labels, tracking
- Product comparability (when applicable)
Product Characterization: Specifications-why you need them

- 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.
  - Quality Assurance/Quality Control Program
- Ensure product integrity and stability.
- Identify 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
Potency

• 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
• BLA: validated functional bioassay
• 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
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
Advice on Preparing For Pivotal Studies-Product

• Understand critical product characteristics & have the controls in place to maintain consistency
• Have meaningful potency assay in place
• Lock down procedures and acceptance criteria based on development experience
• Protocol for stability of Phase 3 material in place, based on earlier stability data
• Shipping qualification
Lot Release Specifications—are you there?

- Guidance: ICH Q6B, Q6A
- Step-wise approach:
  - Phase 1: safety, quality manufacture
  - Phase 2: safety, tightening specifications
  - Phase 3: safety, specifications defined
- BLA:
  - Validated assays
  - Statistical analyses
- Inability to understand critical product characteristics can impact ability to analyze clinical data
Pre-Clinical

• 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
Clinical: Early Phase Considerations

• Optimal dose and administration
  – Starting dose level/dose escalation scheme
  – Route of administration
  – Dose schedule

• Define appropriate patient population

• Staggering of dose escalation

• Safety Monitoring plans

• Safety Reporting requirements
Planning Later Phase Clinical Studies

• End of phase 2 meeting with FDA
  – Justify dose, regimen for phase 3
  – Preliminary safety profile established
  – Target population
    • Specific proposed indication
    • Assays required for eligibility
    • Prior therapy
  – Proposed control arm
  – Statistical considerations
  – Assessments
  – Preliminary evidence of activity/effect size

• Estimate patient effect size for phase 3 planning
  – Interpretation of time to events is problematic in single arm studies
    • Leads to over optimistic interpretation of effect size
Interactions with FDA Throughout the Product Lifecycle

Pre-IND/IDE Phase

IND/IDE Review Phase

Marketing Application Phase

Post-marketing Phase

Development

Pre-Clinical

IND/IDE Review

CLINICAL TRIALS

Ph I

Ph II

Ph III

BLA/PMA Review

Post Marketing

Pre Pre-IND/IDE Meeting (Informal)

Pre-IND/IDE Meeting

End of Ph 2 Meeting

Pre-BLA/PMA Meeting

Safety Meetings

30-day Review Clock

End of Ph 3 Meeting

Post BLA Meeting

Product development is an iterative process, with frequent FDA and sponsor interaction.
Legal Standard for New Drug Approval

• Adequate tests of safety under the conditions prescribed, recommended or suggested in labeling
• Substantial evidence of effectiveness under the conditions prescribed, recommended or suggested in labeling
• Manufacturing, processing and packing is adequate to assure identity, strength [potency], quality and purity

-- Section 505(d)
Examples of mechanisms for ensuring product safety and efficacy

- License application review
- Clinical data auditing and site inspections
- Pre-approval and biennial manufacturing facility inspections
- Appropriate product labeling
- Post marketing commitments and requirements
- Monitoring of adverse event and product deviation reporting
OCTGT Resources & Contact Information

- References for the Regulatory Process for OCTGT:

- Guidance Documents for Cell and Gene Therapies:

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