Assuring the Quality of Raw Materials used to Manufacture Cellular Products: Regulatory Considerations

Donald W. Fink, Jr., Ph.D.
Phone: (301) 827-5153
E-Mail: donald.fink@fda.hhs.gov
Office of Cellular, Tissue and Gene Therapies

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Products Regulated by CBER

OBRR

Blood Derivatives and Recombinant Analogues

Blood Components

Whole Blood

Devices

OVRR

Allergenic Extracts

Prophylactic Vaccines

OCTGT

Therapeutic Vaccines
Somatic
Cellular & Gene
Therapies

Devices
Tissues
Xenotransplantation

Raw Materials Quality Assurance for Cellular Product Manufacturing

- **Raw Materials: Defining the Scope**
- **CMC: Establishing Control of the Manufacture of an Investigational Cellular Product begins with Raw Materials**
- **Assessing Raw Material Quality: 3-Examples**
- **Real Life Challenges**

Defining Raw Materials used During Manufacture of a Cellular Product

- **Raw Material:**

  Any ingredient intended for use in the production of a biologic active pharmaceutical ingredient (BAPI) including source materials, starting materials, components, process aids and reagents.

  BAPI – Material originating from a biological manufacturing process intended to provide pharmacological activity or other direct effect for the cure, treatment, or prevention of disease.

Objectives of Chemistry, Manufacturing and Controls (CMC) for Cellular Products During Clinical Investigation

- Assure the manufacture of safe investigational products through implementation of stringent quality control measures
- Develop established manufacturing process that ensures reproducible, consistent manufacture of cellular product of defined quality suitable for commercial distribution.

Objectives of Chemistry, Manufacturing and Controls (CMC) for Cellular Products During Clinical Investigation

- Demonstrate capability of manufacturing process to reproducibly generate an investigational cellular product of defined quality intended for commercial distribution:
  -
  - Within and Between Clinical Trials
  - Throughout the entirety of clinical/product
  - development

Achieving CMC Objectives Begins with Control of Raw Materials Quality

- Manufacture of a cellular product of defined quality relies on thorough description, characterization, and testing that begins with source materials, reagents, ingredients and components used throughout the manufacturing process.

- Contingent upon developing a qualification program implemented during product development: applies to all raw materials used in production.

Example #1: Source Material

- Determining Donor Eligibility
  - Cellular products containing/consisting of human cells regulated as Human Cellular or Tissue-Based Product under 21 CFR Part 1271.
  - Principal Public Health/Regulatory Concern: preventing transmission of communicable disease.

Example #1: Source Material (cont)

- Donor Eligibility Testing
  - Cell donors to be screened/tested in a way that prevents introduction, transmission, or spread of communicable diseases (§1271.145)
  - §1271.3(r): (1) lists particular communicable disease agents/diseases (RCDADs) and (2) details when RCDADs may be added to the list to accommodate emerging infectious diseases.

Example #1: Source Material (cont)

- Donor Eligibility Testing
  - Testing performed in CLIA-certified/CMS-equivalent laboratories using FDA-licensed approved, cleared test kits on specimens obtained with 7-days before or after collection of cells/tissues.
  - ***Testing may be performed within up to 30-days of collection for peripheral blood stem/progenitor cells, bone marrow (not excepted under §1271.3[d][4]), or oocytes

Example #2: Reagents with Biological Activity

- Biological Reagent with Enzymatic Activity
  - Used during manufacturing process to prepare cellular product; may present inapparent risk.
  - Type of information requested for qualifying a biological reagent:
    - How is the biological reagent manufactured – purified from human/non-human source material or is an expression system involved (bacterial, mammalian, insect)?

Example #2: Reagents with Biological Activity (cont)

- Biological Reagent with Enzymatic Activity
  - Type of information requested for qualifying a biological reagent:
    - If reagent is a recombinant material, information about the banking/testing of cells used for protein expression and vector production is requested.
    - If the reagent is isolated by purification, are physical or affinity chromatography techniques used?

Example #2: Reagents with Biological Activity (cont)

- Biological Reagent with Enzymatic Activity
  - Type of information requested for qualifying a biological reagent:
    - Are bovine materials used either as a tissue source for the reagent or as a component of the expression system culture medium?
      - Identify specific bovine material; when is reagent used during manufacture of the cellular product.
      - Country of origin for source animals.
      - Age of animal used as bovine material source
      - Testing of reagent for bovine adventitious agents
      - Is the material identified as a specified risk material?

Example #3: Process Aid

- Immunopurification of Targeted Cell Phenotype
  - Antibody targeting cell surface, phenotype-specific marker to enrich for unique cell type; may present inapparent risks.
  - Type of information requested for qualification:
    - Antibody type: polyclonal or monoclonal / serum-sourced or derived from hybridomas
    - Method of purification: Protein A/G or antigen-affinity chromatography.
    - Evidence for use of viral inactivation/clearance steps during manufacture of cell selection antibody.

Raw Material Quality Assurance – Critical to IND Review Process

Phase 1 Clinical Trial Considerations

- Evaluation of information provided in an IND for a Phase 1 clinical study focuses on assuring patient safety.
- Proposed Phase 1 clinical study may not be allowed to proceed (clinical hold) if assessment is that the IND contains insufficient information to ascertain the risks to patients associated with the proposed investigation.

Raw Material Quality Assurance – Critical to IND Review Process

Phase 1 Clinical Trial: Some CMC Hold Items

- Absent, inadequate or incomplete information for:
  - "Source Material" – provenance and history not detailed.
  - Insufficient information provided for animal/human-derived reagents/components.
  - Inadequate demonstration of viral inactivation/clearance.
  - Lack of description, omission of results for adventitious agent safety testing for manufacturing process components.

Each of the above may be linked to raw materials

Raw Material Quality Assurance – Challenges

- Difficulty qualifying raw materials used during preclinical development for incorporation in the manufacture of clinical grade cellular product (labeled “for research use only”).
- Incomplete information available pertaining to donor eligibility; unable to obtain (e.g. IVF surplus embryos for derivation of embryonic stem cell lines cryopreserved prior to May 25, 2005).

Raw Material Quality Assurance – Challenges (cont)

- Previously unrecognized issue with respect to raw material quality arises midstream during clinical development.
- Impact of switching to higher quality reagents midstream during product development – conformance issues with respect to investigational clinical product.
- Uncertainty about the type and extent of testing expected for qualification of a raw material for use in manufacture of an investigational cellular product.

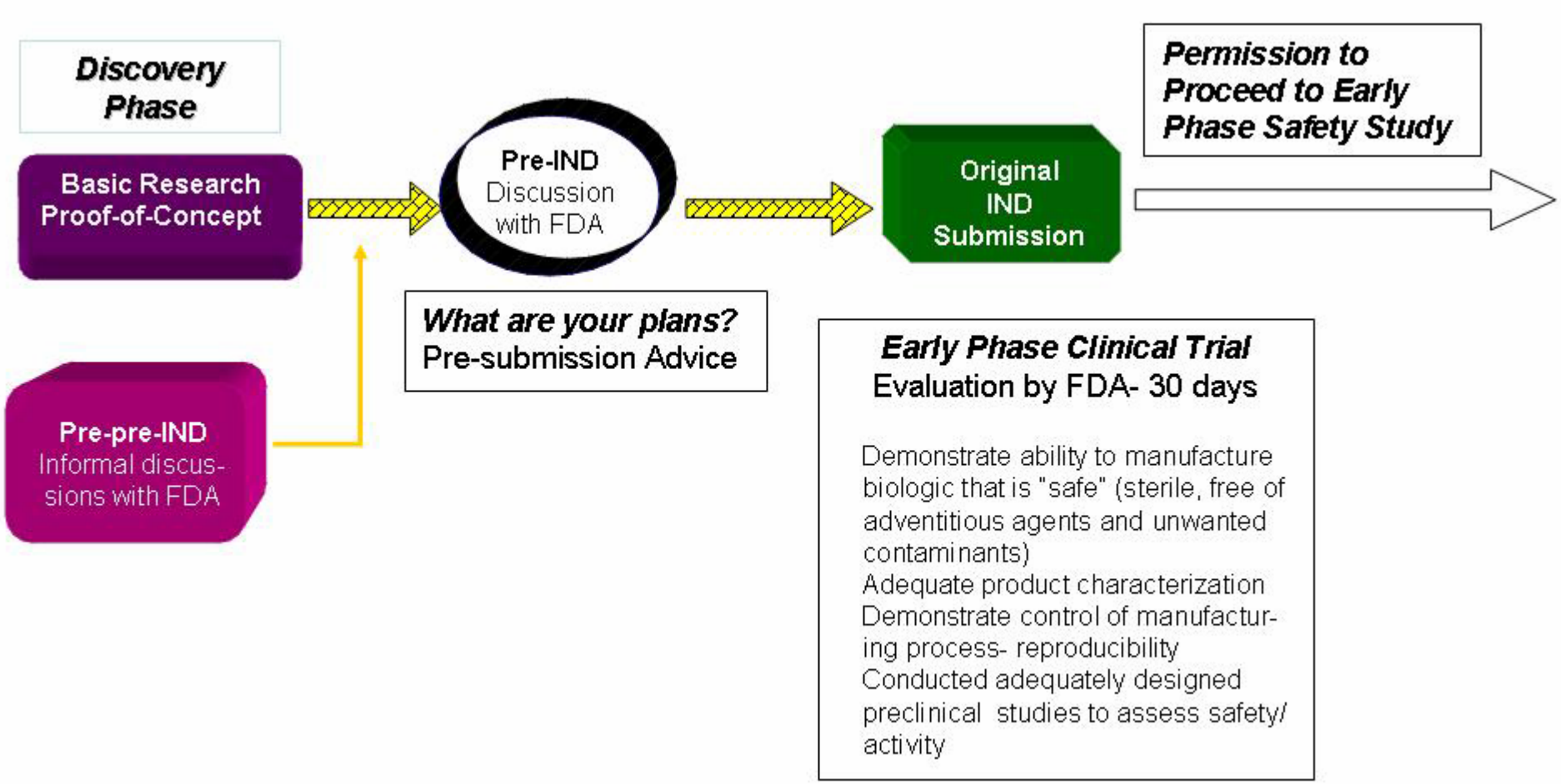
Raw Material Quality Assurance – Recap

- Achieving CMC objective of ensuring manufacture of a safe investigational product begins with control of raw materials quality
- Flexible regulatory approach is key: different type/ extent of information necessary depending on risk associated with biologic product class.
- Increasingly complex/novel platform technologies create greater, more varied number of product development issues.

Raw Material Quality Assurance – Recap

- Encourage performing risk-analysis for raw materials early to identify potential issues that could prove challenging during product development.
- Recommend consultation with CBER early in product development for current thinking regarding raw material quality assessment.
- Sponsors encouraged to contact CBER whenever considering making manufacturing change involving raw materials.

Regulatory Roadmap: Early Phase Clinical Trials



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 Regulatory Documents

- Guidance: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) - **02/27/2007** http://www.fda.gov/cber/gdlns/tissdonor.pdf
- Proposed Rule: Use of Materials Derived from Cattle in Medical Products Intended for Use in Humans and Drugs Intended for Use in Ruminants – **01-12-2007** http://www.fda.gov/cber/rules/catruminant.pdf
- Guidance for Industry: INDs – Approaches to Complying with cGMP During Phase 1 **– 01-12-2006** http://www.fda.gov/cber/gdlns/indcgmf.pdf
- Guidance for Industry and FDA Staff – Pharmacogenetic Tests and Genetic Tests for Heritable Markers – **06-19-2007** http://www.fda.gov/cdrh/oivd/guidance/1549.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

Contacting the Center for Biologics

CBER CONTACT INFORMATION

- Voice Information System
  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
- CBER Regulatory and Guidance Documents on the Internet at: http://www.fda.gov/cber/guidelines.htm