CMC Writing for IND Applications

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CMC Writing for IND Applications

~Outline~

- What is the CMC section?
- Who writes the CMC section?
- When is the CMC section ready to be written?
- How (one way) to write the CMC section
  - Phase I/II cell therapy INDs

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Chemistry, Manufacturing, & Controls (CMC)

What?

- Section 7 of the IND
- Critical component in the trial/IND submission
  - Product manufacturing & characterization information
  - Product testing (including lot release testing) information
  - Product stability information
  - Other
    - Product labeling, tracking, etc.

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Guidance for Reviewers- Instructions and Template for Chemistry, Manufacturing, and Control (CMC) Reviewers of Human Somatic Cell Therapy Investigational New Drug Applications (INDs). U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research (CBER), August 2003.

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What?

- Graded nature of CMC [per 21 CFR 312.23(a)(7)]
- Amount of information submitted may vary with the phase or proposed duration of the study, dosage form, and the amount of information otherwise available
- FDA's primary objective…assure safety and rights of subjects [per 21 CFR 312.22(a)]
  - Emphasis in submission should be placed on providing information to allow proper evaluation of subject safety

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Guidance for Industry- Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well- Characterized, Therapeutic Biotechnology-derived Products. Center for Drug Evaluation and Research (CDER)/Center for Biologics Evaluation and Research (CBER), November 1995.

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What?

- Bottomline: Sufficient information should be submitted to assure proper identification, quality, purity, and strength of investigational product
- E.g. of graded nature: If the planned study utilizing cryopreserved product is brief or the cell therapy will be administered as a fresh product, supporting stability testing may be commensurately limited

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Who?

- Team approach…
  - Lab/medical director
  - Lab/technical staff
  - QA/regulatory staff
  - PI

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When?

- Once acceptable methods established
- Amendments
  - Immediate notification
  - Annual report

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How?

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Writing…

not as painful
as it looks…

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How?

- Many documents (Guidances, PTCs, etc.) from FDA
  - Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy. March 1998.
  - Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products. November 1995.
  - Draft Guidance for Industry: INDs for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products, Chemistry Manufacturing and Controls Content and Format. February 1999.
  - Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use. February 28, 1997.
  - Points to Consider in the Characterization of Cell Lines Used to Produce Biologicals. July 12, 1993.
  - **Guidance for Reviewers- Instructions and Template for Chemistry, Manufacturing, and Control (CMC) Reviewers of Human Somatic Cell Therapy Investigational New Drug Applications (INDs). August 2003.**

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How?

- One approach…
- Guidance for Reviewers (2003) = Framework for CMC Section
- Use others as supportive documents, as needed

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Chemistry, Manufacturing, & Control: (Un)related/Autologous/Allogeneic, UCB-/PB-/BM-Derived, (insert cell type) Therapy

I. Product Manufacturing & Characterization Information

A. General

- -Product type, derivation
- -Where processed?
- -Relevant accreditations (FACT, AABB, CAP,CLIA)
- -Type V MF reference (if filed)

B. Procurement

- -Starting material
- -Apheresis (mobilized/non-mobilized), UCB, marrow aspirate
- -Where collected?
- -Process description

I. Product Manufacturing & Characterization Information (con't)

C. Infectious Disease Testing & Prevention of Cross-Contamination

- -Donor suitability per cGTPs
- -Medical history
- -List of testing
- -Quarantine if positive result
- -Process if product with positive result to be infused

D. Cell Processing

- -Description of processing methods
- -Flow diagram outlining processing and testing

E. Reagents

- -Table indicating reagent, manufacturer, status (reference to FDA-approval, C of A, MF, existent IND)
- -HSA (from countries considered free of vCJD risk?)
- -Reference and include C of As for reagents not approved for human infusion

II. Product Testing

A. Microbiological Testing

- -Sterility testing
  - -Method/test (e.g., BACTEC, USP)
  - -When tested? Final product? In process? Days held?
  - -Indicate sample will not be washed or manipulated before testing
- -Mycoplasma testing
  - -Method/test (e.g., PCR, culture)
  - -When tested? Final product? In process? Days held?
  - -Indicate sample will not be washed or manipulated before testing
- -Gram stain
- -Reference to donor infectious disease testing (Section I.C.)

B. Identity

- -Labeling, segregation, any test methods employed

II. Product Testing(con't)

C. Purity

-Make-up of final suspension (e.g., washed cells in 5% HSA)

-Analysis (e.g., flow cytometry, endotoxin, etc.)

D. Potency

-Analysis (e.g., flow cytometry as in vitro surrogate, in vivo clinical assessment, other functional assays such as MLR-based)

E. Additional Testing

i. Viability

-Method (e.g., microscopy, flow cytometry)

-When?

ii. Cell Dose

-Method (e.g., hematology analyzer)

-Actual doses (always provide range)

-Minimum dose to allow for infusion?

iii. Other

-Retain aliquot?

III. Product Release Criteria Testing and Additional Testing

- One table with lot release testing (assay, method, where tested, specification)
  - -E.g., Endotoxin, LAL Method (manufacturer of kit), cell therapy lab, ≤ 5EU/kg; Viability, Flow Cytometry (7-AAD), clinical flow cytometry lab, ≥ 70%
- Second table with additional (not lot release) testing
  - -E.g., Sterility/Mycoplasma testing on final product that will not be available prior to release; research-type assays (MLR-based)

IV. Product Stability

- Stability testing to support post-production clinical use
- Fresh? Cryopreserved? Transit time/conditions

V. Other Issues

A. Product Tracking

- -Labeling per standards/regs
- -Unique identifiers (#, name)
- -Confirmation prior to administration
- -Segregation system

B. Labeling

- -Per standards/regs
- -Additional items on label
- -Include “Caution: New Drug – Limited by Federal Law to Investigational Use” per 21 CFR 312.6
- -Attach sample label/hangtag

C. Container/Closure

- -Bags, tubing sets, flasks, etc.
- -Indicate compatibility with cells

V. Other Issues (con't)

D. Environmental Impact

-"The sponsor claims categorical exclusion [under 21 CFR25.31(e)] for the study under this IND. To the sponsor's knowledge, no extraordinary circumstances exist."

E. Validation and Qualification of the Manufacturing Process and Facility

-Indicate process validation performed prior to clinical use

-Reference Facility MF if on file

Thank You!

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