CMC Writing for IND Applications

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~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
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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*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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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

- Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products. November 1995.
- Points to Consider in the Characterization of Cell Lines Used to Produce Biologicals. July 12, 1993.
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How?

- One approach…
- Use others as supportive documents, as needed
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?
      iv.
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, \( \leq 5 \text{EU/kg} \); Viability, Flow Cytometry (7-AAD), clinical flow cytometry lab, \( \geq 70\% \)
- 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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