

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

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?

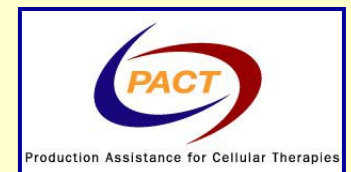
- ↳ Graded nature of CMC [per 21 CFR 312.23(a)(7)]
- ↳ Amount of information submitted may vary with the phase or proposed duration of the study, dosage form, and the amount of information otherwise available
- ↳ FDA's primary objective...assure safety and rights of subjects [per 21 CFR 312.22(a)]
 - ↳ 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...



Pony International

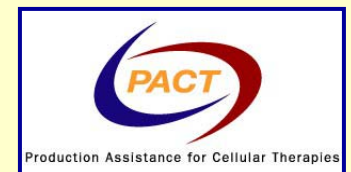


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How?

➤ 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

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.



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

iii.



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.



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



Minnesota Molecular & Cellular Therapeutics Facility

Thank You!
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