IND 202 Tutorial: Cellular Therapy INDs- The CMC Section

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IND 202 Tutorial: Cellular Therapy INDs

PURPOSE:

To inform and educate so as to facilitate the drafting of a cellular therapy IND CMC section that contains sufficient information as required to assess the risks to subjects enrolled in the proposed clinical investigations.

Presentation Outline

Addressing Your (ISCT) CMC Questions

- **IND CMC Section**
  - **What's expected**
  - **Troubleshooting - Featured Topic: Cross-Referencing**
- **Annual Reports**

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What's Expected in the CMC Portion of a Cellular Therapy IND Submission

21 CFR 312.23(7)(i): …a section describing the composition, manufacture and control of drug substance and drug product ….. sufficient information is required to assure the proper identification, quality, purity…the amount of information needed to make that assurance will vary with the phase of the investigation (and) the proposed duration…

Described in detail by Mercy Quagraine, Ph.D., Cell Therapy Branch, OCTGT, in her presentation entitled ***How to Prepare the CMC Section of a Cellular Therapy IND*** (IND 101 / ISCT Somatic Cell Therapy Symposium, September 15, 2005)

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What's Expected in the CMC Portion of a Cellular Therapy IND Submission

- Helpful Resources for Content / Format / Organization:
  - 21 CFR 312.23: **IND Content and Format** http://a257.g.akamaitech.net/7/257/2422/12feb20041500/edocket.access.gpo.gov/cfr_2004/aprqtr/21cfr312.23.htm
  - Draft Guidance : Instructions and Template for CMC Reviewers of Human Somatic Cell Therapy IND Applications http://www.fda.gov/cber/gdlns/cmcsomcell.pdf

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PROBLEM	RECOMMENDATION
Poor organization, key elements omitted.	•Prepare as stand-alone section •Consult CFR and Reviewer Guidance template for content-format. •Attention to detail
Information describing critical materials/reagents is incomplete	Include table listing all manufacturing materials/reagents: report concentration/amount, supplier, clinical or non-clinical grade, provide CoAs for non-clinical grade reagents
Inadequate description of manufacturing process	Provide detailed flow diagram outlining manufacturing process, identify in-process hold steps and in-process/final product testing

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PROBLEM	RECOMMENDATION
Insufficient information describing manufacturing facility and personnel involved	Include description of facility where product is manufactured mentioning any certifications/accreditations, identify critical personnel involved and detail their training/qualifications
Final product release testing and test methods not adequately described	Include table listing final product release tests performed, test methods used, proposed acceptance criteria for test results: (1) sterility, (2) endotoxin, (3) identity, (4) viability, (5) cell number, (6) potency, and (7) mycoplasma if cultured/passaged *ex vivo*.

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PROBLEM	RECOMMENDATION
Referencing Standard Operating Procedure documents	•Provide list of ALL SOP documents applicable to manufacture of cellular product •Include in IND copies of critical SOP documents: control of manufacturing process, final product testing, formulation, storage, tracking/labeling, stability testing

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- Cross-Referencing of Other Regulatory Files (MFs, INDs, IDEs)

  PURPOSE: allows for incorporation of proprietary information from other regulatory files related to the manufacturing process by authorized reference in support of an IND submission without risk of disclosure of that information to the IND sponsor requesting cross-reference permission.

  PRO: Reduction in the repetitive submission of the same information, facilitates review.

  CON: FDA not permitted to communicate to IND sponsor specific information about deficiencies in a cross-referenced file.

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WHAT'S REQUIRED IN AN IND SUBMISSION?

- Correct citation of the regulatory file number cross-referenced.
- Copy of the letter of cross-reference authorization obtained from the holder of the cross-referenced regulatory file.
- The letter of cross-reference authorization should specify the information for which permission to cross-reference is being granted as well as location: Volume #, Section Heading, Page #'s.

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Regulatory Status of IND and Cross-Referenced Linked

- If a cross-referenced file is closed, withdrawn, found to be deficient or placed on clinical hold the cross-referencing IND will go on hold for cause (safety concern or other reason): insufficient information in IND to adequately assess safety and risk posed to the patient.
- When an IND is placed on clinical hold due to problems with the cross-referenced file, general deficiency letter sent to IND sponsor
- Holder of the cross-referenced file found deficient receives letter detailing deficiencies, sponsor of cross-referencing IND is not informed of the deficiency details due to confidentiality
- Holder of deficient cross-referenced file must address deficiencies in order for clinical hold to be removed for the cross-referencing IND

The Bottom Line

Familiarity with content and format expectations, clarity of organization, attention to detail and taking advantage of pre-submission consultation opportunities will facilitate both drafting and review of the IND CMC Section.

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What to Submit in an Annual Report - Required

- A summary of any significant manufacturing changes made during the past year (21 CFR § 312.33[b][7])

CAUTION

Implementation of significant manufacturing changes with the potential to impact product safety, efficacy and stability should be reported in real time as amendments to the IND

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What Else to Include in an Annual Report - Recommended

- Identify all attempts (lot number, unique identifier, date of manufacture) to produce a cellular product for which product was not or could not be administered.
  - Report reason why product could not be used
  - Include results from investigations of outcome, where applicable.
- Describe product characterization progress – information used to support improved in-process/final lot-release tests, acceptance criteria.

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What Else to Include in an Annual Report - Recommended

- Provide a summary of stability testing results for any cell banks, stored intermediates and final product.
- Include a list of all ***other*** clinical products / research grade products prepared within the manufacturing facility during the past 12-months.

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

Contacting the Center for Biologics

CBER Contact Information

- 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