

# Basics of IND Submission

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# Office of Cellular, Tissue and Gene Therapies (OCTGT) Learn Webinars

<http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm>

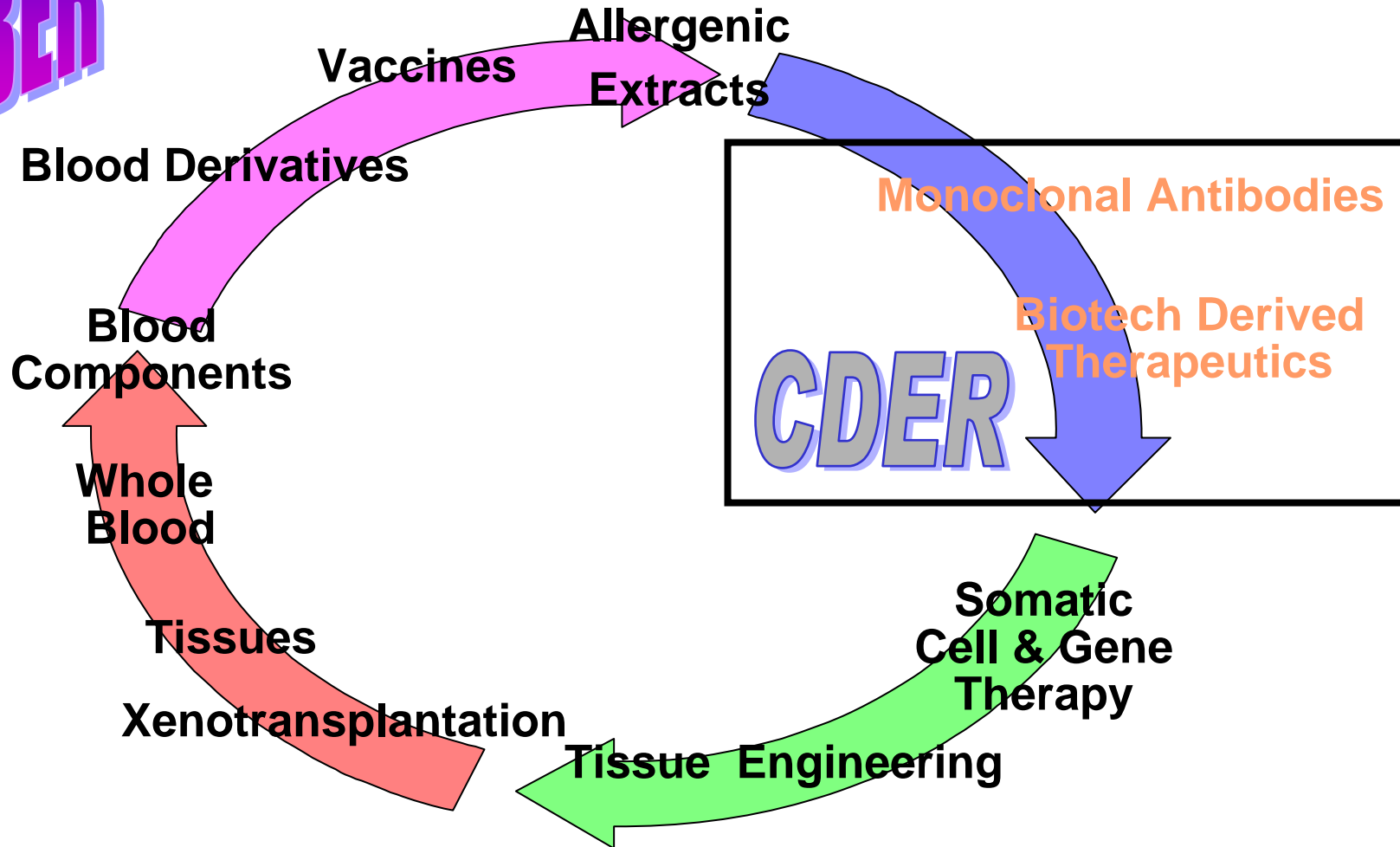
- Introduction and Scope of OCTGT
- IND Basics in OCTGT
- Sponsor Meetings with OCTGT
- The Chemistry, Manufacturing and Controls (CMC) Section of a Gene Therapy IND
- Advanced Topics: Successful Development of Quality Cell and Gene Therapy Products
- Cellular Therapy Products
- Preclinical Considerations for Products Regulated in OCTGT

# Discussion Points

- Regulation of Human Biologics in the U.S.
- Products regulated by OCTGT
- Basics on how to file an IND
- IND Submission: Do's and Don'ts
- FDA Resources pertaining to IND submission

# Regulation of Human Biologics in the U.S.

**CDER**



# Regulatory Framework

- Federal regulatory authority is a 3-tiered system
- Statutes (Laws)
  - Passed by Congress and signed into law by the President
    - Food, Drug & Cosmetic Act, Public Health Service Act
- Regulations (full force of Law)
  - Promulgated by the Agency
    - IND Regulations 21 CFR 312
    - IRB and Consent Regulations 21 CFR 50 and 56
    - Good Laboratory Practice 21 CFR 58
    - Human Cells, Tissues, and Cellular and Tissue Based Products 21 CFR 1271
- Guidance Documents (Not legally binding)
  - Provides Agency's current thinking on specific issues

# Guidance Document for Human Gene Therapy INDs

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm072587.htm>

Guidance for FDA Reviewers and Sponsors

Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)

# Guidance Document for Human Somatic Cell Therapy INDs

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Xenotransplantation/ucm074131.htm>

Guidance for FDA Reviewers and Sponsors

Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs)

# Products regulated by OCTGT

- Cellular Therapy Products
- Gene Therapy Products
  - Including gene modified cells
- Therapeutic Vaccines
  - Peptides
  - Dendritic Cells
- Xenogeneic Products
- Tissues/Tissue-based Products
- Some Combination Products
- Devices

# IND Submission Process

- Step 1: Pre-IND teleconference with OCTGT
  - Highly recommended for new products
- Step 2: Submission of complete IND package
  - All forms, all sections
- Step 3: IND Review
  - FDA will notify Sponsor within 30 calendar days of receipt of the IND whether the study may proceed or is placed on clinical hold
    - Studies may not begin until 30 day review is complete or FDA notifies Sponsor studies may proceed

# Elements of an IND Application

- Form FDA 1571 21 CFR 312.23(a)(1)
- Table of Contents 21 CFR 312.23(a)(2)
- Introductory statement and general  
investigational plan 21 CFR 312.23(a)(3)
- Investigator's Brochure 21 CFR 312.23(a)(5)
- Protocols 21 CFR 312.23(a)(6)
- Product/CMC information 21 CFR 312.23(a)(7)
- Pharmacology/Toxicology information 21 CFR 312.23(a)(8)
- Previous human experience 21 CFR 312.23(a)(9)
- Additional Information 21 CFR 312.23(a)(10)

# IND Review Process

- A Team Approach to IND Review
  - Regulatory Project Manager
  - Product/CMC reviewer
  - Pharmacology/Toxicology reviewer
  - Clinical Reviewer
  - Statistical Reviewer
  - Consults as needed
    - e.g. from CDRH for review of a device component
- Within 30 days the file is Active or On Hold
  - Outstanding Hold and Non-hold issues conveyed by phone/email and a detailed letter may be issued
  - All hold issues must be satisfactorily resolved in order to proceed

# Chemistry, Manufacturing and Controls

- CMC = Product Manufacturing and Testing Information
- Details of product manufacturing
- Product safety and quality testing
- Product stability and shelf life
- Container, label, and tracking information
- Can cross reference prior INDs or Master Files

# Preclinical Studies

- Scientific basis for conducting the clinical study
- Data from animal or in vitro studies to establish an initial safe dose in humans
- Proof of concept animal models, if appropriate
- Toxicology studies in relevant animal model
- Complete study reports to be submitted

# Clinical Information

- Protocols
  - Starting dose and dose escalation schemes
  - Route of administration
  - Dosing schedules
  - Definition of patient population
    - Detailed entry and exclusion criteria
  - Safety monitoring plans
    - Study stopping rules
    - 21 CFR 312.32
  - Statement of the desired endpoints and objectives
  - Statement of the phase of the investigation
- Form FDA 1572

# Phases of Investigation

- 21 CFR 312.21
- Phase 1
  - Designed to predominantly evaluate safety
  - Limited number of subjects
- Phase 2
  - Preliminary efficacy studies and dose ranging
- Phase 3
  - Confirmatory efficacy studies intended to provide statistical evidence of effectiveness
  - Much larger number of subjects
- Primary concern in all phases is SAFETY

# CMC Do's (1)

- Incorporate Pre-IND meeting comments
- Consult CFR and Guidance for Reviewers and Sponsors for content format
- Indicate what information is being cross-referenced and (ideally) where it can be found in the cross-referenced file
- Provide a clear rationale for why the product was developed the way it was
- Provide detailed flow charts and diagrams outlining the manufacturing process
- Include tables listing all manufacturing materials/reagents
- Provide a list of reagents with Certificates of Analysis (COAs) attached

# CMC Do's (2)

- Include description of facility where product is manufactured
- Include table listing final product release tests performed, test methods used and proposed acceptance criteria for test results
- Provide list of all Standard Operating Procedure (SOP) documents applicable to the product
- Include copies of critical SOP documents: Control of manufacturing process, final product testing, formulation, storage, tracking/labeling, stability testing
- Provide information related to qualification of assays being used (e.g. assay variability, description of sensitivity and reproducibility)

# CMC Don'ts

- Don't just provide a list of SOPs or COAs without a description of the assays being used
- Don't submit an IND that is internally inconsistent (i.e. make sure that the product and product manufacturing details described under CMC, investigator brochure, and clinical protocol/informed consent are consistent)
- Do not supply an application lacking pilot data to support manufacturing feasibility or consistency
- Do not submit raw vector sequence data without an annotated summary of findings

# Pharm/Tox Do's (1)

- Use biologically responsive animal species/models – justify the use of the species/model
- Apply the 3 R's [Reduce, Refine, Replace] – minimize the number of animals necessary to adequately evaluate the safety and potential efficacy of the product
- Use the intended clinical product (identical vector backbone/promoter/transgene, cell type, final formulation, etc.), if at all possible/feasible
- Consider the effect of the immune response of the animal species on the product and to the product
- Mimic the proposed clinical scenario as closely as possible (e.g., route of administration, delivery procedure, timing of product administration)

# Pharm/Tox Do's (2)

- Include multiple dose levels
- Include adequate group sizes and appropriate control groups to allow interpretation of the data
- Provide the calculation and justification for the dose extrapolation from animals to humans
- Include relevant endpoints to assess safety and activity in the study designs
- Conduct toxicology studies in compliance with GLP
- Submit complete study reports for all preclinical studies conducted
- Follow applicable guidances
- Approach CBER early in your product development program

# Pharm/Tox Don'ts

- Don't assume that nonhuman primates are required for preclinical testing for every product
- Don't assume that the two-species (one rodent/one nonrodent) rule applies
- Don't conduct non-GLP studies without a prospectively designed protocol or discussing the potential impact of all protocol deviations on study integrity
- Don't submit a poorly organized and incomplete submission – Pre-IND or IND – to CBER
- Don't assume that CBER Pharmacology/Toxicology personnel are going to design your preclinical studies

# OCTGT Regulatory Resources

- OCTGT Learn Webinar Series:  
<http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm>
- Regulatory Questions:  
[CBEROCTGTRMS@fda.hhs.gov](mailto:CBEROCTGTRMS@fda.hhs.gov) or  
[Patrick.Riggins@fda.hhs.gov](mailto:Patrick.Riggins@fda.hhs.gov)
- References for the Regulatory Process for (OCTGT)
- <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/ucm094338.htm>