

Pre Pre-IND and Pre-IND Interactions for Cell and Gene Therapy Products

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Conflict of Interest

I have no financial interest or affiliation with a commercial organization. I have no actual or potential conflict of interest in relation to this presentation.

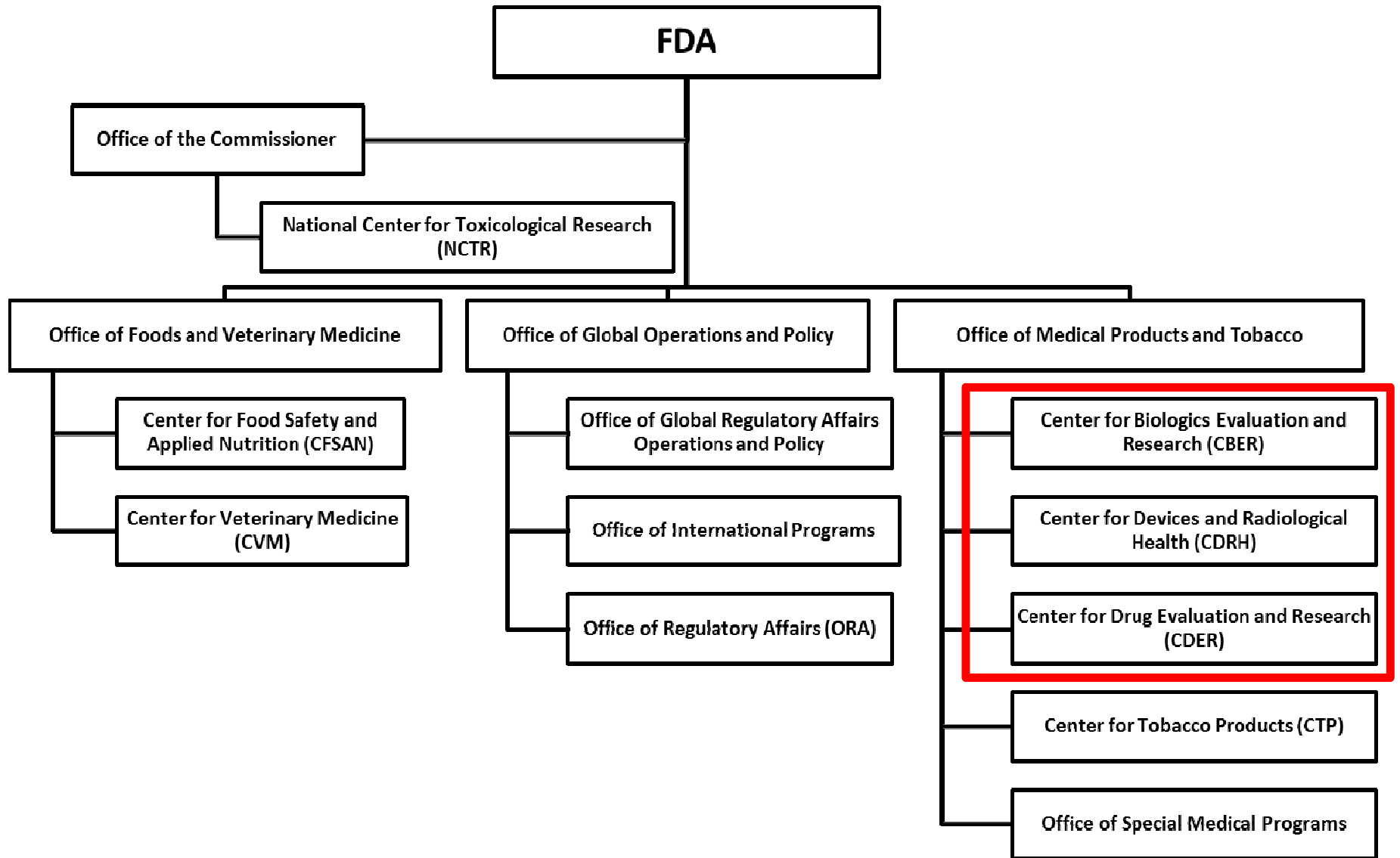


Presentation Overview

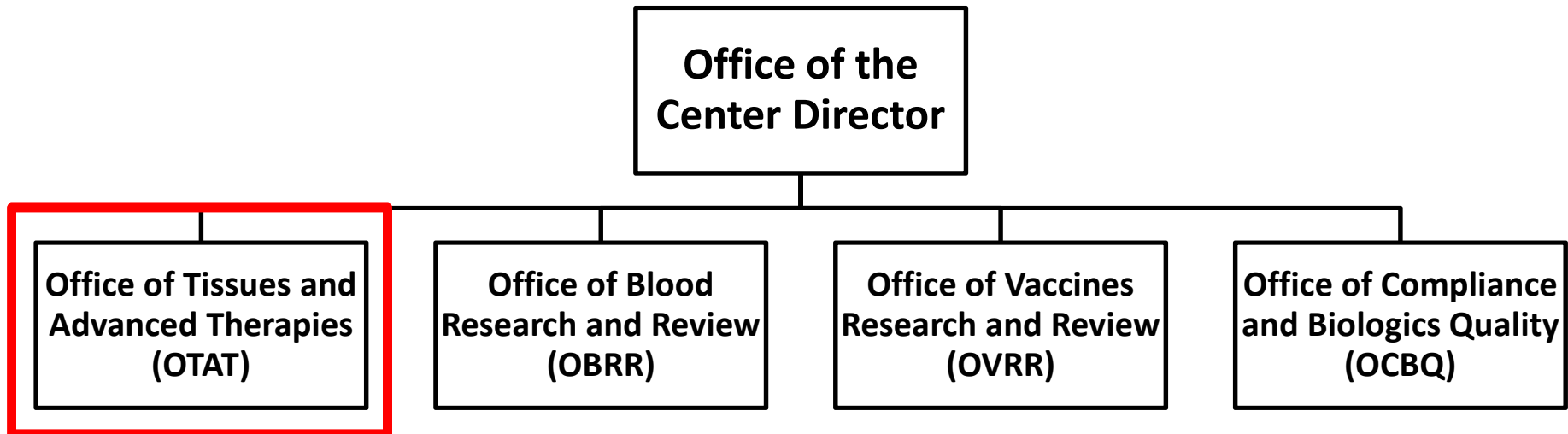
- Introduction to the Office of Tissues and Advanced Therapies (OTAT)
- Your IND Submission and Preclinical Testing Program
- Pre-pre-IND and Pre-IND Interactions
- Do's and Don'ts for your Pre-pre-IND and Pre-IND Interactions



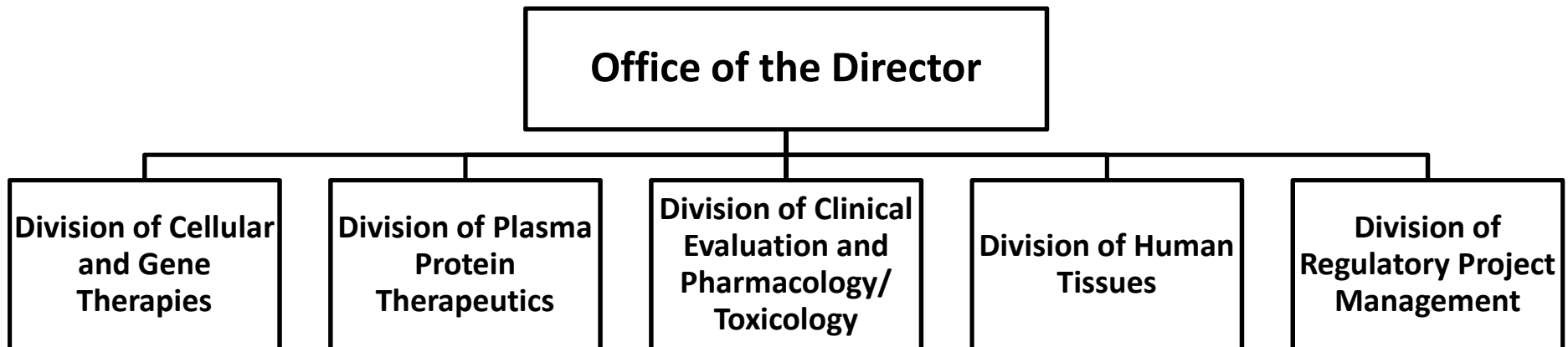
FDA Organization



Center for Biologics Evaluation and Research (CBER): Organization



Office of Tissues and Advanced Therapies (OTAT): Organization



OTAT-Regulated Products

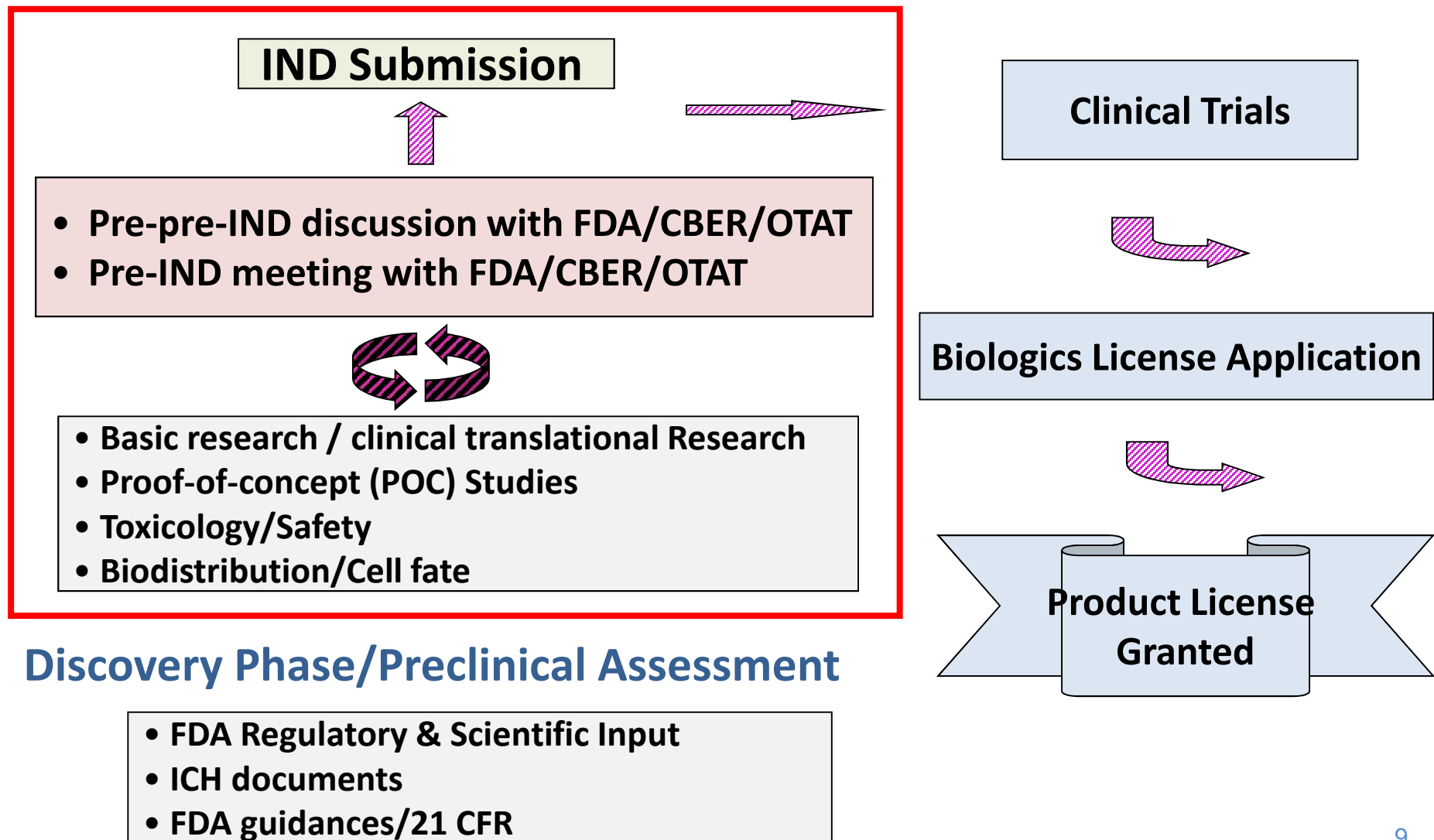
- **Gene therapies**
 - Viral vectors
 - Non-viral vectors
 - Replication-competent vectors
 - Genetically-modified cells and/or organisms
- **Stem cells/stem cell-derived**
 - Fetal, embryonic
 - Induced pluripotent stem cells (iPSCs)
 - Hematopoietic, neural, mesenchymal
 - Placental, umbilical cord blood
- **Somatic cells**
 - Retinal pigment epithelial cells
 - Pancreatic islet cells
 - Chondrocytes
- **Blood products**
 - Coagulation factors
 - Fibrin sealants
 - Fibrinogen
 - Thrombin
 - Plasminogen
 - Immune globulins
 - Snake venom antisera
- **Combination products**
 - Engineered tissues/organs
 - In combination with novel delivery device
- **Devices**
- **Tissues**

Investigational New Drug (IND) Submission



- **Required to conduct a clinical trial (21 U.S.C 355):**
 - Using an unapproved product
 - Using an approved product for a new indication or in a new patient population
- **Sponsor (21 CFR 312. Subpart D):**
 - Applicant of the IND who is responsible for the IND (**21 CFR 312.50**)
 - Can be a company, institution, or investigator
- **IND review team:**
 - Chemistry, Manufacturing and Controls (CMC) reviewer
 - Pharmacology/Toxicology (P/T) reviewer
 - Clinical reviewer
 - Statistical reviewer
 - Consult reviewer (as needed)
 - Regulatory Project Manager (RPM)
 - Handles administrative processing
 - Point of contact

Developmental Pathway for Cell and Gene Therapy Products



Preclinical Program Objectives and Testing Strategy



- Support the rationale for the clinical trial
 - Understanding the product’s putative mechanism of action
- Make recommendations regarding clinical trial design
 - Eligibility criteria/‘at risk’ patient population
 - Starting dose level, dose-escalation scheme, dosing schedule
 - Clinical route of administration/anatomic location of product delivery
 - Clinical monitoring (safety, activity, duration of follow-up)
- Assess preliminary benefit:risk profile
- No ‘one-size-fits-all’ regulatory approach
 - Science based and flexible approach

Preclinical Testing Program



Studies	To Assess
Proof-of-concept (POC)	Bioactivity of the intended product in vitro (i.e., enzymatic assay, T cell activation, cytokine secretion, etc.) and in vivo (i.e., animal model of disease/injury) to substantiate the feasibility and rationale for the proposed clinical trial
Safety	Overall safety profile of the investigational product and the administration procedure (using the intended clinical device, as applicable) <u>Product-specific/Disease-specific</u> Tumorigenicity, immunogenicity, neurotoxicity, cardiotoxicity, developmental and reproductive toxicity (DART), and/or other studies, as applicable
Vector Biodistribution/Cell Fate	Distribution profile to target and non-target tissues following administration by the intended route at various time intervals; cell fate and transgene expression as applicable



Preclinical Testing Program (cont'd)

- **General considerations for the design of preclinical studies**
 - Nonbiased design
 - Mimic the planned clinical scenario as closely as possible
 - Administration of clinical vehicle formulation and multiple dose levels of the investigational product
 - Include adequate numbers of animals per group
 - Multiple sacrifice time points and sufficient study duration
 - Comprehensive bioactivity and safety assessments
 - Bioactivity, functional and morphological assessment
 - Mortality, clinical observations, body weights, clinical pathology, immunogenicity, necropsy, organ weights, histopathology, etc.
 - Other specific non-terminal/terminal assessments (e.g., imaging, PCR, immunohistochemistry, etc.)

Preclinical Testing Program (cont'd)



- Preclinical study considerations for cell therapy, gene therapy, and therapeutic vaccines
 - Objectives
 - General program design
 - Recommendations for study design
- Explicitly incorporates the 3Rs for animal testing
 - Reduce, refine, replace

Guidance for Industry

**Preclinical Assessment of
Investigational Cellular and Gene
Therapy Products**

Published November 2013

Pre-pre-IND Interaction



- **Primary Objective**
 - A mechanism for early communication with OTAT to obtain feedback on an overall preclinical testing program
- **Purpose**
 - A non-binding, informal scientific discussion primarily between the CBER/OTAT nonclinical review disciplines (P/T and CMC) and the sponsor
 - The clinical review discipline may also participate to a limited extent
 - To initiate targeted discussion of specific issues
- **Process**
 - Primary contact: Mercedes Serabian, Chief Pharmacology/ Toxicology Branch¹, at: mercedes.serabian@fda.hhs.gov
 - Email OTAT to receive an instructional document about the process

Pre-pre-IND Interaction (cont'd)



- **Timing and Format**

- A pre-pre-IND interaction should be requested when you have generated preliminary preclinical data (proof-of-concept and some safety), but you are not yet at the stage of discussing definitive preclinical safety studies
- A concise pre-pre-IND briefing package (no more than approximately 25 pages) should be provided, and key issues for consideration clearly identified
- OTAT P/T will review the package and determine if appropriate for a pre-pre-IND interaction based on development stage, complexity of the product, completed preclinical studies, etc.
- OTAT may grant one pre-pre-IND interaction
- The interaction is always via teleconference (scheduled by OTAT)
- There is no required timeline for holding the teleconference

Contents of a Pre-pre-IND Briefing Package



- **A background synopsis**
 - Rationale for the use of the product in the proposed clinical population
- **A description of the investigational clinical product**
 - Summary of the manufacturing process
- **A brief outline of the clinical plan**
 - Indication and patient population
 - Possible dose levels and dosing regimen
 - Route of administration
 - Dosing procedure – delivery device to be used, as applicable

Contents of a Pre-pre-IND Briefing Package (cont'd)



- **A comprehensive summary of all completed *in vitro* and *in vivo* preclinical studies**
 - POC studies, pilot safety studies, relevant cited references, etc.
- **A description of the preclinical development plan**
 - Completed and planned studies intended to support the rationale and safety of product administration in the proposed clinical trial
- **Specific questions (CMC, P/T) you would like to discuss regarding your submission**

Note:

- *The definitive safety study designs are discussed in detail in the pre-IND meeting*



Pre-pre-IND Interaction

- **OTAT provides:**
 - Non-binding comments prior to the scheduled teleconference, as feasible
 - No formal meeting minutes are generated by OTAT
- **To facilitate a future pre-IND meeting:**
 - Include the OTAT pre-pre-IND comments and your responses in the pre-IND package
 - The advice from the pre-pre-IND interaction should be considered when preparing the pre-IND meeting package and the final protocols for the definitive preclinical studies

Pre-IND Meeting

- A non-binding, formal scientific discussion between all CBER/OTAT review disciplines (CMC, P/T, and Clinical) and the sponsor
- **Purpose**
 - To allow early communication between the sponsor and the FDA
 - To discuss the format for the IND submission
 - To communicate the initial product and clinical development plan
 - Product characterization issues
 - Preclinical testing program
 - The scope and design of planned clinical trial
 - The development plan to address requirements for the Pediatric Research Equity Act (PREA) of 2003 (21 CFR 312.82)
 - To achieve an eventual successful IND submission

Pre-IND Meeting (cont'd)



- **Process**

- OTAT grants one pre-IND meeting
- The primary contact: Lori Tull lori.tull@fda.hhs.gov
- Meeting is scheduled within 60 days of receipt of the meeting request
- The meeting format can be: written response, teleconference, or face-to-face meeting
- A pre-IND meeting package needs to be submitted no later than 30 days prior to the scheduled meeting date
- Meeting emphasis – summary data and sound scientific principles to support the use of specific product in a specific patient population

- **Timing**

- A pre-IND meeting should be requested prior to the conduct of the definitive preclinical safety studies

Contents of a Pre-IND Meeting Package



- **A background synopsis and summary describing the manufacturing development of the subject investigational clinical product**
 - A description of the product manufacturing process and testing conducted (in-process/final product) to demonstrate product identity, quality, and safety.
 - A description of product formulation and storage conditions

Refer to FDA guidance documents:

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

Contents of a Pre-IND Meeting Package (cont'd)



- **Clinical study synopsis/protocol**
 - Trial design
 - Objectives
 - Intended patient population
 - Dosing regimen
 - Delivery procedure, including device
 - Monitoring plan
 - Outcome measures

Refer to FDA guidance document:

1. *Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products*



Contents of a Pre-IND Meeting Package (cont'd)

- **Preclinical development program**
 - **A comprehensive summary of all completed preclinical studies** (*in vitro* and *in vivo* studies, animal models, study designs, resulting data and interpretation, etc.)
 - **Complete protocols for your definitive preclinical safety/toxicology and biodistribution studies** (animal species/models, dose levels, dosing regimen and procedure, route of administration, sacrifice intervals, study endpoints, etc.)
- **Specific questions for all review disciplines you would like to discuss**



Pre-IND Meeting

**Formal Meetings
Between the FDA and
Sponsors or Applicants
of PDUFA Products
Guidance for Industry**

Draft Guidance

March 2015

Do's for Pre-pre-IND Interactions and Pre-IND Meetings



- Do include specific questions that you would like to discuss
- Do include the information that is needed to obtain CBER/OTAT input on your specific questions
- Do include the preclinical development plan
- Do include the design of your completed and proposed preclinical (POC, safety, biodistribution) studies
- Do specify similarities and differences between the preclinical and clinical products
- Do number the pages of your briefing package

Don'ts for Pre-pre-IND Interactions and Pre-IND Meetings



- Don't avoid issues or concerns
- Don't conduct the definitive preclinical safety/toxicology studies without seeking input from CBER/OTAT in the pre-IND meeting regarding study design
- Don't submit complete study reports in the briefing packages



Summary

- The complexity of the OTAT-regulated products necessitate case-by-case approach to preclinical development.
- CBER/OTAT encourages the sponsor to initiate communication at an early stage of the product development program to enable identification of potential issues to be addressed and the appropriate pathways to their resolution.



Thank You !

- **Theresa Chen, Ph.D.**
 - Theresa.chen@fda.hhs.gov
- **Regulatory Questions:**
 - Contact the Regulatory Management Staff in OTAT at: OTATRPMS@fda.hhs.gov
 - Contact Lori Tull at Lori.Tull@fda.hhs.gov or (240) 402-8361
- **OCTGT Learn Webinar Series**
 - <http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm>

Selected Guidance Documents



- Guidance for Industry: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs) (April 2008)
<https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Xenotransplantation/ucm092705.pdf>
- 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) (April 2008)
<https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm078694.pdf>
- Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products (November 2013)
<https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM376521.pdf>

Selected Guidance Documents (cont'd)



- Draft Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products (March 2015)
<https://www.fda.gov/downloads/drugs/guidances/ucm437431.pdf>
- Guidance for Industry: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (June 2015)
<https://www.fda.gov/downloads/Biologi.../UCM359073.pdf>

Public Access to CBER

- **CBER website:**
 - <http://www.fda.gov/BiologicsBloodVaccines/default.htm>
- **CBER Toll Free Number**
 - 1-800-835-4709
- **Consumer Affairs Branch (CAB)**
 - Email: ocod@fda.hhs.gov
 - Phone: 240-402-7800
- **Manufacturers Assistance and Technical Training Branch (MATTB)**
 - Email: industry.biologics@fda.gov
- Follow us on Twitter: <https://www.twitter.com/fdacer>



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CMC

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