

Nonclinical Development for Cellular and Gene Therapy Products from the perspective of CBER/FDA

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FDA-Small Business Regulatory Education for Industry (REdI)

Meeting

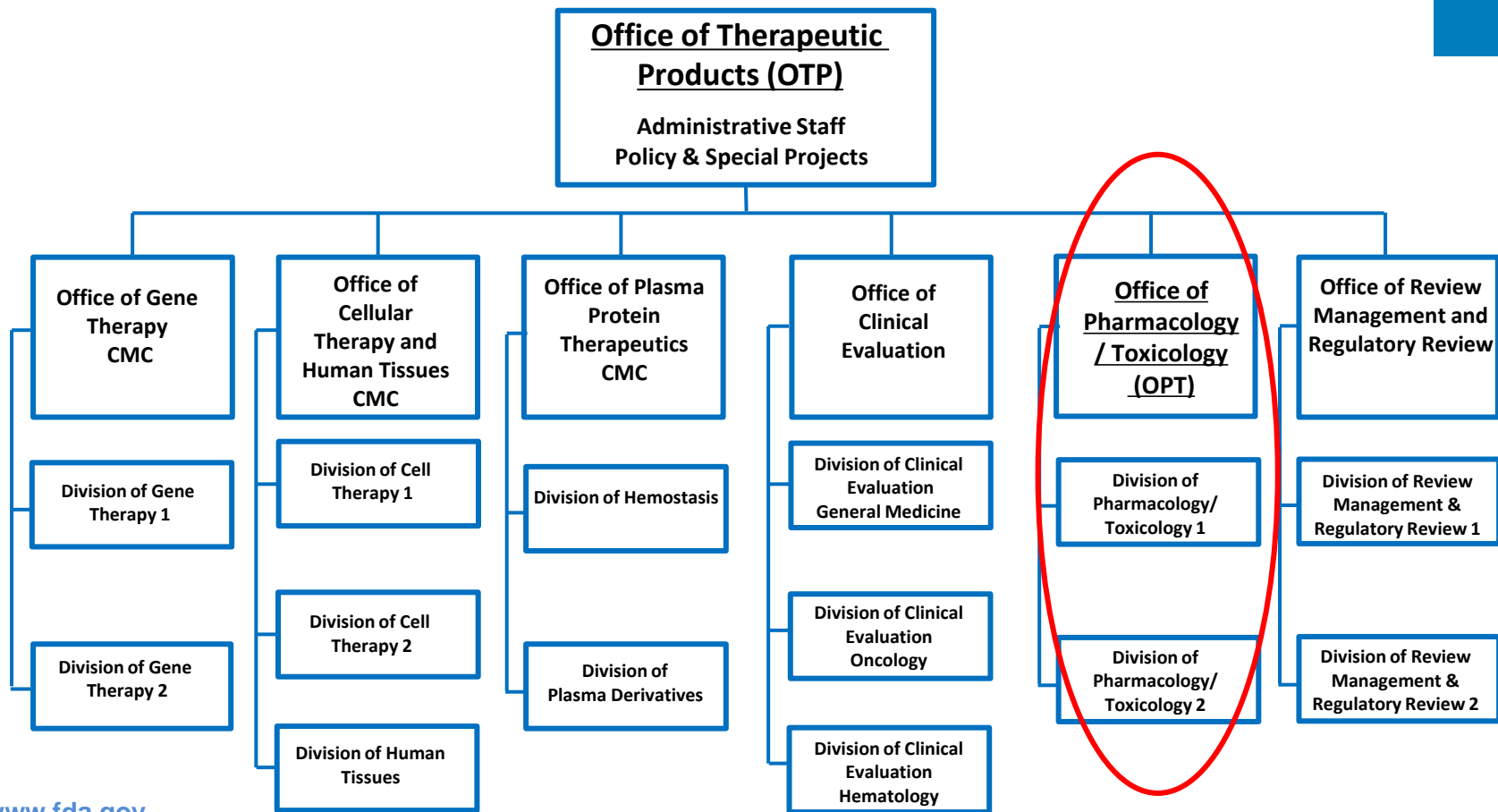
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Learning Objectives

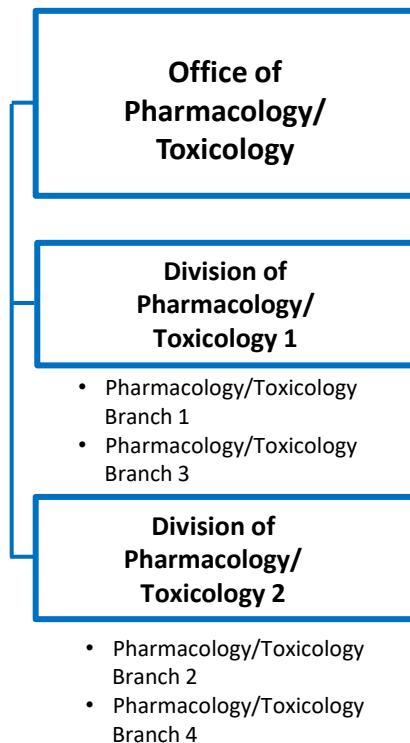


- Describe the new organizational structure of CBER/ Office of Therapeutic Products (OTP)/Office of Pharmacology and Toxicology (OPT)
- Describe CBER/OTP regulated products
- Understand some nonclinical considerations for assessing the safety of cell therapy (CT) and gene therapy (GT) products
- Be informed about opportunities for early interaction with CBER/OPT
- Understand the principles for selecting appropriate animal species/models for nonclinical studies

The new organizational structure of CBER/OTP/OPT



The new organizational structure of CBER/OTP/OPT





Products Regulated by OTP

CBER/OTP Regulated Products



CBER/OTP-Regulated Products

- **Gene therapies**
 - Viral vectors: Replication-deficient (e.g., adeno-associated virus) and replication-competent (e.g., adenovirus, vaccinia)
 - Non-viral vectors (e.g., plasmids)
 - Microbial vectors (e.g., Listeria)
 - Ex vivo genetically modified cells
- **Stem cells/stem cell-derived therapies**
 - Adult (e.g., hematopoietic, neural, mesenchymal)
 - Perinatal (e.g., placental, umbilical cord blood)
 - Fetal (e.g., neural)
 - Embryonic and Induced pluripotent stem cells (iPSCs)
- **Functionally mature/differentiated cells**
 - Examples: retinal pigment epithelial cells, pancreatic islets, chondrocytes, etc.)
- **Products for xenotransplantation**
- **Therapeutic vaccines and other antigen-specific immunotherapies**
- **Blood- and Plasma-derived products**
 - Coagulation factors, Fibrin sealants, Fibrinogen, Thrombin, Plasminogen
 - Immune globulins
 - Anti-toxins and Snake venom antisera
- **Tissues**
- **Devices**
- **Combination products**
 - Engineered tissues/organs

Considerations for Nonclinical Evaluation of Gene Therapy (GT) and Cell Therapy (CT) Products

- How does CBER/OTP evaluate nonclinical safety and activity?
- What are important elements to consider when developing a nonclinical program for a CT/GT product?



Guidance for Industry

Preclinical Assessment of Investigational Cellular and Gene Therapy Products

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or e-mail ocod@fda.hhs.gov, or from the Internet at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

For questions on the content of this guidance, contact OCOD at the phone numbers or e-mail address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
November 2013

How Does Nonclinical Data Support the Proposed Clinical Study Plan?



- Provides justification for first-in-human clinical trials in subjects with the target disease or condition
- Supports patient eligibility criteria
- Supports the starting clinical dose level, dosing regimen, and route of administration (ROA)
- Establishes feasibility and reasonable safety of the product administration procedure
- Identifies potential toxicities and physiologic parameters to help guide clinical monitoring
- Translation of benefit:risk to humans

Considerations for a Nonclinical Testing Program

- The putative mechanism of action and the intrinsic properties of the investigational product
- The proposed clinical indication
- Appropriate animal species/model
 - Judicious use of animals
 - The 3Rs – **R**educe, **R**efine, **R**eplace
- The quality and applicability of existing accessible data (Nonclinical and clinical) for:
 - The proposed clinical product or a similar product
 - The proposed subject population
 - The proposed clinical ROA

Considerations for a Nonclinical Testing Program

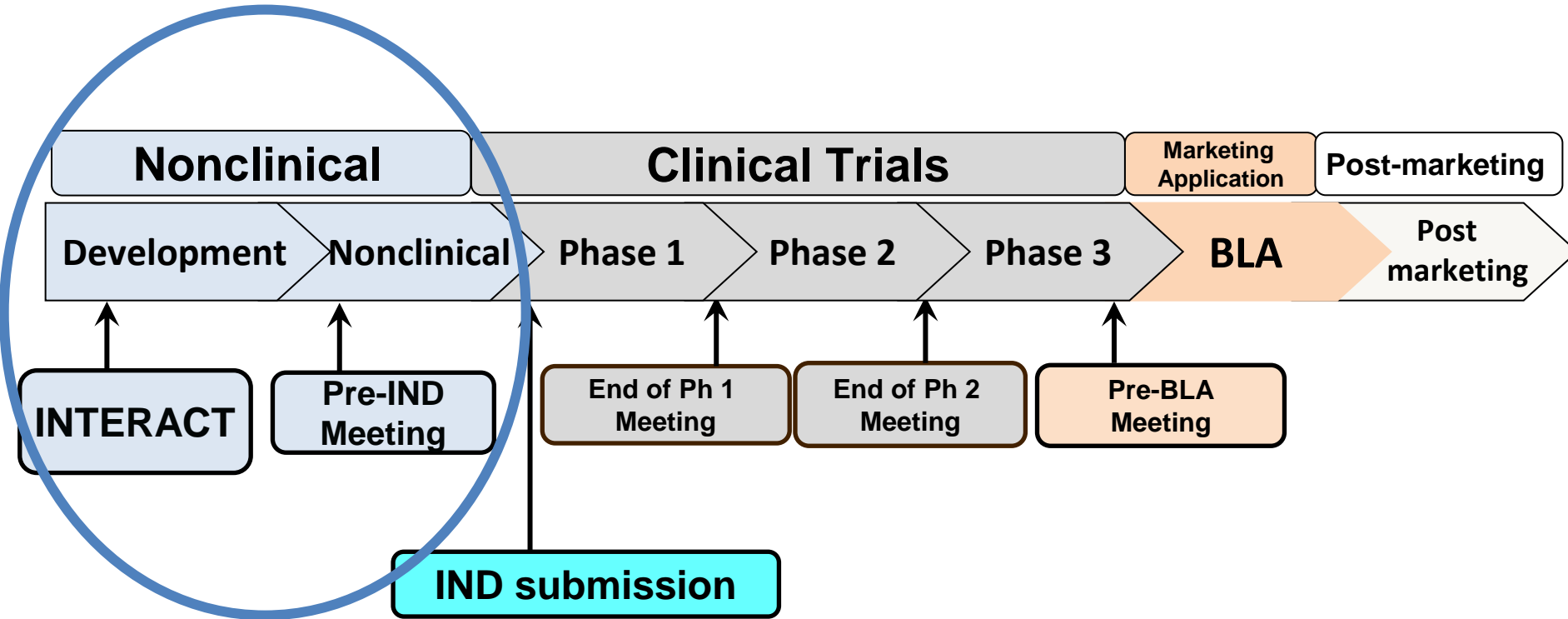


- The diversity and biological properties of CT and GT products necessitate a flexible testing strategy - no “one size fits all”
 - Science-based and data-driven
 - Based on accumulated knowledge and experience
 - Based on available technology(ies) and methods



Early Communication Opportunities

Early Interactions with CBER/OTP



INTERACT Meetings



Initial Targeted Engagement for Regulatory Advice on CBER productTs

(<https://www.fda.gov/vaccines-blood-biologics/industry-biologics/interact-meetings>)

- **Goal:** To obtain early feedback on a product development program for a novel investigational agent
- **Purpose:**
 - Non-binding, informal scientific discussions between CBER review disciplines (Pharmacology/Toxicology and CMC) and the sponsor
 - Initial targeted discussion of specific issues

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- **Timing:** When you have generated preliminary nonclinical data (proof-of-concept [POC] and some safety), but are not yet ready to conduct definitive nonclinical studies
- **Examples of nonclinical discussions:**
 - Design of POC or other pilot safety/biodistribution (BD)/cell fate studies
 - Adequacy of the selected animal species/models
 - Suitability of innovative nonclinical testing strategies, products and/or delivery modalities
 - Advice on modification of a nonclinical program or study design, as applicable, to ensure judicious use of animals

Some Do's and Don'ts for INTERACT Meetings

Do

- Include specific questions that you would like to discuss.
- Include all relevant information that CBER/OTP needs to provide useful feedback on your specific questions.
- Make the package (maximum of 50 pages) reader-friendly.
- Provide copies of key supporting publications.
- Refer to the INTERACT SOPP
<https://www.fda.gov/media/124044/download>

Don't

- Forget that the meeting package is due with the meeting request.
- Conduct the definitive POC and safety studies at this stage.
- Forget to include a comprehensive summary of your available nonclinical data.
- Forget to provide your rationale, with supporting data, for selection of a specific animal model or test system.
- Forget to convey all issues and findings of concern that arise from your nonclinical studies.

- **Goal:** To achieve a successful IND submission
- **Purpose:**
 - Non-binding, formal scientific discussion between core review disciplines (CMC, P/T, and Clinical) and the sponsor
 - Comprehensively communicate the product/clinical development plan
 - Discuss the key elements of the IND submission
- **Timing:**
 - POC and preliminary safety studies completed
 - Ready to conduct definitive safety studies

Pre-IND Meetings – Nonclinical Program

A comprehensive summary of all completed nonclinical studies

In vitro and *in vivo* studies, animal species/ models, study designs, resulting data and interpretation

Comprehensive protocols for the proposed definitive nonclinical safety studies

Animal species/models, dose levels, dosing regimen and procedure (including delivery device), study parameters, sacrifice intervals, etc.

Some Do's and Don'ts for Pre-IND Meetings

Do

- Include specific questions that you would like to discuss.
- Specify similarities and differences between the nonclinical and clinical products.
- Include the design and findings of your completed studies and protocols outlines for your proposed studies.
- Provide the scientific rationale for the dose levels, dosing regimen, and duration of your completed and planned studies
- Discuss POC data to support a prospect of direct benefit (PDB) for pediatric First-in-Human studies (21 CFR 50.52), when applicable
- Make the package reader-friendly.

Don't

- Start your definitive safety/distribution studies until obtaining FDA feedback in a pre-IND setting.
- Forget to provide adequate justification and discussion regarding the limitations of your selected animal models/test systems
- Forget to discuss issues and concerns that arise from your completed nonclinical studies.
- Forget to provide a copy of the key publications cited in your comprehensive summaries.
- Forget to consider/incorporate FDA-provided comments from an INTERACT meeting (if one was held).

Selecting appropriate animal species/models for nonclinical studies

Considerations for Appropriate Animal Species / Model(s)



- There is no 'default' to the use of nonhuman primates
- There is no 'default' to the use of both a rodent and a non-rodent species
- Assess safety and bioactivity using an appropriate animal disease model
- Understand the limitations of the species / model used
- Scientific justification should be provided for the animal species / model used

Selection of Animal Species/Model(s)

- Comparability to the target patient population
 - Phenotype, pathophysiology, clinical outcomes
- Permissiveness to cell product
 - Human derived, autologous, allogeneic
- Anatomic site of product delivery
 - Comparable to clinical, if feasible
- Feasibility of using the intended clinical delivery system/procedure





Challenge Question #1

What type of earliest possible interaction with CBER/OTP can be requested to discuss a novel product development?

- A. End-of-Phase 1 Meeting
- B. Pre-IND
- C. INTERACT
- D. Both B and C



Challenge Question #2

You should not include complete study reports in your pre-IND package.

- A. True
- B. False

Summary



- OTP regulates a diverse and complex group of products.
- The complex biological properties and risks associated with OTP products necessitate a case-by-case approach for the P/T program.
- Nonclinical data submitted in an IND should support the safety and biological activity of the product for the proposed clinical indication.
- Early communication with CBER/OTP can mitigate potential issues with nonclinical programs and help to ensure a successful IND submission.

FDA Guidance Documents



- [Human Gene Therapy Products Incorporating Human Genome Editing; Draft Guidance for Industry \(March 2022\)](#)
- [Considerations for the Development of Chimeric Antigen Receptor \(CAR\) T Cell Products; Draft Guidance for Industry \(March 2022\)](#)
- [Human Gene Therapy for Neurodegenerative Diseases; Draft Guidance for Industry \(January 2021\)](#)
- [Human Gene Therapy for Hemophilia; Guidance for Industry \(January 2021\)](#)
- [Human Gene Therapy for Rare Diseases; Guidance for Industry \(January 2021\)](#)
- [Human Gene Therapy for Retinal Disorders; Guidance for Industry \(January 2021\)](#)
- [Draft Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products \(December 2017\)](#)
- [Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products \(November 2013\)](#)

Contact Information

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- **OTP Learn Webinar Series:**
<http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm>
- **CBER website:**
www.fda.gov/BiologicsBloodVaccines/default.htm
- **Phone:** 1-800-835-4709 or 240-402-8010
- **Consumer Affairs Branch:** ocod@fda.hhs.gov
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