

Common Preclinical Challenges in the Development of Cellular and Gene Therapy Products

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Learning Objectives

- Describe CBER/OTAT regulated products
- Understand preclinical considerations for assessing the safety of cell therapy (CT) and gene therapy (GT) products
- Introduce the opportunities for early interaction with CBER/OTAT
- Discuss common challenges with the preclinical elements of an IND submission



Products Regulated by OTAT

Diversity of CBER Regulated Products

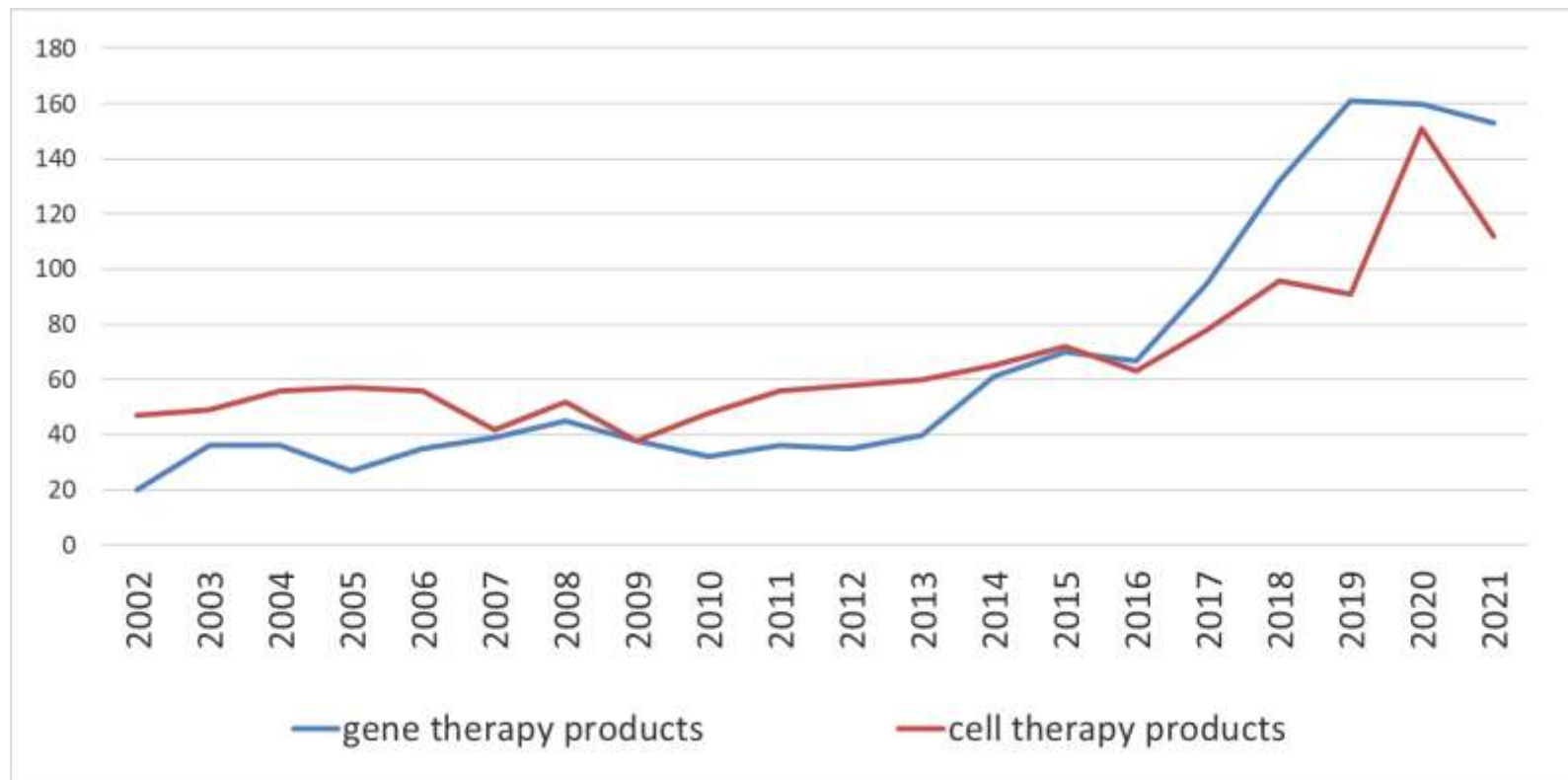


Diversity of CBER/OTAT-Regulated Products



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

GT and CT IND Submissions: 2002 – 2021





Considerations for Preclinical Evaluation of CT and GT Products

General Considerations for Preclinical Testing Programs



- How does CBER/OTAT evaluate preclinical safety and activity?
- What are important elements to consider when developing a preclinical 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 OCOB 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 Preclinical 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, 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 Preclinical 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 (preclinical and clinical) for:
 - The proposed clinical product or a similar product
 - The proposed subject population
 - The proposed clinical ROA

Considerations for a Preclinical Testing Program

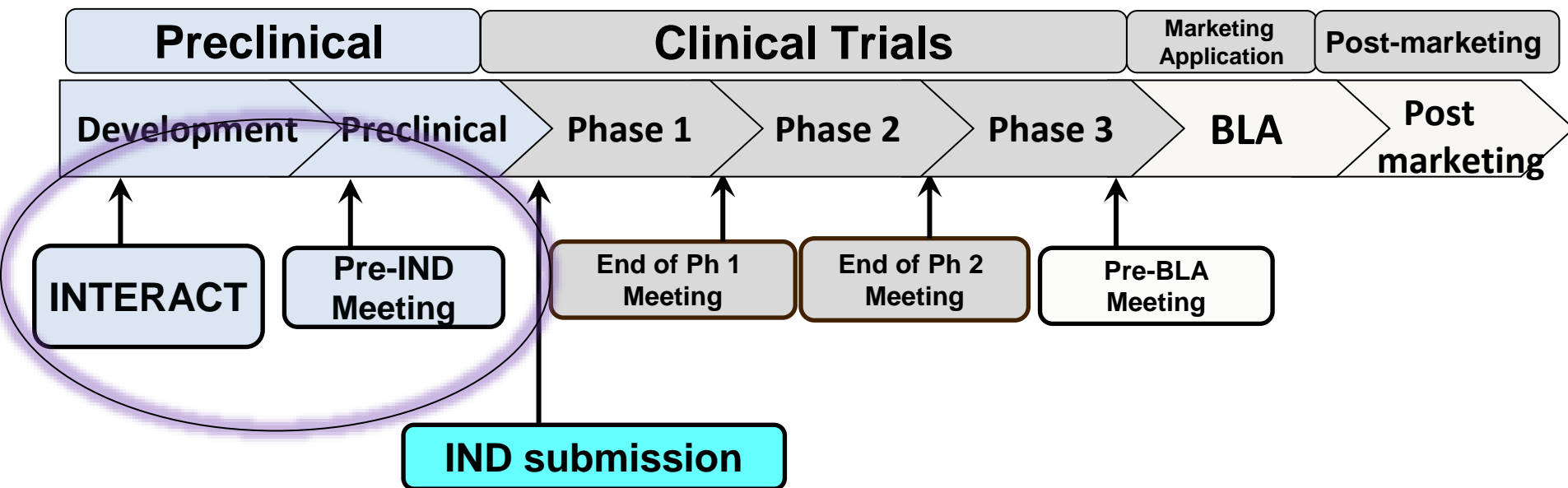


- The diversity and biological properties of CT and GT products necessitate a flexible testing strategy - no “one size fits all”
 - Science-based and data-driven
 - Based on accumulated knowledge and experience
 - Based on available technology(ies) and methods



Early Communication Opportunities

Opportunities for Early Interactions with CBER/OTAT



INTERACT Meetings

Initial Targeted Engagement for Regulatory Advice on CBER products

(<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

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

Pre-IND Meetings – Preclinical Program

- **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 completed¹⁷
 - Ready to conduct definitive safety studies

Pre-IND Meetings – Preclinical Program



A comprehensive summary of all completed preclinical studies

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

Comprehensive protocols for the proposed definitive preclinical 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 preclinical and clinical products.
- Include the design and findings of your completed studies and protocols/detailed outlines for your proposed studies.
- Provide the scientific rationale for the dose levels, dosing regimen, and duration of your completed and planned studies
- Discuss the 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 (include page numbers and copies of key supporting publications).

Don't

- Start your definitive safety/distribution studies until obtaining FDA feedback in a pre-IND setting.
- Forget to provide adequate justification and discussion of limitations of your selected animal models/test systems
- Forget to discuss issues and concerns that arise from your completed preclinical 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).



Investigational New Drug (IND) Applications

IND Applications

- Under 21 CFR 312, any use in the United States (US) of a drug (or a biological product) not previously authorized for marketing in the US requires submission of an IND application to the FDA
- Any human research study must be conducted under an IND application if the research:
 - Involves **a drug** (or a biological product)
 - Is **a clinical investigation**
 - Is **not exempt** from the IND requirements
- INDs should include all necessary information regarding product manufacturing (CMC), Pharmacology/Toxicology (P/T) and trial design (Clinical)

IND Application: Documents Containing P/T Information

- Investigational Brochure (IB), (as appropriate, (21 CFR 312.55)
- P/T overview
- P/T study reports
- Letter(s) of Authorization allowing cross-reference to other regulatory files
- Applicable publications

Some Do's and Don'ts for the P/T Section of INDs



Do

- Include the IB, when applicable. Ensure that the P/T section of the IB contains summaries that are not misleading and accurately and sufficiently reflect each conducted study.
- Provide the rationale, with supporting data, for selection of each animal model/test system.
- Provide rationale and supporting calculation method for dose level extrapolation from animal to human.
- Highlight data from the preclinical studies to support elements of the clinical study design (dose levels, ROA). Include preclinical POC data to support prospect of direct benefit (pediatric First-in-Human studies)
- Include POC data to support a novel device.
- Provide **complete, final** study reports for all completed preclinical studies.

Don't

- Forget to consider previous INTERACT/pre-IND comments.
- Forget to provide sufficient data to support the safety of the proposed starting dose level and dose escalation scheme.
- Forget to explain the similarities and differences between the preclinical product lots and your intended clinical product.
- Forget to conduct definitive safety studies per Good Laboratory Practice (GLP; 21 CFR Part 58).
- Forget to discuss any toxicity signals observed in animal studies.
- Include incomplete, unsigned study reports.
- Forget to respond to FDA requests for information within the FDA-specified time interval.



Practical Points for GT and CT P/T Programs

The P/T Program: Practical Points (Do's)

- Use biologically responsive animal species and models/test systems – justify the model/test system.
- Apply the 3Rs principle [Reduce, Refine, Replace].
- Administer the intended clinical product, if feasible.
- Mimic the proposed clinical scenario as closely as possible (e.g., ROA, delivery device, delivery procedure, timing of product administration, etc.), ensure adequate study duration.
- Design studies as controlled, masked, randomized, with adequate group sizes and sufficient duration to allow assessment of the activity, safety, and distribution profiles.
- Conduct comprehensive analyses of every unscheduled death.
- Provide the calculation and justification for the dose level extrapolation from animals to humans.
- Conduct the toxicology studies in compliance with GLP (21 CFR Part 58).
- Submit complete study reports for all preclinical studies conducted.
- Follow applicable guidance documents.
- Approach CBER/OTAT early in your product development program.

The P/T Program: Practical Points (Don't's)

- Assume that FDA personnel are going to design your preclinical studies.
- Assume that testing in one rodent and one non-rodent animal species is necessary.
- Assume that nonhuman primates are required for preclinical testing for every investigational CT and GT product.
- Conduct definitive preclinical studies without obtaining appropriate POC data (*in vitro* and *in vivo*) essential for guiding study design(s).
- Conduct non-GLP toxicology studies without oversight by a Quality Assurance unit/person that is independent of the personnel responsible for the conduct of this study.
- Provide a poorly written/organized and incomplete pre-IND or IND submission.
- Submit summary animal data without study reports.
- Assume that inclusion of publications alone in an IND is sufficient to support a clinical trial.



Challenge Question #1

What is a type of early interaction with CBER/OTAT that can be requested to prepare for your IND submission?

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



Challenge Question #2

You should include all complete study reports in your pre-IND package.

- A. True
- B. False

Challenge Question #3

What information for a completed P/T study should be included an IND submission?

- A. An accurate summary in the IB.
- B. Letter of authorization allowing cross-reference to other regulatory files.
- C. Final, signed study report.
- D. All of the above.

Challenge Question #4

Definitive toxicology studies should always be conducted in nonhuman primates.

- A. True
- B. False

Summary

- OTAT regulates a diverse and complex group of products.
- The complex biological properties and risks associated with OTAT products necessitate a case-by-case approach for the P/T program.
- Preclinical data submitted in an IND should support the safety and biological activity of the product for the proposed clinical indication.
- Early communication with CBER/OTAT can mitigate potential issues with preclinical 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 \(November 2013\)](#)

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<http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm>
- **CBER website:**
www.fda.gov/BiologicsBloodVaccines/default.htm
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