

Nonclinical Considerations for the Development of Cell and Gene Therapy Products for IND Submissions

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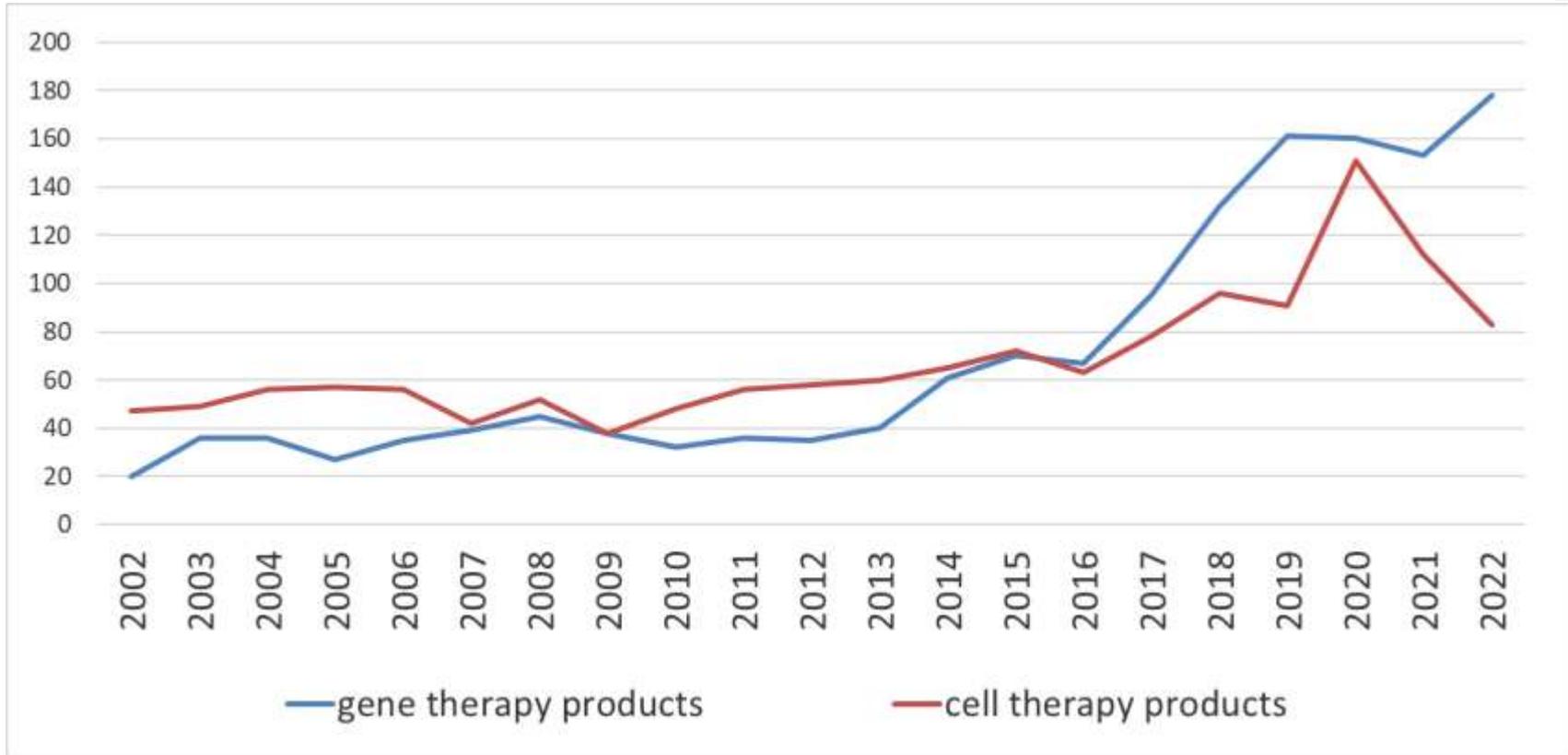
Learning Objectives

- Introduce the pharmacology and toxicology components of an IND application
- Understand the concept of prospect of direct benefit (PDB) and product development for pediatrics
- Discuss common challenges with the nonclinical elements of an IND submission

Diversity of CBER Regulated Products



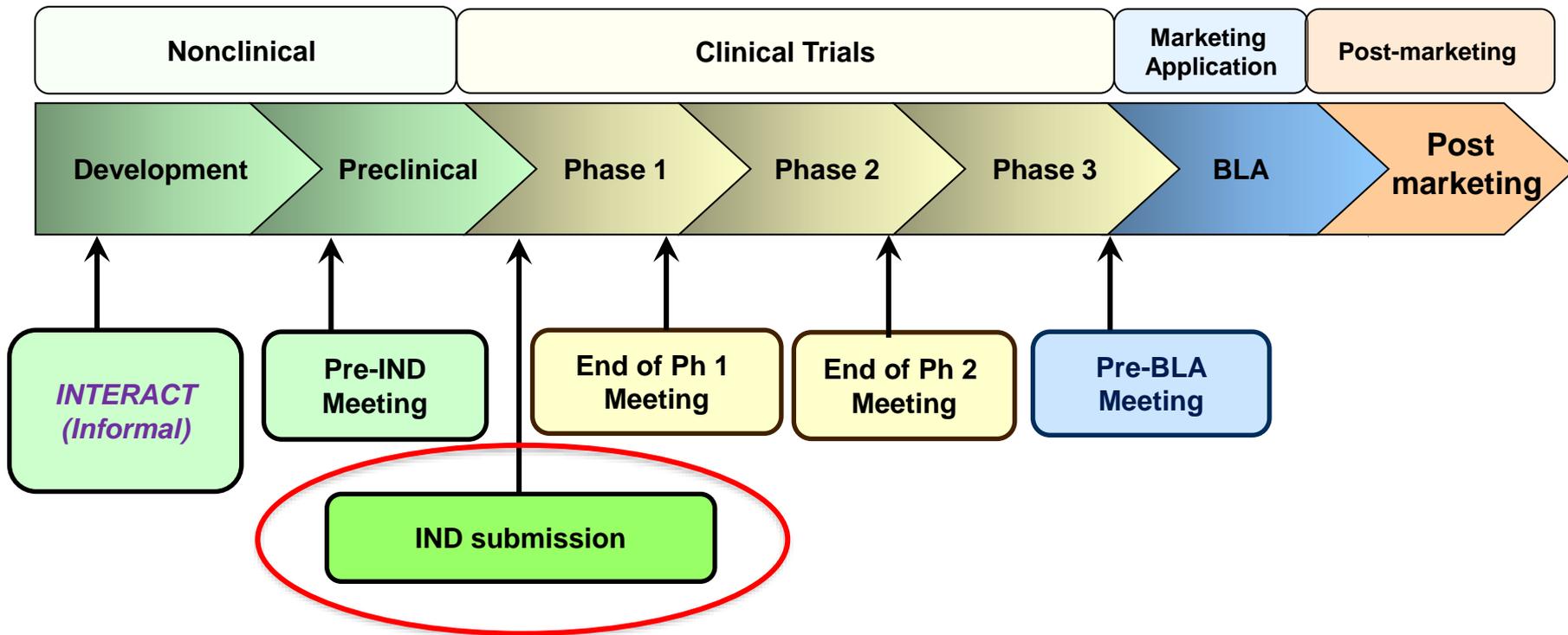
Gene Therapy (GT) and Cell Therapy (CT) IND Submissions



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
- 30-day FDA review clock to make a ‘hold / no hold’ decision for an IND

Pathway to Marketing



Components of an IND Submission



| | | |
|--------------------------|---|----------------------|
| <input type="checkbox"/> | Form FDA 1571 | 21 CFR 312.23(a)(1) |
| <input type="checkbox"/> | Table of Contents | 21 CFR 312.23(a)(2) |
| <input type="checkbox"/> | Introductory statement and general investigational plan | 21 CFR 312.23(a)(3) |
| <input type="checkbox"/> | Investigator's Brochure | 21 CFR 312.23(a)(5) |
| <input type="checkbox"/> | Clinical Protocol(s) | 21 CFR 312.23(a)(6) |
| <input type="checkbox"/> | Chemistry, manufacturing, and control data | 21 CFR 312.23(a)(7) |
| <input type="checkbox"/> | Pharmacology and Toxicology (P/T) data | 21 CFR 312.23(a)(8) |
| <input type="checkbox"/> | Previous human experience | 21 CFR 312.23(a)(9) |
| <input type="checkbox"/> | Additional information | 21 CFR 312.23(a)(10) |

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Investigator's Brochure (IB)

- **A compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects**
- Purpose:
 - To provide investigators with information to facilitate their understanding of the rationale for, and their compliance with, key features of the protocol
 - Presented in a way that enables an investigator to make an unbiased risk-benefit assessment of the proposed trial
- The sponsor should update the Investigator's Brochure as significant new information becomes available

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IND Application: Documents Included in P/T Section



- P/T overview and summary documents
- P/T study reports
 - Proof-of-concept (POC) studies
 - Toxicology and biodistribution studies
 - For all studies, a final signed and complete report should be included
- Applicable publications



Goals of the P/T Section of an IND

- Provide justification for the first-in-human clinical trial in subjects with the target disease/injury
- Support the starting clinical dose level, dosing regimen, route of administration (ROA)
- Establish feasibility and reasonable safety of the product administration procedure
- Support subject eligibility criteria
- Identify potential toxicities and physiologic parameters to help guide clinical monitoring

Considerations for a Nonclinical Testing Program

- The diversity and biological properties of cell therapy (CT) and gene therapy (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

Nonclinical Testing Program for CT Products



- Proof-of-concept (POC) studies
 - Demonstrate evidence of therapeutic effect in animal models that recapitulate aspects of the clinical disease / medical condition
- Cell fate assessment
 - Persistence, distribution, phenotype, proliferation
 - Affected by route of administration and the *in vivo* microenvironment
 - Help in the interpretation of product activity and safety
 - Tumorigenicity
- Immunogenicity and host response

Nonclinical Testing Program for GT Products



- Nonclinical programs for gene therapy products must address many similar issues of cell therapy products (dose range finding, route of administration, safety, etc.)
- In addition, the extent and pattern to which some gene therapy products integrate into the genome must be well characterized
 - Vector biodistribution and persistence
 - Potential for germline transmission
- Depending on the product, long term follow-up plans (for up to 15 years) should be in place
- Safety issues related to shedding concerns for certain gene therapy products

Safety is Always Primary

“FDA’s primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug’s effectiveness and safety...”

[IND Regulations [21 CFR 312.22 (a) - General Principles of the IND Submission]

Nonclinical Toxicology Study Design



- Standard toxicology endpoints
 - Mortality
 - Clinical observations, body weights, appetite, etc.
 - Clinical pathology - hematology, coagulation, serum chemistry, urinalysis
 - Terminal assessments – macroscopic exam, organ weights, histopathology
- Adequate numbers of animals / group for study robustness
- Multiple sacrifice time points and sufficient study duration to evaluate both acute and long-term safety endpoints
- Identification of a No-Observed-Adverse-Effect-Level (NOAEL)
- As of March 15 2023, standardized datasets in the Standard for the Exchange of Nonclinical Data (SEND) format will be required for applicable nonclinical studies

Pediatric Subjects: Prospect of Direct Benefit (PDB)

- Clinical investigations in pediatric subjects may involve more than a minor increase over minimal risk only if they offer a prospect of direct benefit to the individual subjects (21 CFR 50.52)
- The necessary level of evidence to support PDB may be based on nonclinical POC studies or available human data

Potential Nonclinical Pitfalls When Submitting an IND



- **Missing information**
 - Missing pharmacology/toxicology section
 - Insufficient safety evaluation (i.e., important studies not conducted)
 - Incomplete study reports
- **Nonclinical product**
 - Significant differences between nonclinical and clinical products
 - Inadequate characterization of nonclinical product
- **Inadequate nonclinical study design**
 - Safety monitoring (safety/activity endpoints)
 - Animal numbers
 - Study duration
 - Route of administration/anatomic site of delivery

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 nonclinical studies to support elements of the clinical study design (dose levels, ROA). Include nonclinical 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 nonclinical studies.

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



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 nonclinical 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.
- Provide a poorly written/organized or incomplete IND submission.

Challenge Question #1



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, if applicable.
- C. Final, signed study report.
- D. All of the above.

Challenge Question #2

Evidence to support PDB must be based on previously generated human data in adult subjects.

- A. True
- B. False

Summary

- 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.
- Understand the benefit: risk profile of your product.
- 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; Guidance for Industry \(October 2022\)](#)
- [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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- **CBER website:**
www.fda.gov/BiologicsBloodVaccines/default.htm
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