Preclinical Development Considerations for Gene Therapies - A CBER/FDA Perspective

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FDA Small Business Regulatory Education for Industry (REdI)
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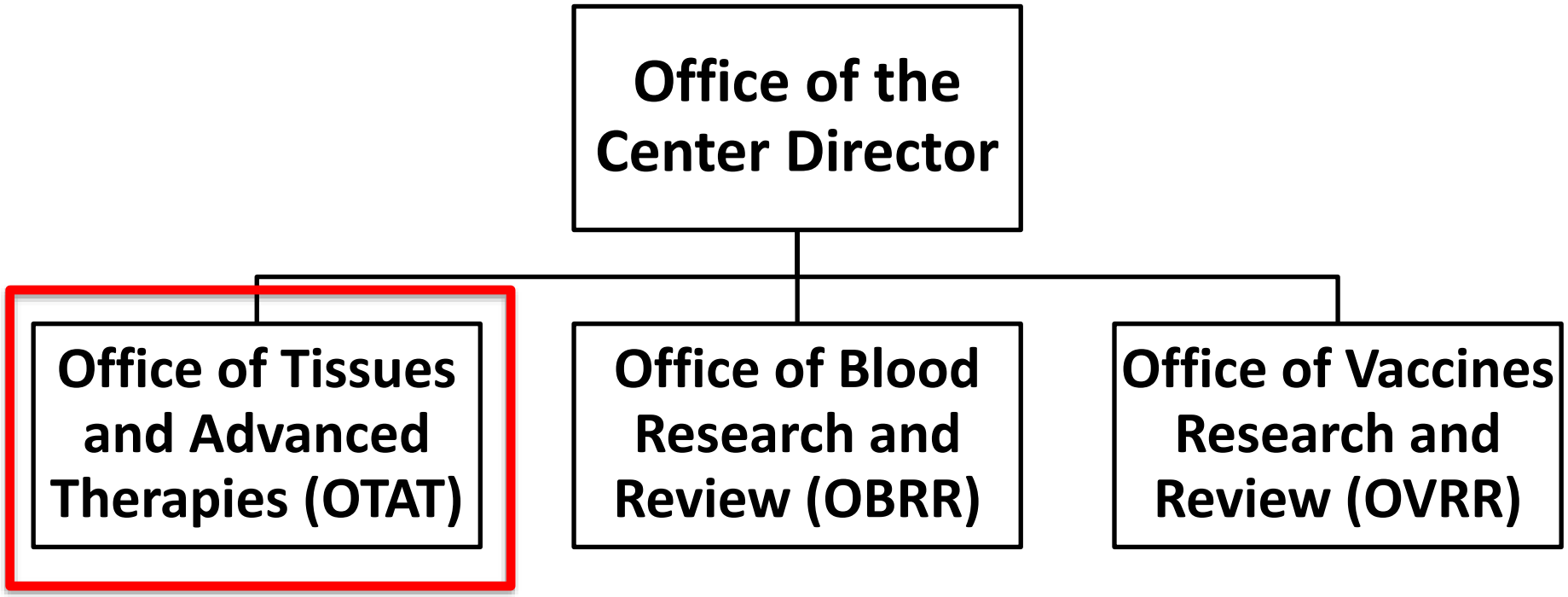
Learning Objectives

- List the types of gene therapy (GT) products regulated by FDA/CBER/OTAT and their associated risks
- Explain the preclinical expectations and testing strategy for GT products
- Understand preclinical considerations for assessing the safety/activity of GT products
- Understand the benefits of early communication with CBER/OTAT

Types of GT products regulated by FDA/CBER/OTAT and their associated risks

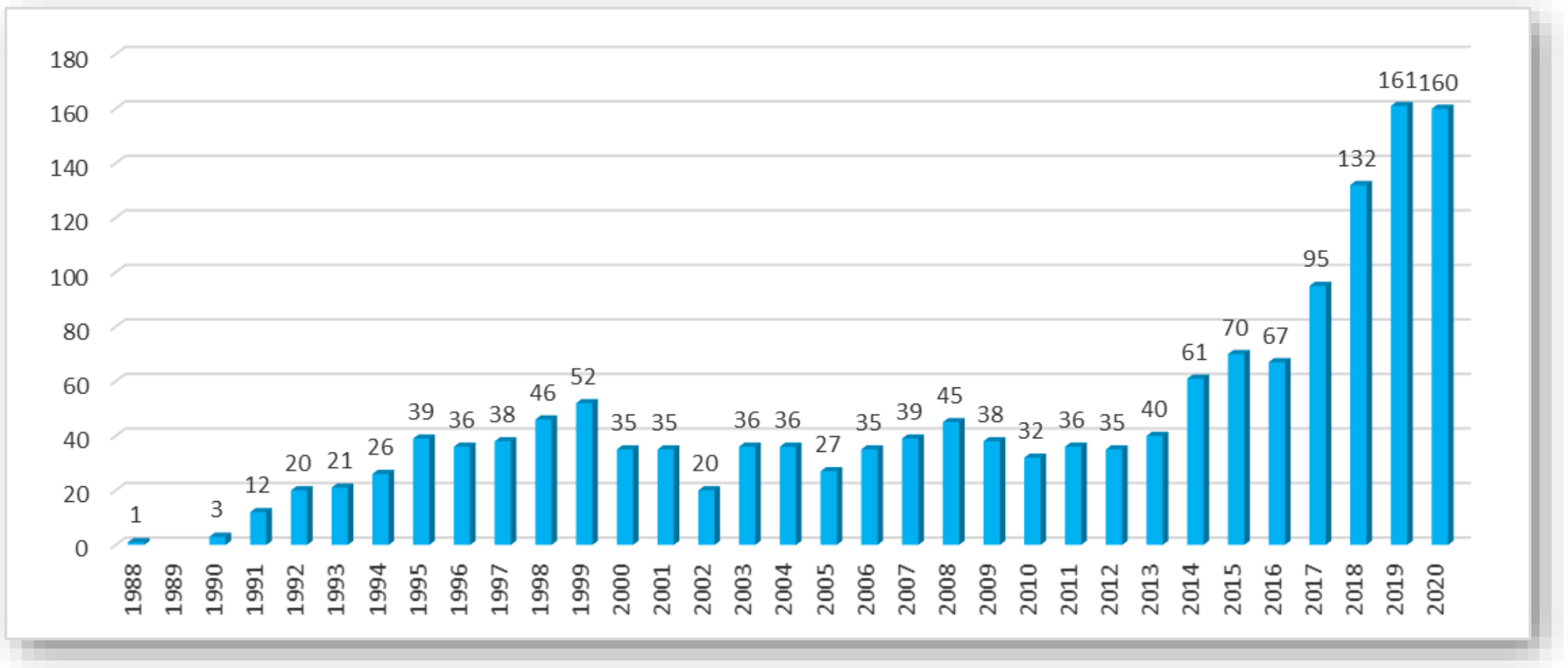
CBER Product Review Offices



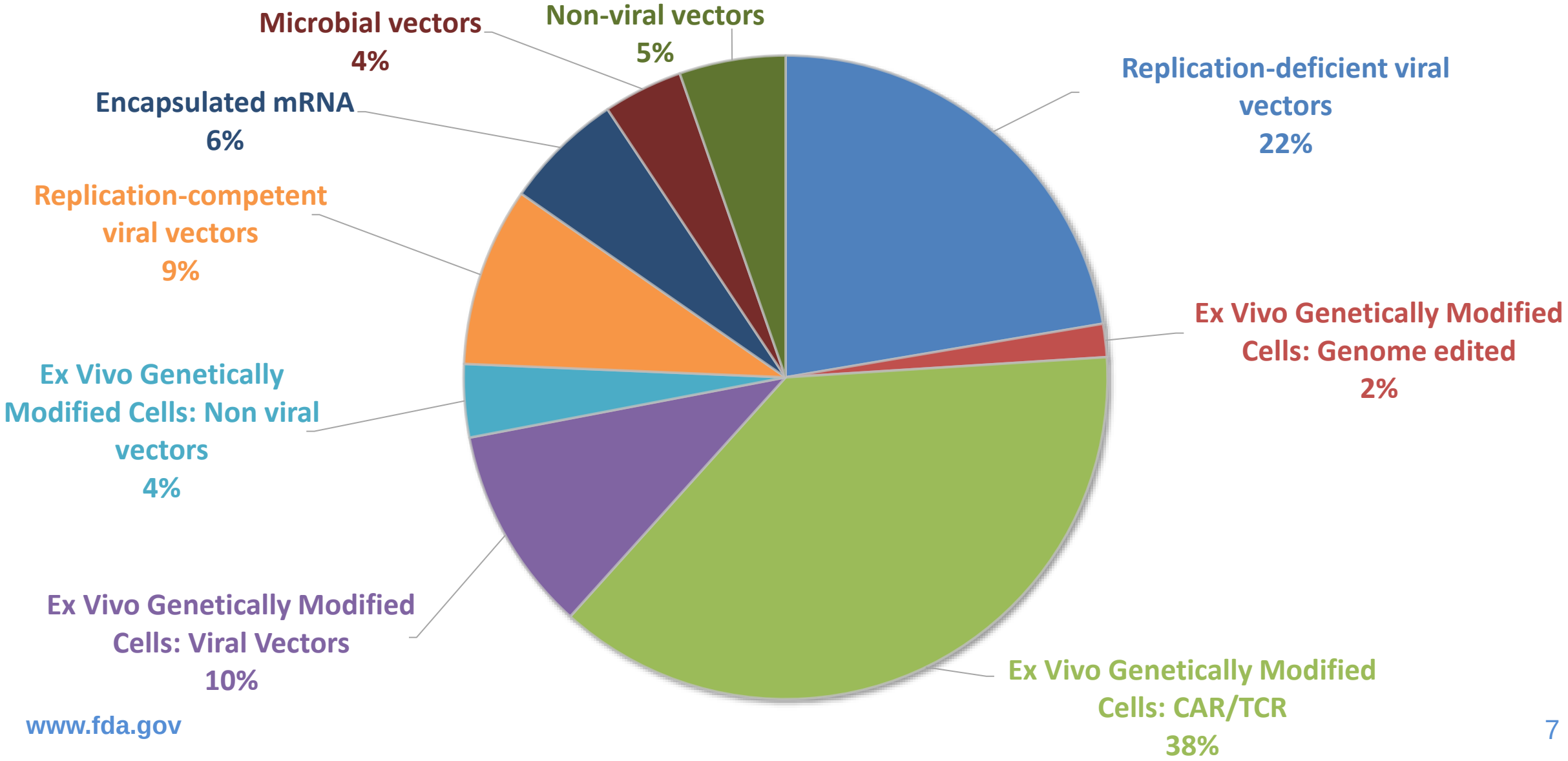
GT Products Regulated by OTAT

- Ex vivo genetically modified cells (e.g., CAR-T cells)
- Replication-deficient viral vectors (e.g., adeno-associated virus)
- Replication-competent viral vectors (e.g., oncolytic viruses)
- Encapsulated mRNA
- Non-viral vectors (e.g., plasmids)
- Microbial vectors (e.g., Listeria)
- Genome edited products

Investigational New Drug (IND) Submissions: GT Products



IND Submissions: GT Products - 2019-2020



Safety Concerns for GT Products

- Distribution to non-target sites/tissues
- Viral replication and persistence in non-target tissues
- Immune response to the vector and/or transgene
- Transgene-related toxicities
- Potential for oncogenicity

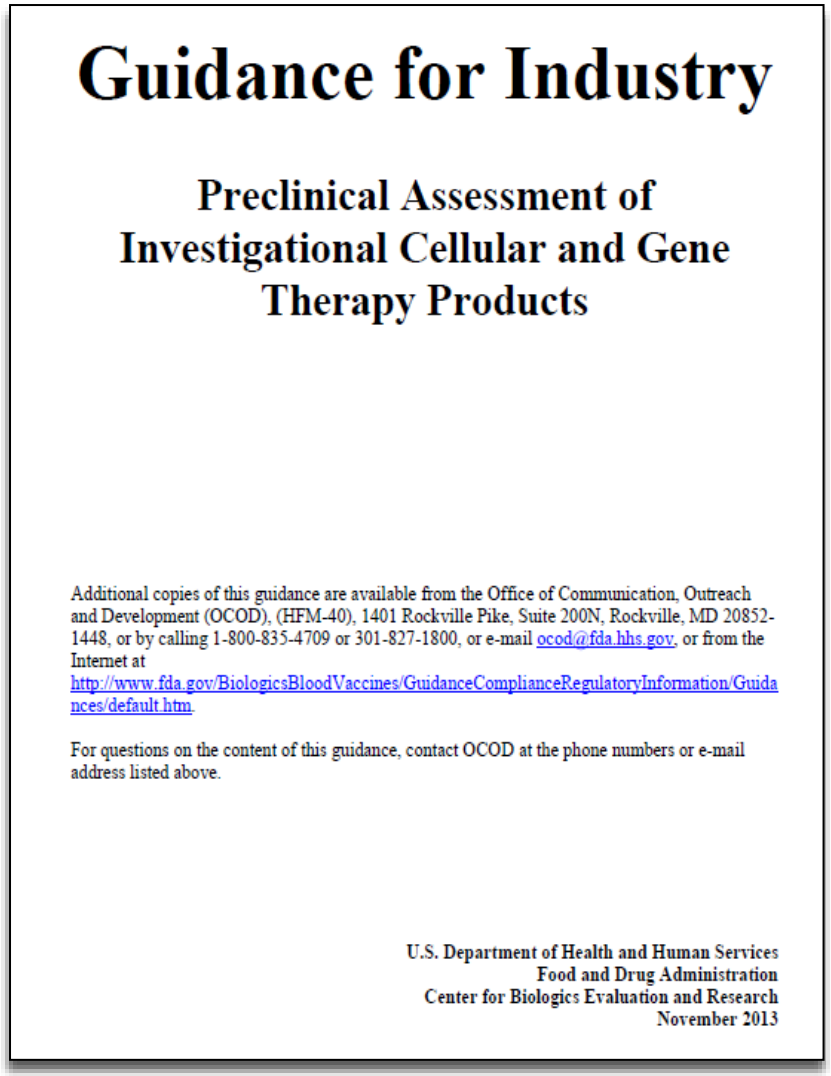
Safety Concerns for GT Products (cont'd)

- Genetically modified cells – inappropriate cell proliferation, differentiation, distribution to non-target tissues
- Toxicities related to the formulation
- Potential for germline transmission, developmental and reproductive toxicology (DART)
- Interactions with concomitant therapies (i.e., immunosuppressive agents)
- Risks of the delivery procedure

Preclinical expectations and testing strategy of investigational GT products

Expectations from Preclinical Data

- Establish rationale and proof-of-concept (POC) for administration of a specific product to a specific patient population
  - Understand biological activity and mechanism of action
  - *In vitro* and *in vivo* studies in an animal model of disease/injury
- Perform a comprehensive safety assessment of the GT product following administration via the intended clinical route
  - Characterize safety profile (local and systemic toxicities, acute and delayed toxicities)



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.

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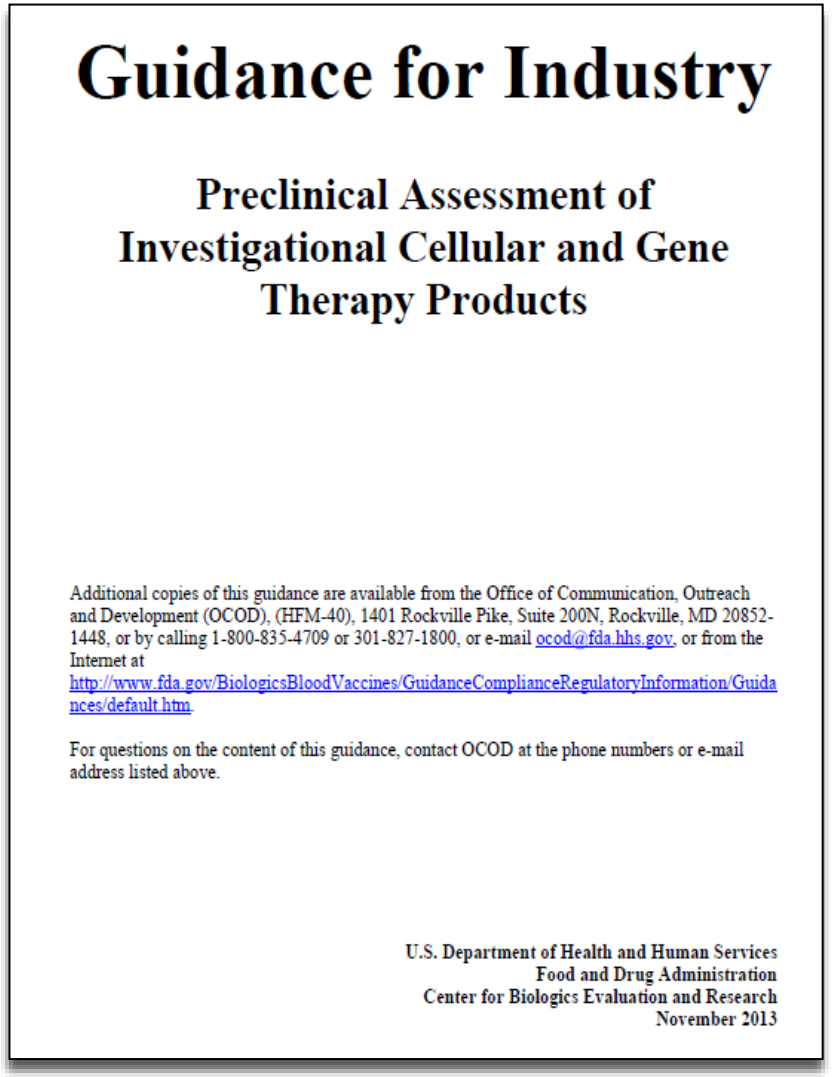
Food and Drug Administration
Center for Biologics Evaluation and Research
November 2013

Expectations from Preclinical Data (con't)

- Provide recommendations to inform clinical trial design
  - Eligibility criteria
  - Initial safe starting dose, dose-escalation scheme, dosing regimen
  - Route of administration
  - Clinical monitoring and risk mitigation

- Meet regulatory requirements
  - 21 CFR 312.23 (a)(8)
  - 21 CFR 58 (Good Laboratory Practice (GLP) compliance)



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Preclinical Testing Strategy for GT Products

- The diversity and biological properties of GT products necessitate a flexible testing strategy - no “one size fits all”
  - Based on accumulated knowledge and experience
  - Based on available technology
  - Data-driven

- Weight-of-evidence approach – evaluating the benefit:risk profile

Preclinical Testing Strategy for GT Products

- Proof-of-concept studies in relevant *in vitro* testing systems and animal species/models of disease
  - To understand the mechanism of action and overall biological activity
  - To establish feasibility and support the scientific rationale for the clinical trial
- Product fate: biodistribution or transduced cell fate in animal species/model of disease
  - Biodistribution: distribution, persistence, and clearance of vector/transgene in target and non-target tissues
  - Transduced cell fate: persistence, distribution, phenotype, proliferation, and differentiation of genetically modified cells

Preclinical Testing Strategy for GT Products

- Safety assessment in animal species/model of disease
  - Considerations: standard safety assessments, clinical route of administration, bracket the clinical dose level range
  - Product specific assessments:
    - Immunogenicity
    - On- and off-target toxicities
    - Vector integration
    - On and off-target editing
    - Insertions/deletions
    - Chromosomal translocations
    - Tumorgenicity

Key preclinical considerations for investigational GT products

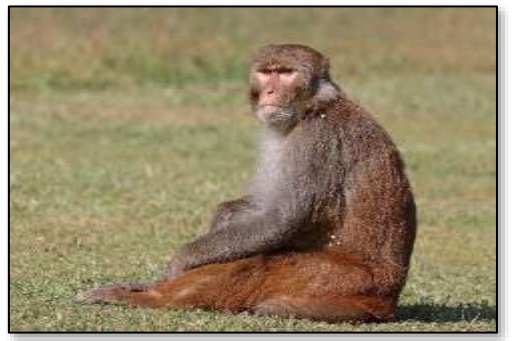
GT Preclinical Testing Considerations: Preclinical Product

Preclinical product should be as similar as possible to the intended clinical product:

- Identity
- Viral genome titer and infectivity
- Transduction/editing efficiency
- Manufacturing process
- Cellular morphology and phenotype
- Final formulation and storage
- Molecular/biochemical markers
- Reflects product release criteria

GT Preclinical Testing Considerations: Animal Species/Model (s)

- Scientific justification – no default species
- Understand animal species/model(s) limitations
- Permissive to vector transduction/replication/genome editing
- Pharmacological response to the product
- Comparative physiology/pathophysiology to human
- Feasibility of clinical delivery system/delivery procedure



GT Preclinical Testing Considerations: Animal Study Design Considerations

- Mimic the planned clinical trial to the extent possible
- Adequate numbers of animals/sex/group to enable study interpretation
- Inclusion of multiple dose levels with justification of dosing regimen
- Nonbiased design
- Multiple sacrifice intervals (as appropriate) and sufficient study duration
- Comprehensive bioactivity, biodistribution, and safety assessments

GT Preclinical Testing Considerations: Dose Level Extrapolation

- Preclinical data should support the starting clinical dose level and dose-escalation scheme by:
  - Proof-of-concept data may define a Minimal Effective Dose level (MED)
  - Safety data may define a No-Observed-Adverse-Effect-Level (NOAEL)

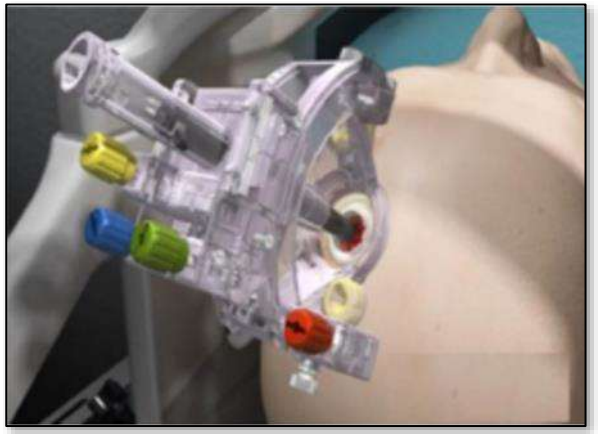
- Extrapolation method from animal to human dose level(s):
  - Depends on the product and target route of administration
  - Incorporates the preclinical dose levels required for the correction of disease pathology
  - Methods use body weight, organ volume/weight, or volume of space (e.g. cerebral spinal fluid)

GT Preclinical Testing Considerations: Pediatric Indications

- GT products can be associated with more than a minor increase over minimal risk
- 21 CFR 50.52, Subpart D: requires evidence of Prospect of Direct Benefit (PDB) for each subject
- Evidence to support PDB = animal or adult human data using a key clinical endpoint, or a “surrogate” based on disease pathophysiology

GT Preclinical Testing Considerations: Delivery Device

- Use the intended clinical delivery device (as feasible)
- Bench testing to determine compatibility of the GT product with the device
- Novel delivery devices may require additional preclinical safety studies
- Biocompatibility testing

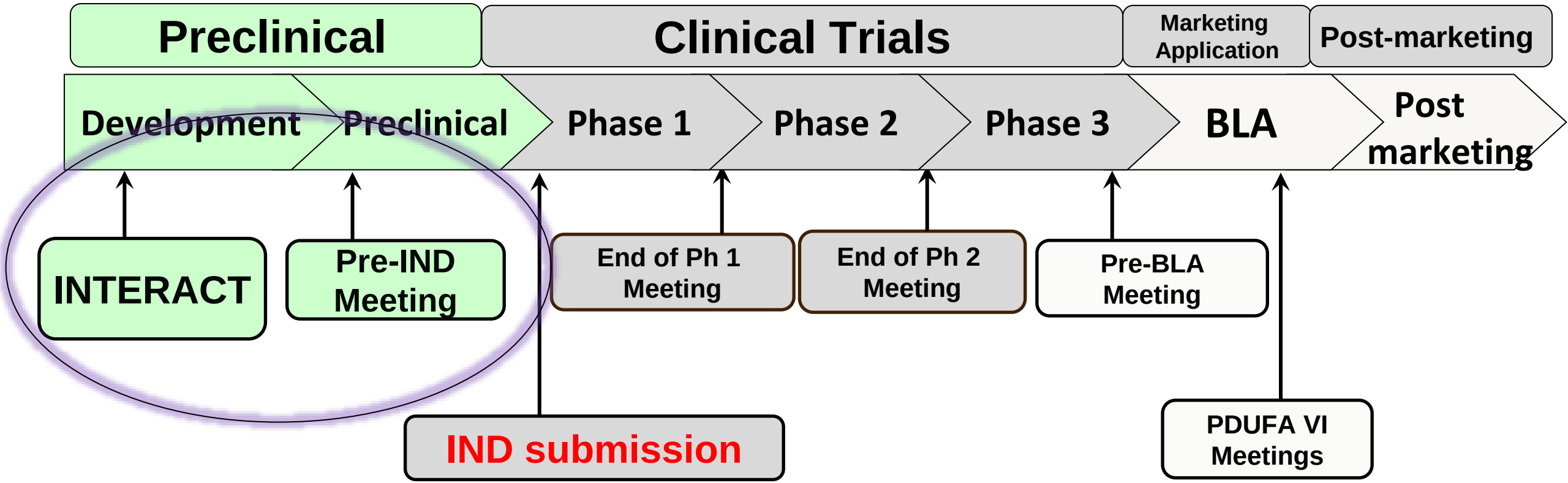


GT Preclinical Testing Considerations: Additional Safety Studies

- Tumorigenicity/Carcinogenicity Studies
  - Product specific and can be incorporated into the definitive safety study design
- Developmental and Reproductive Toxicity (DART) Studies
  - Later phases of the clinical development program
  - Concerns depend on many factors
- Testing approaches/paradigms will depend on the product and the target clinical population

Early communication with CBER/OTAT

Opportunities for Interaction - Preclinical Development



Product development is an iterative process that may involve multiple FDA and sponsor interactions

Early Communication with CBER/OTAT: INTERACT Meeting

INitial Targeted Engagement for Regulatory Advice on CBER producTs

- **Purpose:**
  - A mechanism for early communication with OTAT
  - Non-binding, informal scientific discussion between CBER/OTAT review disciplines and the sponsor
  - Initial targeted discussion of specific issues for novel investigational agents
- **Timing:**
  - When a sponsor has generated preliminary preclinical data (proof-of-concept and some safety), but is not yet ready to conduct definitive preclinical studies
- **Requests** for INTERACT meetings should be sent to: INTERACT-CBER@fda.hhs.gov
  - * https://www.fda.gov/vaccines-blood-biologics/industry-biologics/interact-meetings

Early Communication with CBER/OTAT: Pre-IND Meeting

- A non-binding, formal scientific discussion between all CBER/OTAT review disciplines (Chemistry/Manufacturing/Controls [CMC], Pharmacology/Toxicology, and Clinical) and the sponsor
- **Goal:** To achieve a successful IND submission
- **Purpose:**
  - To allow early communication between the sponsor and CBER/OTAT
  - To comprehensively communicate the product/clinical development plan
    - Product characterization issues
    - Preclinical testing program
    - The scope and design of the planned clinical trial
- **Timing:** Prior to the conduct of the definitive preclinical safety studies

Early Communication with CBER/OTAT: Pre-IND Meeting

- **Format / Process**
  - CBER/OTAT grants one pre-IND meeting
  - Primary contact: Nannette Cagungun at

    Nanette.Cagungun@fda.hhs.gov and OTATRPMS@fda.hhs.gov
  - Meeting is scheduled within 60 days of receipt of the meeting request
  - The meeting package needs to be submitted no later than 30 days prior to the scheduled meeting date
  - Consult: SOPP 8101.1 at https://www.fda.gov/media/84040/download

Challenge Question #1

Which statement is incorrect:

A. Proof-of-concept studies establish the scientific rationale for the clinical trial

B. Biodistribution/cell fate data are not required to interpret preclinical safety data and initiate a first-in-human clinical trial

C. Preclinical safety data should support the clinical dose level range, dosing regimen, and route of administration.

D. The diversity and complex biological properties of GT products require a product and indication-specific testing strategy

Challenge Question #2

Which statement is correct:

A. Evidence to support a prospect of direct benefit must come from preclinical data demonstrating a functional improvement in disease pathophysiology.

B. A straight body weight-based dose extrapolation method is always used for GT products

C. Pre-IND meetings should take place before the conduct of the definitive preclinical safety/toxicology studies.

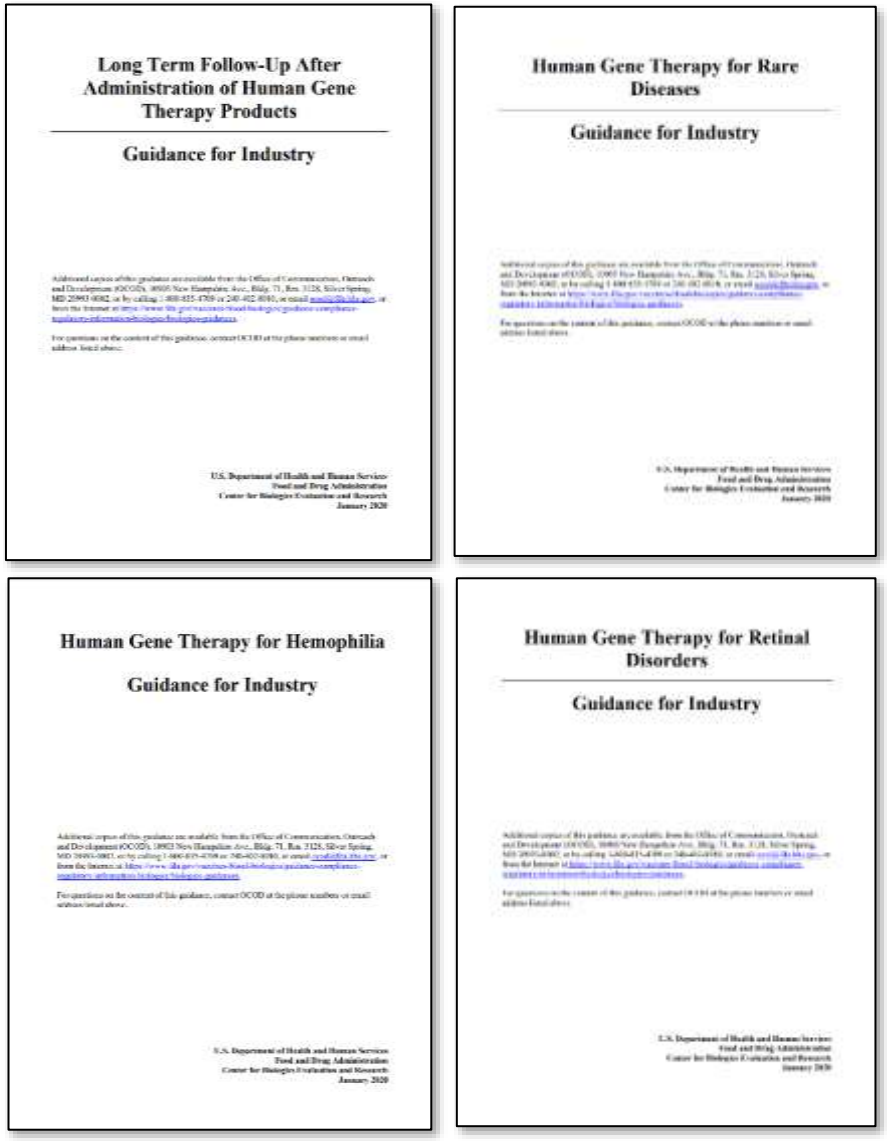
D. Preclinical safety data from studies conducted in a rodent and non-rodent species are required for an IND submission

Summary

- OTAT regulates the diverse and complex group of GT products
- The complex biological properties and risks associated with GT products necessitate a case-by-case approach
- Preclinical evaluation of GT products should inform key design elements of the clinical trial
- Early communication with CBER/OTAT can mitigate potential issues with GT preclinical programs

Recent FDA Guidances for Human GT Products

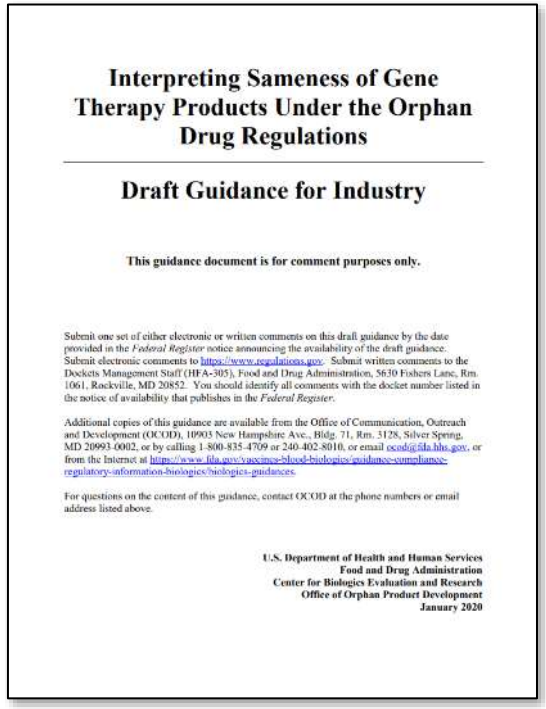
- Long Term Follow-Up After Administration of Human Gene Therapy Products (January 2020)
- Human Gene Therapy for Hemophilia (January 2020)
- Human Gene Therapy for Rare Diseases (January 2020)
- Human Gene Therapy for Retinal Disorders (January 2020)



Recent FDA Guidances for Human GT Products

- Draft Guidance for Industry: Human Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations (January 2020)

- Draft Guidance for Industry: Human Gene Therapy for Neurodegenerative Diseases (January 2021)



Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations

Draft Guidance for Industry

This guidance document is for comment purposes only.

Submit one set of either electronic or written comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, or email ocod@fda.hhs.gov, or from the Internet at https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances.

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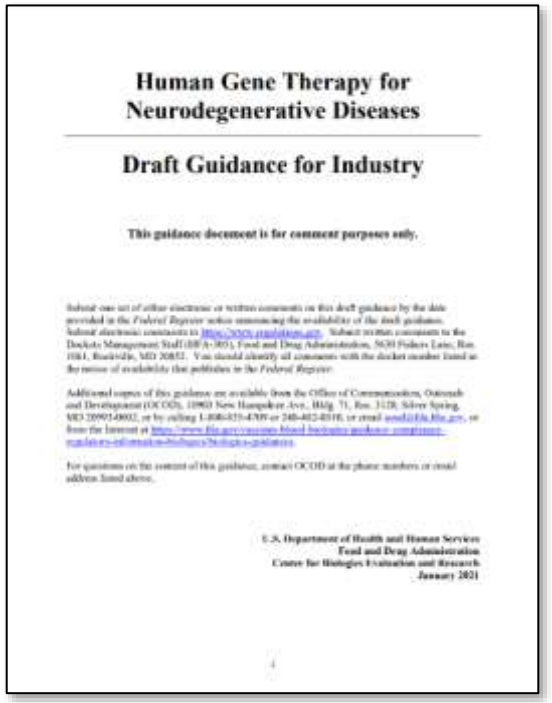
January 2020



Human Gene Therapy for Neurodegenerative Diseases

Draft Guidance for Industry

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Additional FDA Guidances

- Guidance for Industry: Use of International Standard ISO 10993-1, “Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process” (September 2020)
- Guidance for Industry: Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (IND) (January 2020)
- Draft Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products (December 2017)
- Guidance for Industry: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (June 2015)
- Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products (November 2013)

Contact Information

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- **Regulatory Questions:**

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  Email: OTATRPMS@fda.hhs.gov and

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FDA Headquarters

- **OTAT 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
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Thank you!