U.S. FOOD & DRUG ADMINISTRATION

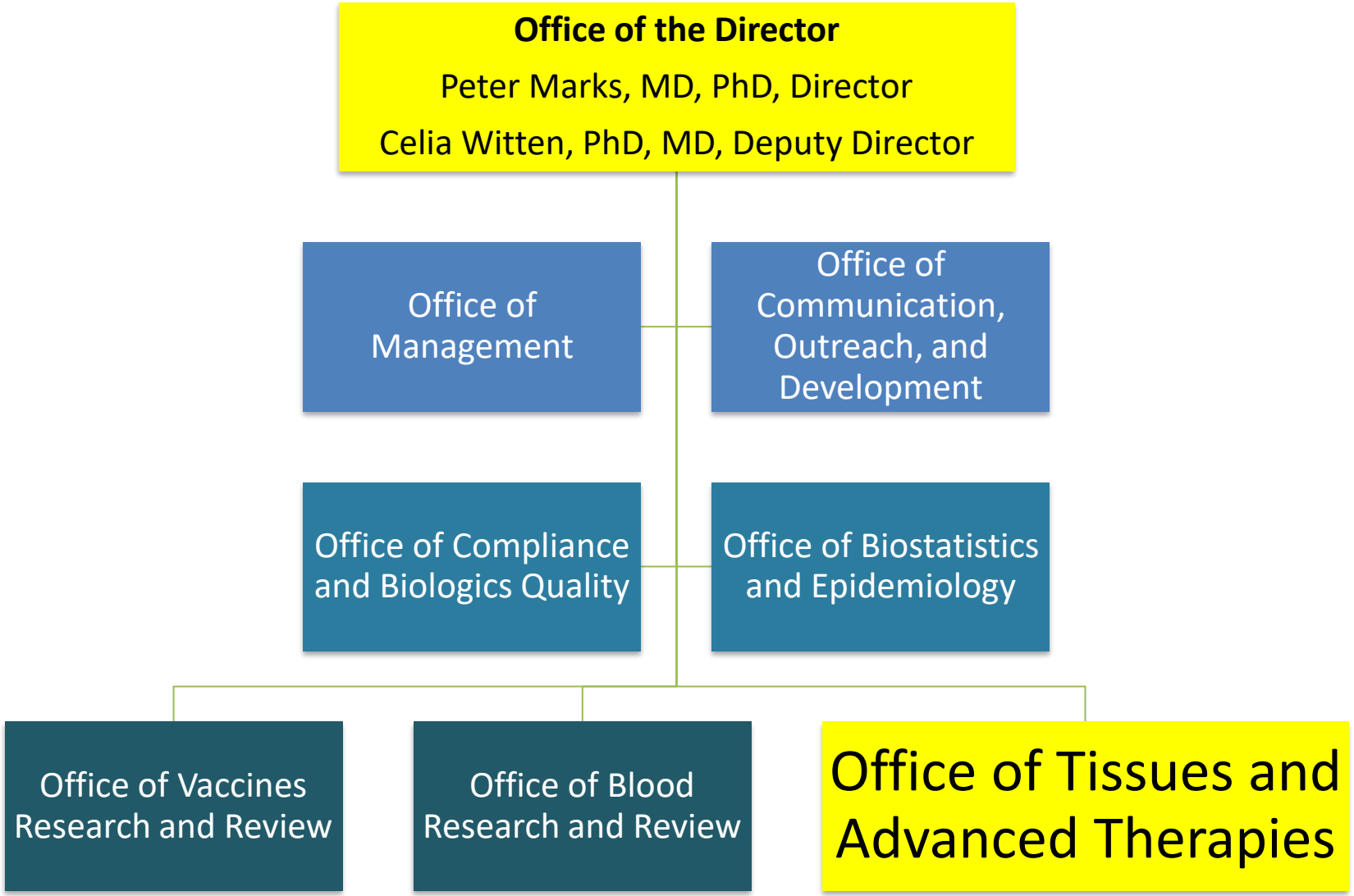
FDA / CBER
Office of Tissues and Advanced Therapies (OTAT)
Selected Topics

American Society of Gene & Cell Therapy (ASGCT)
Liaison Meeting

November 16, 2020

Wilson W. Bryan, MD

Center for Biologics Evaluation and Research (CBER)



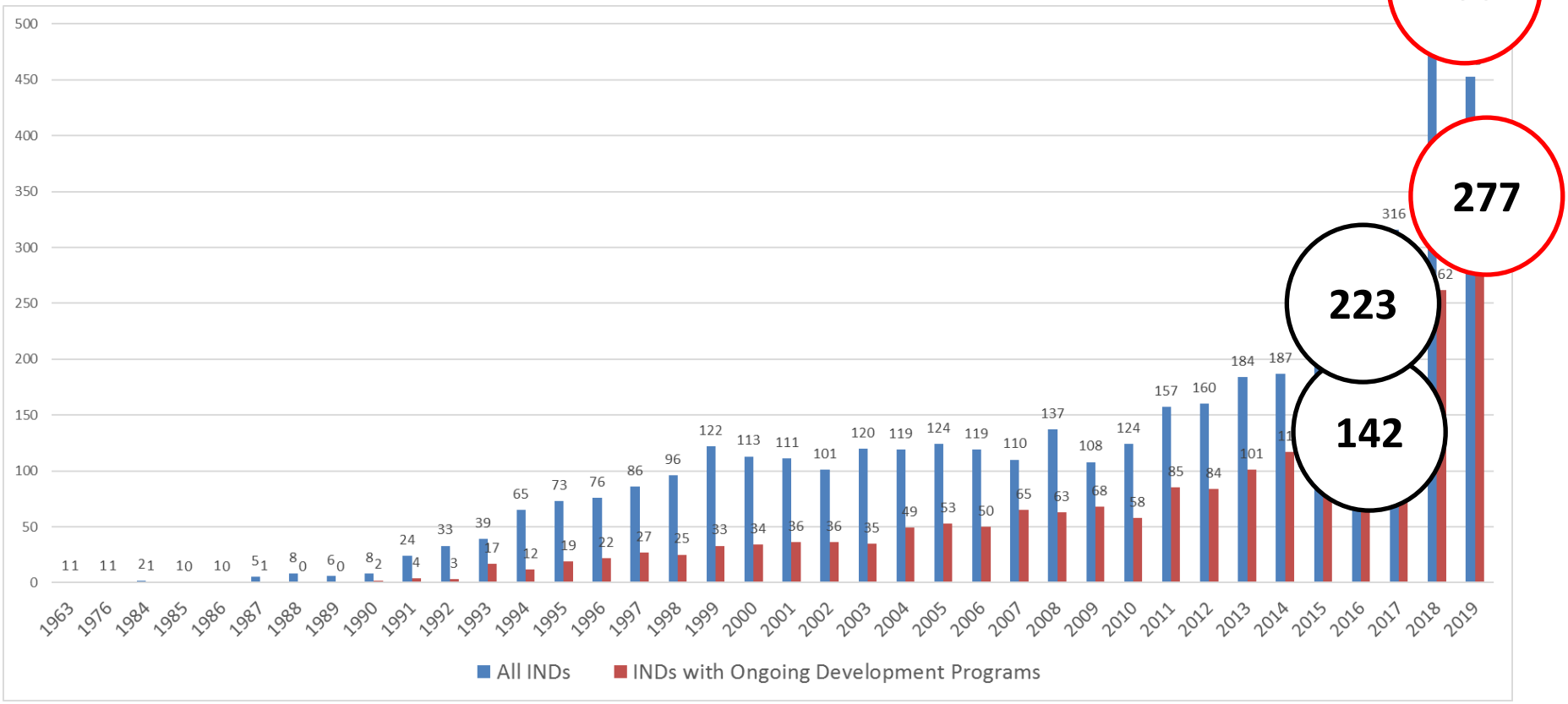
Diversity of OTAT-Regulated Products

- **Gene therapies (GT)**
  - 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**
  - 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)
- **Products for xenotransplantation**

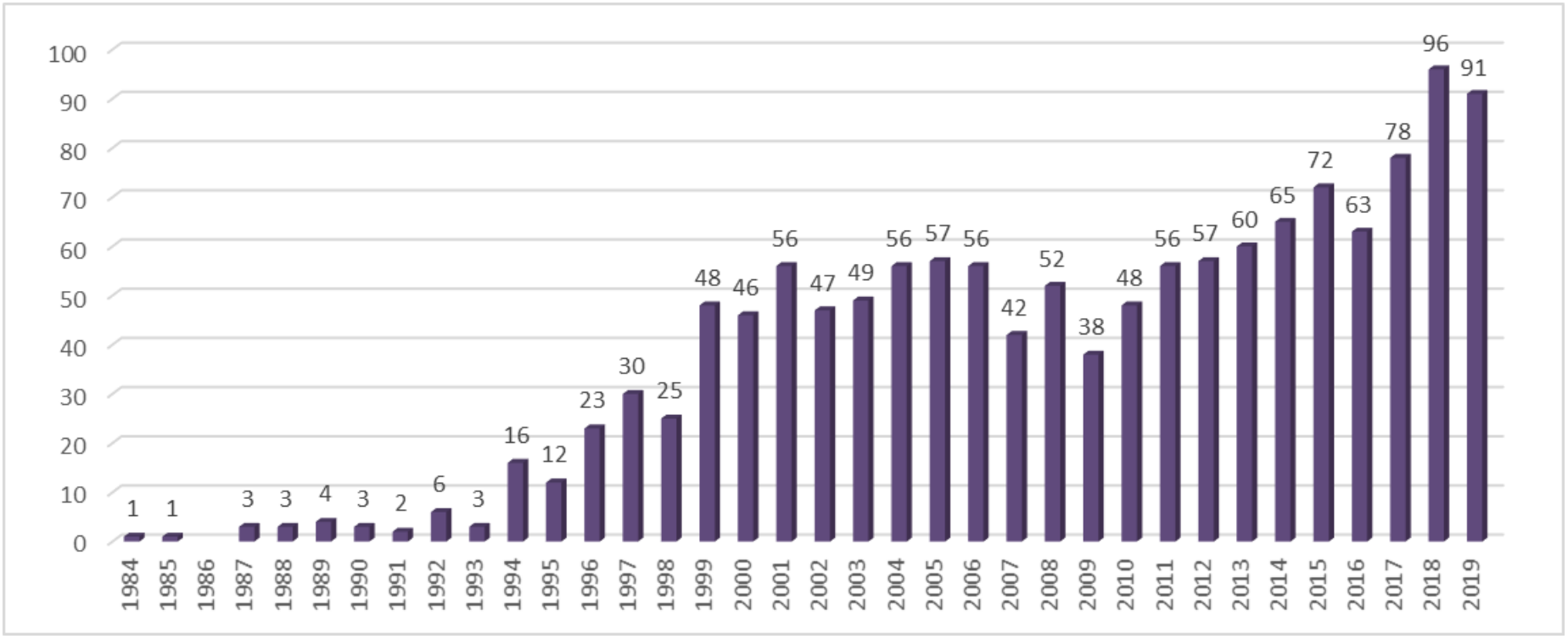
- **Functionally mature/differentiated cells** (e.g., retinal pigment epithelial cells, pancreatic islets, chondrocytes, keratinocytes)
- **Therapeutic vaccines and cellular immunotherapies** including antigen-specific active immunotherapies
- **Blood- and Plasma-derived products**
  - Coagulation factors
  - Fibrin sealants
  - Fibrinogen
  - Thrombin
  - Plasminogen
  - Immune globulins
  - Anti-toxins
  - Venom antisera for snakes, scorpions, and spiders
- **Combination products**
  - Engineered tissues/organs
- **Devices**
- **Tissues**

All New OTAT Investigational New Drug Applications (INDs) and Investigational Device Exemptions (IDEs)

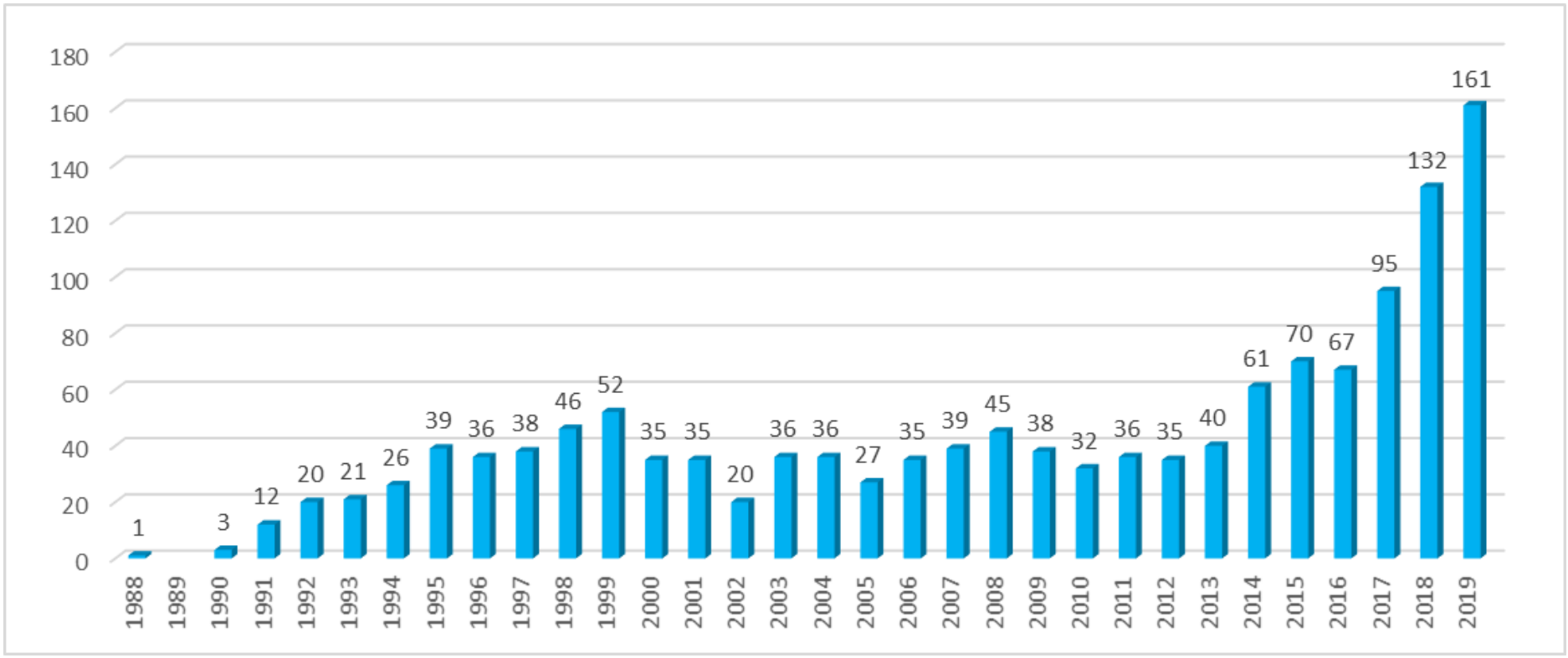
2016 vs. 2019



New INDs with Cell Therapy Development Programs, by year



New INDs with Gene Therapy Development Programs, by year



Topics

- Disease model selection
- Common issues with pre-clinical studies
- Endpoint selection (novel endpoints, biomarkers, surrogates)
- Trial design: open-label studies, leveraging first-in-human study data in the pivotal study
- Appropriate collection of patient experience data during product development
- Ideal time for sponsors to first interact with CBER
- Overcoming COVID-19 effects on gene therapy development programs
- Recommendations on pre-existing antibodies to vectors and re-administration considerations
- Requirements for contemporaneous development of a companion diagnostic for an antibody-screening assay

Animal Model Selection

- Pharmacologically responsive to the investigational product / availability of an appropriate surrogate product
- Similarity in vector tropism and transduction efficiency
- Anatomic similarity to humans
- Extent to which the model recapitulates aspects of the human disease / condition
- Disease severity / lifespan of the animal
- Ability to administer the product via the clinical route of administration and clinical dosing procedure / device

Common Issues with Preclinical Studies

- Differences between preclinical and clinical products
- Insufficient assessment of safety (e.g., study design issues)
- Inadequate data to support a favorable benefit-risk profile
- Insufficient data to establish prospect of direct benefit for pediatric subjects

Clinical Trial Design Issues

- Single-arm vs. Randomized studies
  - First-in-human studies
  - Natural History studies
- Endpoint selection (novel endpoints, biomarkers, surrogates)
- Patient experience data

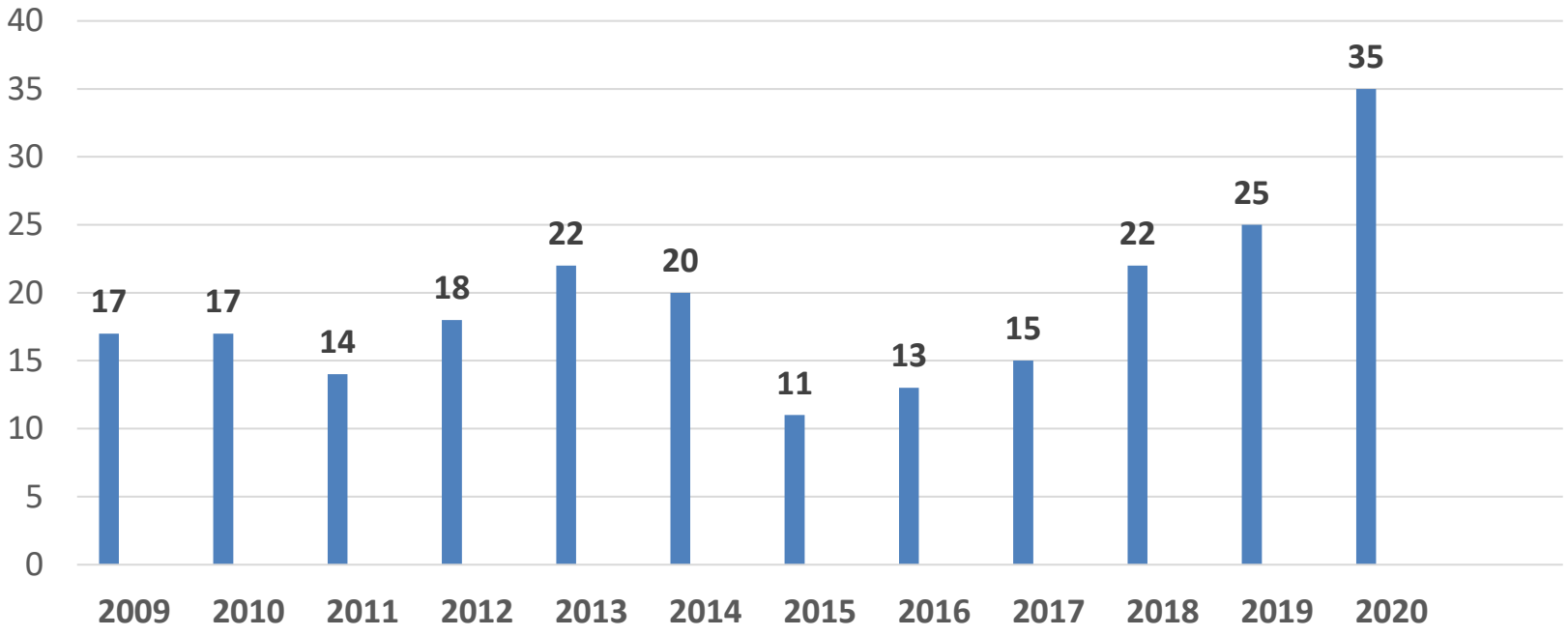
Communications with FDA

- Ideal time for sponsors to first interact with CBER
- Overcoming COVID-19 effects on gene therapy development programs
- FDA Guidances

INitial Targeted Engagement for Regulatory Advice on CBER producTs

(previously known as pre-pre-IND interactions)

Pre-Pre-IND and INTERACT Meetings

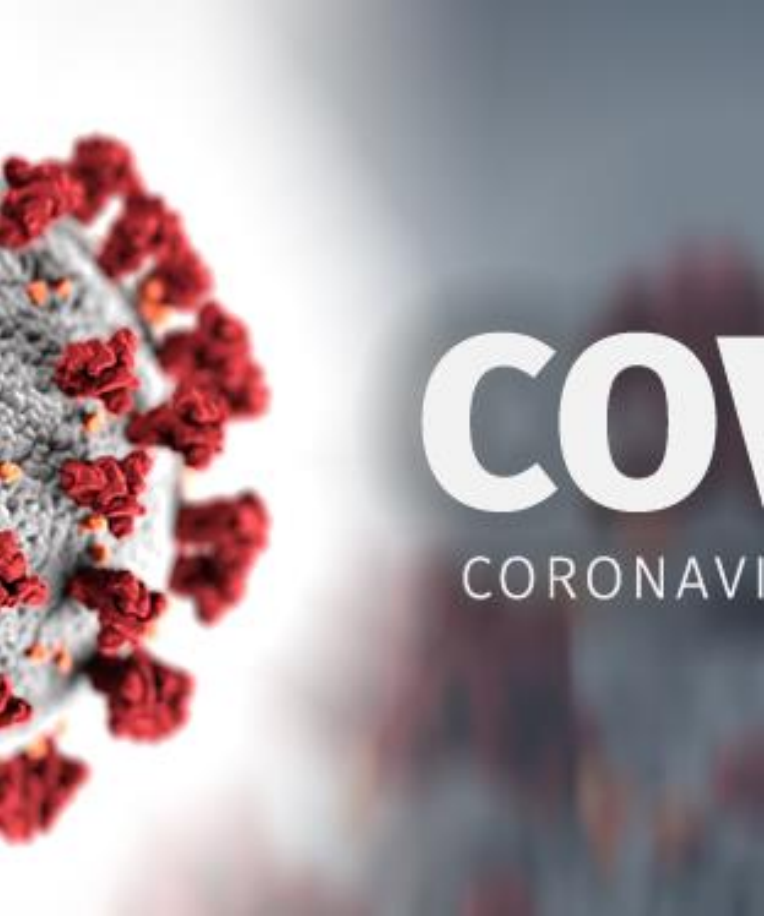


INTERACT Meetings: Denials

- Intended clinical product has not been selected
- Insufficient CMC information
- No preliminary preclinical data available from pilot studies
- Questions are focused on adequacy of definitive preclinical safety studies for an IND
- Sponsor has initiated or completed all of their preclinical studies
- Sponsor has previously received feedback on a similar product and indication

INTERACT Meetings: Granted

- Questions regarding the appropriate animal model(s) for assessment of a particular investigational product
- Questions regarding preclinical study endpoints and design for definitive proof-of-concept (POC) and/or hybrid POC/safety studies
- Acceptability of novel preclinical testing strategies, products, delivery modalities, etc.



COVID-19

Gene Therapy Guidances

FINAL GUIDANCES

- Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)
- Testing of Retroviral Vector-Based Gene Therapy Products for Replication Competent Retrovirus (RCR) during Product Manufacture and Patient Follow-up
- Long Term Follow-Up After Administration of Human Gene Therapy Products
- Human Gene Therapy for Hemophilia
- Human Gene Therapy for Retinal Disorders
- Human Gene Therapy for Rare Diseases

DRAFT GUIDANCE

- Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations

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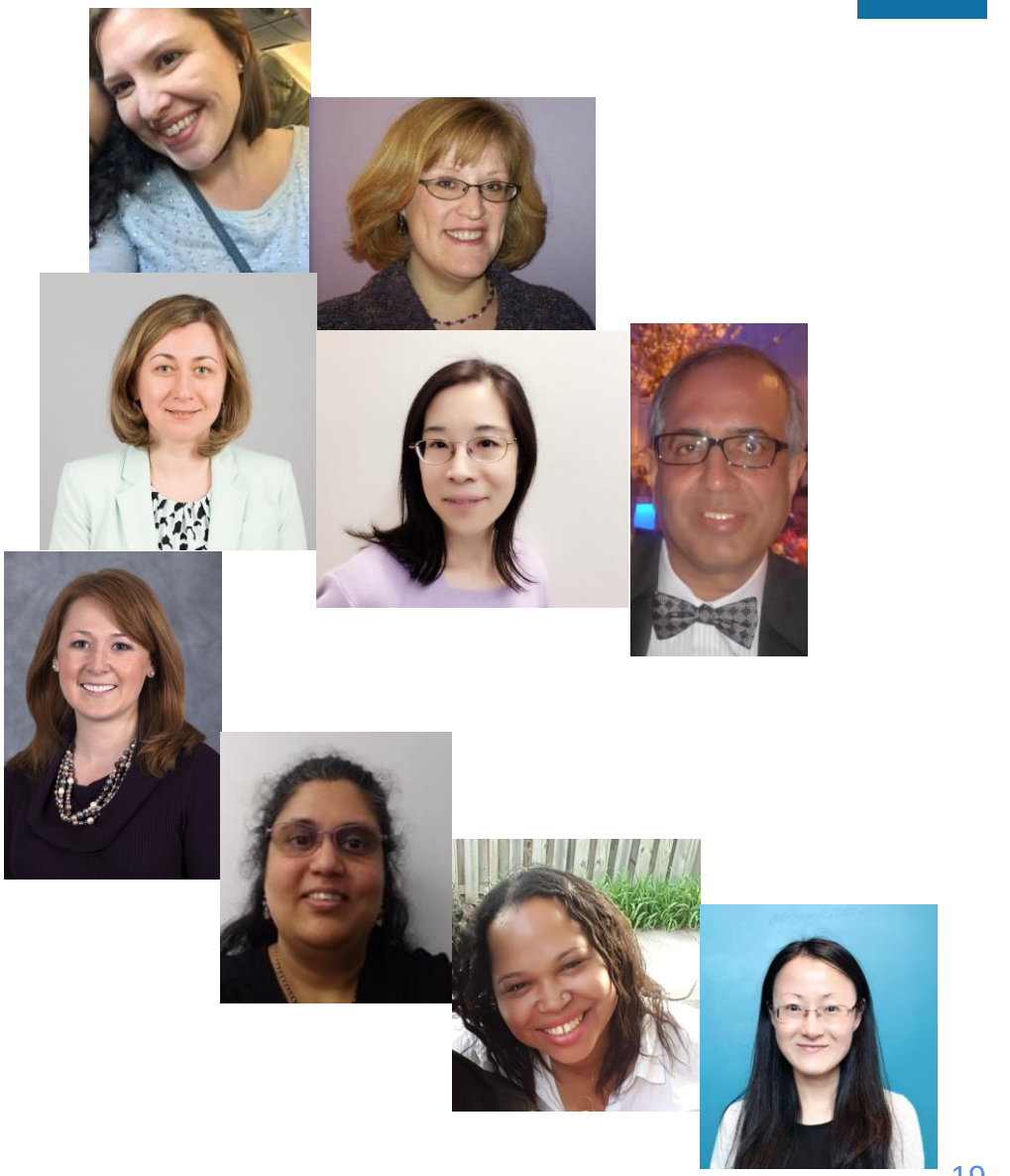

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FDA Headquarters

- **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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