Innovative Therapeutics: Gene Therapy

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FDA's Clinical Investigator Training Course, 2024

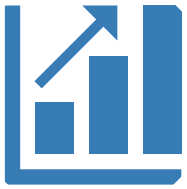
Center for Biologics Evaluation and Research (CBER) Mission

Ensure the **safety, purity, potency, and effectiveness** of biological products including **vaccines, allergenics, blood and blood products, cells, tissues, and gene therapies** for the prevention, diagnosis, and treatment of human diseases, conditions, or injury.

Through CBER's mission, the Center also seeks to protect the public against the threats of emerging infectious diseases and bioterrorism.

Super Office of Therapeutic Products (OTP)

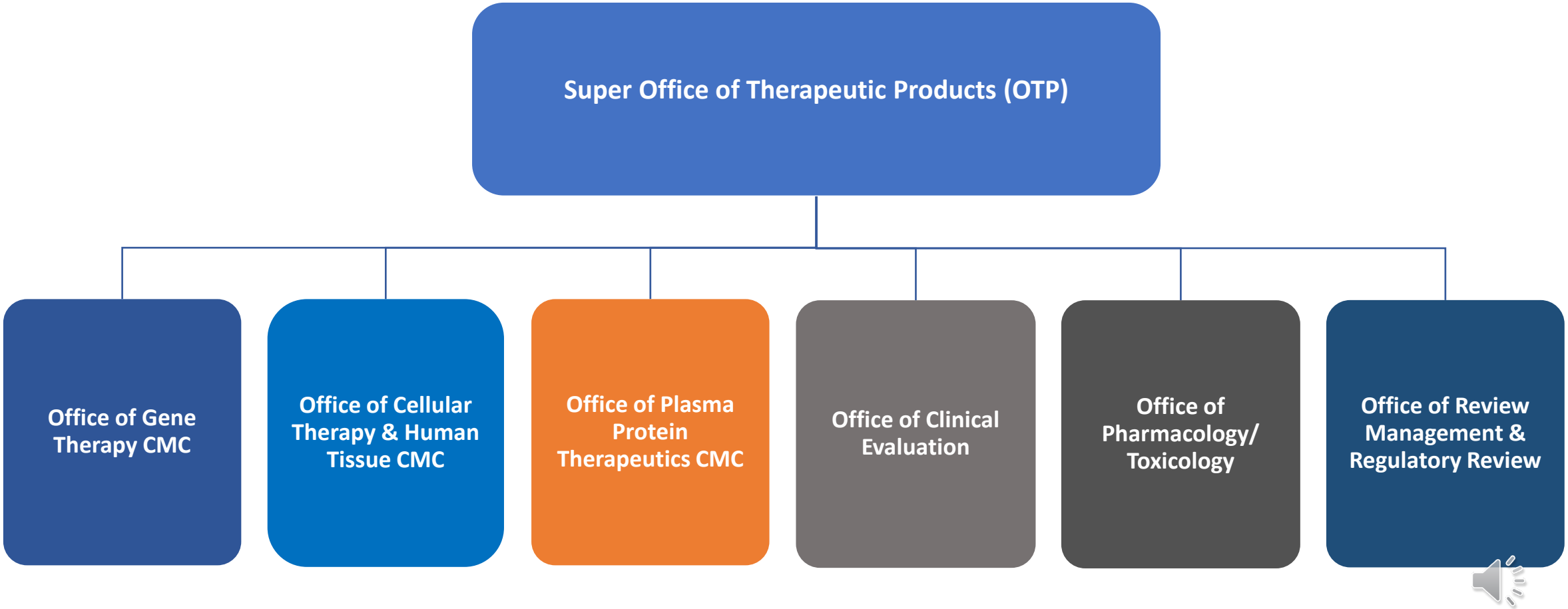
Established March 2023



Creates flexibility and capacity for future growth

Improve discipline alignment, increase review capacity, and enhance expertise in cell and GTs

OTP Organizational Structure

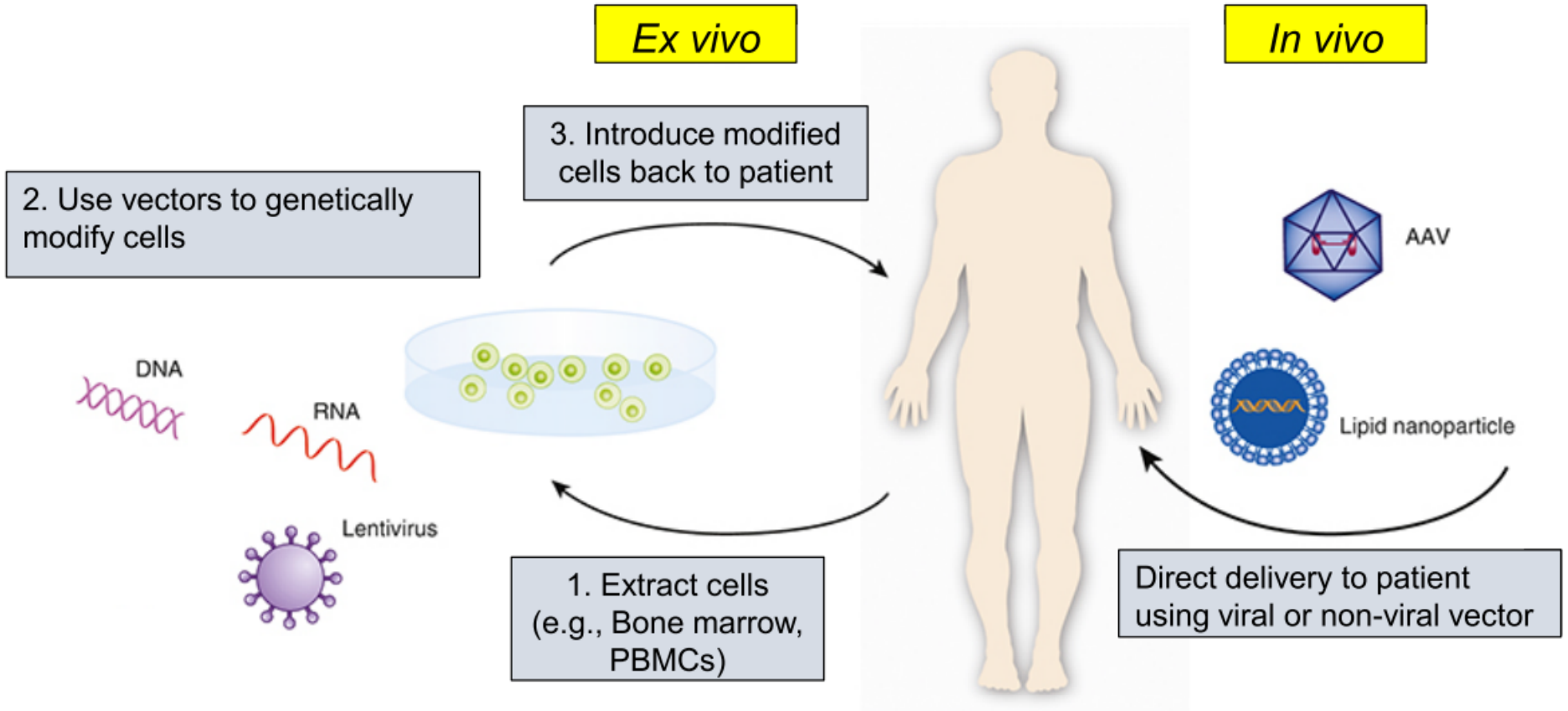


Diversity of OTP-Regulated Products

- **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 cell and stem cell-derived products:** Hematopoietic, mesenchymal, cord blood, embryonic, induced pluripotent stem cells (iPSCs)
- **Terminally-differentiated cell therapies:** Pancreatic islets, chondrocytes, myoblasts, keratinocytes, hepatocytes
- **Therapeutic vaccines and other antigen-specific active immunotherapies:** Cancer vaccines and immunotherapies, such as dendritic cells, lymphocyte-based therapies, cancer cell-based therapies, peptides, proteins; non-infectious disease therapeutic vaccines, such as peptides, proteins, small molecules
- **Blood- and Plasma-derived products:** Purified and recombinant proteins for hematology (e.g., coagulation factors)
- **Xenotransplantation**
- **Human Tissues**
- **Some Devices**

Gene Therapy Product Development

Gene Therapy
Ex Vivo and In Vivo Administration



Diversity of Gene Therapy Products

- *Ex vivo* genetically modified cells
- Non-viral vectors (e.g., plasmids, mRNA)
- Replication-deficient viral vectors [e.g., adenovirus (Ad), adeno-associated virus (AAV), herpes simplex virus (HSV), retroviruses, lentivirus, modified vaccinia ankara (MVA)]
- Replication-competent viral vectors [e.g., measles, adenovirus, vaccinia virus (VV)]
- Microbial vectors (e.g., *Listeria*, *Salmonella*)

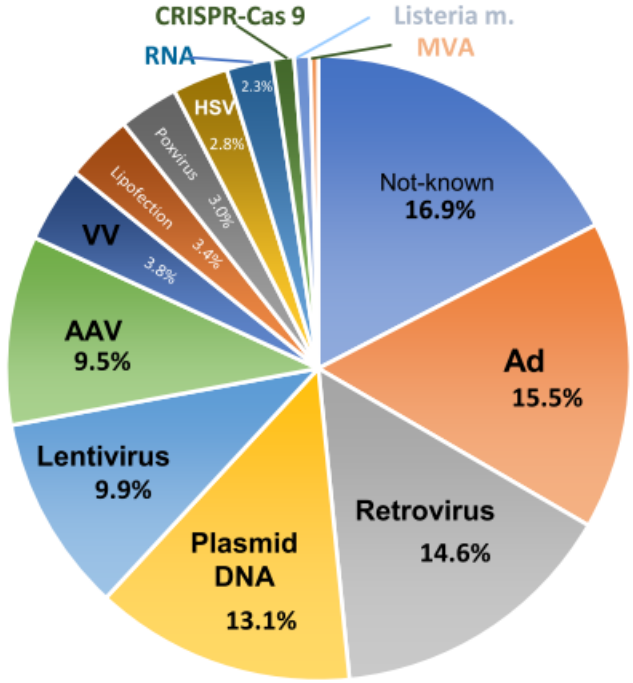
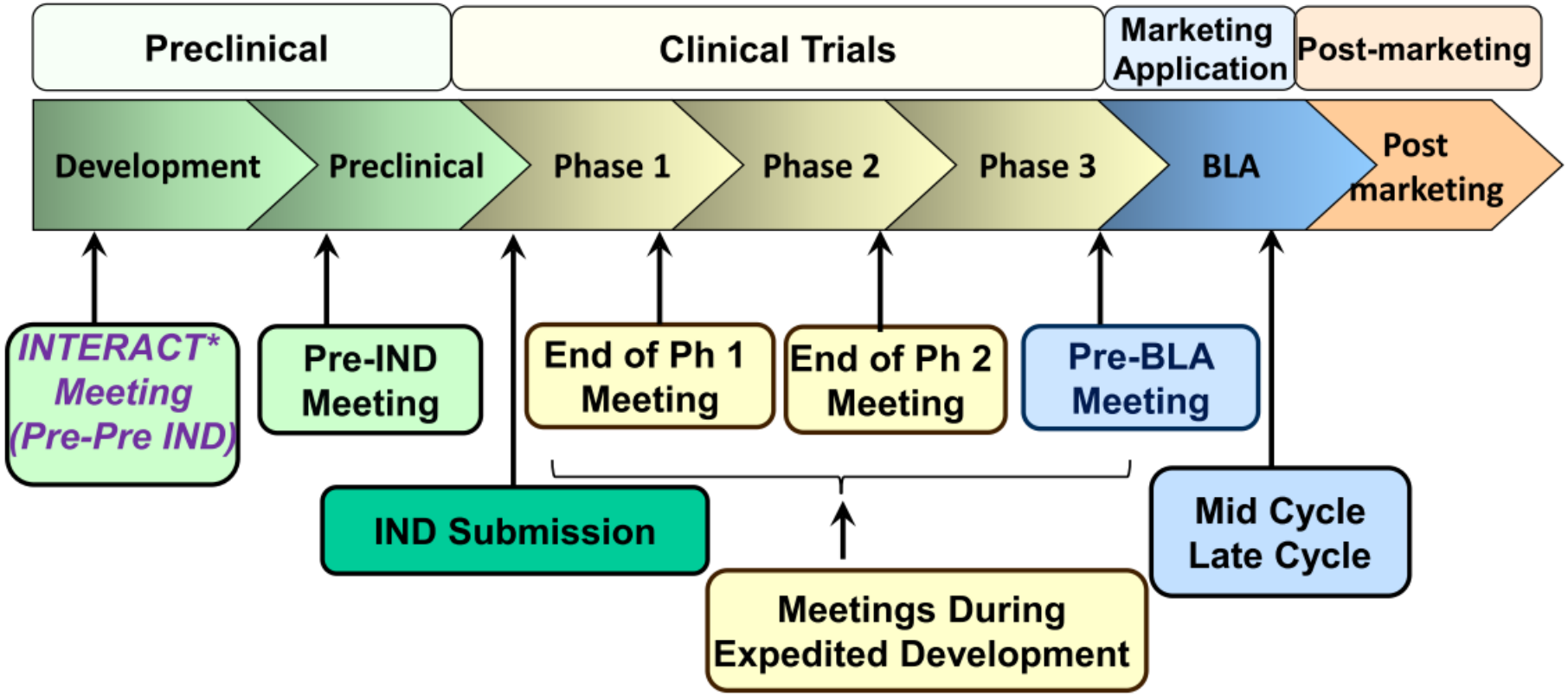


Figure Reproduced from The Journal of Gene Medicine© **2022** John Wiley and Sons LTD;
http://www.genetherapynet.com/clinical-trials.html

Opportunities for Interaction with OTP During Product Development



Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products; Draft Guidance for Industry
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547.pdf

INitial** T**argeted** E**ngagement for** R**egulatory** A**dvice on** C**BER/CDER produc**T**s (previously known as pre-pre-IND interactions)*

Key Differences in Gene Therapy

Unlike other medical products, gene therapies often involve:

New technologies to manufacture the product

Invasive procedures to administer the treatment

Potential Long-lasting effects

Potential risk of unintended changes in DNA or rejection by the body

Considerations for CMC GT Product Development

- Manufacturing: Product complexity
  - Early phase: characterization, MOA, cellular kinetics and vector biodistribution
  - Later phase: quality and potency
  - Major manufacturing change may require demonstration of product comparability
- Prolonged biological activity and the need for long-term follow-up
- Procedures for product delivery; product-device compatibility
- Monitoring for Immunogenicity
- Off-target effects: tumorigenicity and insertional mutagenesis

Considerations for Preclinical Development

- **Animal models:** healthy and disease-related
    - Scientific justification for model selection
    - Comparative physiology in tissue type helps with extrapolation to clinical dose levels
- **Product kinetic profile:** cell fate or vector biodistribution
- **Route of administration:** as close as possible to the clinical scenario
    - Timing and rate of administration, anatomical location, activity of the product in local micro-environment
- **Standard toxicology assessments:** mortality, laboratory observations on treatment, body weights, gross and histopathology, and other endpoints as recommended in the current guidance documents and ICH guidelines
- **Informative design:** randomized group assignments, appropriate controls, masked assessments, adequate study duration, and evaluation of product's persistence

Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products, 2013
https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM376521.pdf

Regulatory Considerations for Clinical Development
Early Phase

- **Dosing:**
  - Pre-clinical data to inform/support dosing (potential toxicity)
  - Scientific rationale for dose escalation or de-escalation
  - Adequate characterization of safety profile of the feasible doses
  - Delivery devices or route of administration
- **Safety:**
  - Dose-limiting toxicity
  - Duration of follow-up to be tailored to individual products
  - Staggering regimen; stopping criteria for both individual subjects and the entire study
  - Monitoring for immunogenicity, evaluation of viral vector shedding
  - Acceptable safety for the population in the context of the disease or condition
  - Evaluation of product persistence and long-term effects

Guidance for Industry: Long-Term Follow-Up Administration of Human Gene Therapy Products, January 2020
https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM610797.pdf

Regulatory Considerations for Clinical Development
Late Phase

- **Efficacy:**
  - Approval of drugs and biologics must be based on substantial evidence of effectiveness and evidence of safety.
  - Available data demonstrate that product's benefits outweigh its risks at the time of approval, and throughout the product's lifecycle
  - Certain aspects of product development that are feasible for common diseases may not be feasible for rare diseases. Examples:
    - Single arm studies to support regulatory decision
    - Large magnitude of benefit
    - A well-designed natural history study may be supportive for rapidly progressing, serious, and rare conditions
  - Any associated companion diagnostics or devices co-developed to become available with the product
  - Expedited programs and other incentives for serious diseases with unmet medical needs

Expedited Development Programs

Fast Track	Breakthrough Therapy	Regenerative Medicine Advanced Therapy (RMAT)	Accelerated Approval	Priority Review
-**Serious condition** AND -**Nonclinical or clinical data** demonstrate the ***potential*** to address ~~unmet medical~~ need Note: Information to demonstrate *potential* depends upon stage of development at which FT is requested	-**Serious condition** AND -Preliminary **clinical evidence** indicates that the drug may demonstrate **substantial improvement over available therapy** on one or more clinically significant endpoints	-**Serious condition** AND -It is a regenerative medicine therapy - Preliminary **clinical evidence** indicates that the drug has the **potential** to address unmet medical needs for such disease or condition	-**Serious condition** AND - Meaningful advantage over available therapies - Demonstrates an **effect on** either: a **surrogate endpoint or an intermediate clinical endpoint**	-**Serious condition** AND -Demonstrates potential to be a significant **improvement in safety or effectiveness**

https://www.fda.gov/downloads/Drugs/Guidances/UCM358301.pdf

Investigational and Approved Gene Therapies

Gene Therapies Hold Great Promise

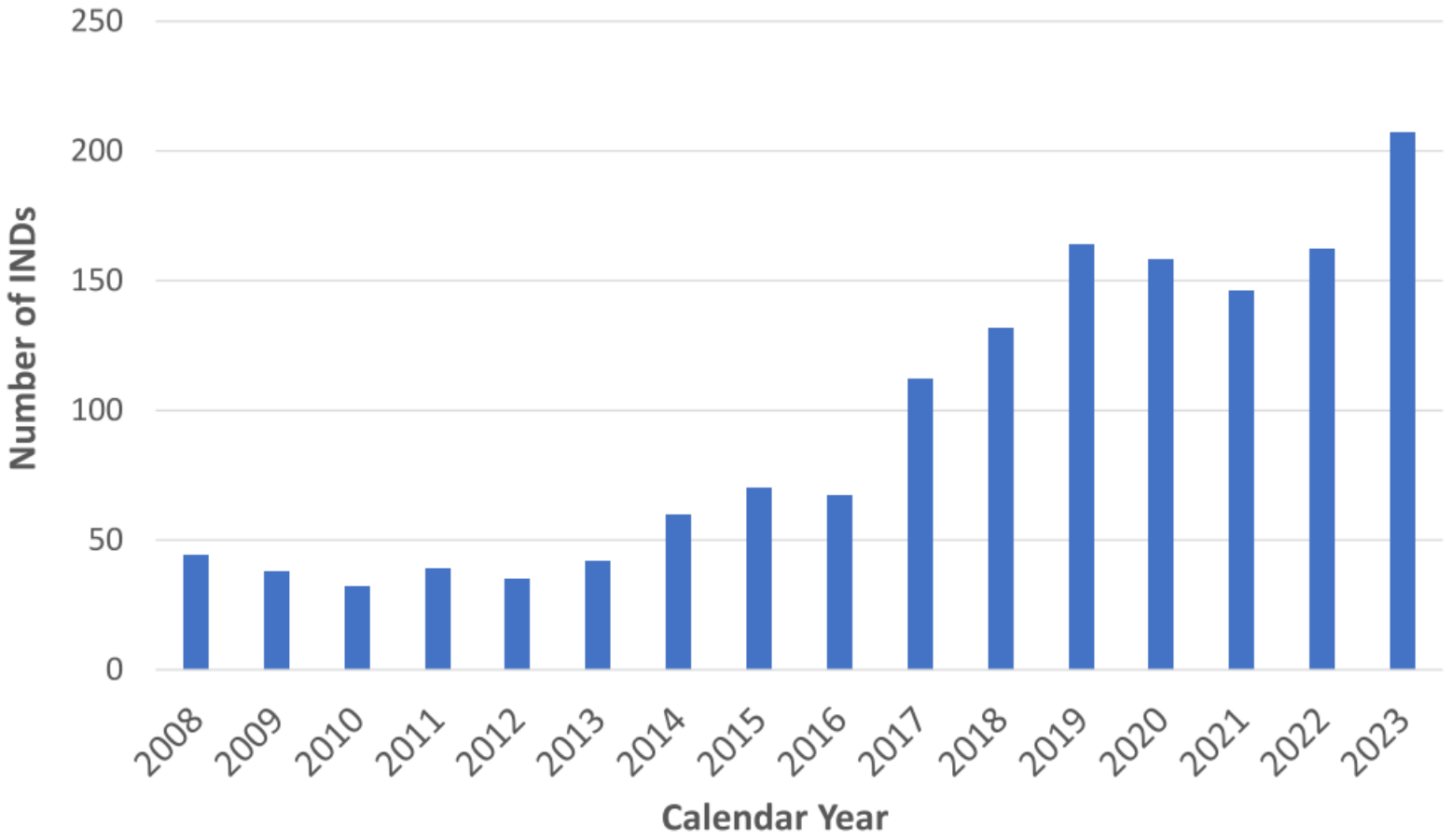
Over 80% of rare diseases have a known genetic basis.

FDA has approved **22 gene therapy products**, most of which are for rare disorders.

OTP currently oversees more than **2,600** active investigational products.

Collaboration and flexibilities are critical in development of cell and gene therapy products

OTP Original INDs (excl Expanded Access) for Gene Therapy



U.S. Approved Gene Therapies

- Kymriah (2017)
- Yescarta (2017)
- Luxturna (2017)
- Zolgensma (2019)
- Tecartus (2020)
- Breyanzi (2021)
- Abecma (2021)
- Carvykti (2022)
- Zynteglo (2022)
- Skysona (2022)
- Hemgenix (2022)
- Adstiladrin (2022)
- Vyjuvek (2023)
- Elevidys (2023)
- Roctavian (2023)
- Lyfgenia (2023)
- Casgevy (2023, 2024)
- Lenmeldy (2024)
- Beqvez (2024)
- Tecelra (2024)
- Aucatzyl (2024)
- Kebilidi (2024)

Stem cell T cell Directly administered

Recent Cell and Gene Therapy Approvals

LENMELDY: Orchard Therapeutics

- 3/18/24
- Treatment of children with pre-symptomatic late infantile (PSLI), pre-symptomatic early juvenile (PSEJ) or early symptomatic early juvenile (ESEJ) metachromatic leukodystrophy (MLD)

BEQVEZ: Pfizer

- 4/25/24
- Treatment of adults with moderate to severe hemophilia B (congenital factor IX deficiency) who currently use factor IX prophylaxis therapy, or have current or historical life-threatening hemorrhage, or have repeated, serious spontaneous bleeding episodes, and, do not have neutralizing antibodies to adeno-associated virus serotype Rh74var (AAVRh74var) capsid as detected by an FDA-approved test

TECELRA: Adaptimmune

- 8/1/24
- For treatment of adults with unresectable or metastatic synovial sarcoma who have received prior chemotherapy, are HLA-A*02:01P, -A*02:02P, -A*02:03P, or -A*02:06P positive and whose tumor expresses the MAGE-A4 antigen as determined by FDA-approved or cleared Companion Diagnostic devices

AUCATZYL: Autolus Limited

- 11/8/24
- For the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)

KEBILIDI: PTC Therapeutics

- 11/13/24
- For the treatment of adult and pediatric patients with aromatic L amino acid decarboxylase (AADC) deficiency.

CBER's 2024 Priority: Rare Disease Product Development

CBER 2024 Priority: Rare Disease Product Development

Out of thousands of rare hereditary and acquired diseases there are hundreds of disorders affecting one to thousands per year that could be addressed with novel gene therapies (GT)

Addressing molecular defects may reduce some more common diseases to very rare diseases

Actions at CBER to Address Rare Disease Development

- Advancing manufacturing technologies for cell and GT through research
- Application of platform technology provision
- Work to more clearly define the use of accelerated approval for GT
- Exploring concurrent submission and product review with other regulatory authorities
- Communication pilot for rare diseases

Collaboration on **Gen**e **T**herapies Global (CoGenT Global) Pilot

- Initial participation by Standing Regulatory Members of ICH
- Partners may participate in internal regulatory meetings and meetings that include the sponsor
- Specific regulatory reviews are shared and discussed with partners
- All meetings conducted and information shared under strict confidentiality agreements
- Goal is to increase the efficiency of the regulatory process, reducing time and cost for agencies and sponsors

Support for clinical Trials Advancing Rare disease Therapeutics (START) Pilot

- **Goal**: Further accelerate the pace of development for products that are intended to address an unmet medical need as a treatment for a rare disease

- Four CBER programs have been chosen and 3 CDER programs
  - Product is being developed toward a marketing application
  - Intended to address an unmet medical need as a treatment for a rare disease
  - Likely to lead to significant disability or death within the first decade of life
  - Enhanced communications
  - Additional ad hoc email or live interactions on an as needed basis

START Pilot Selections

Sponsor	Product Description	Indication
Grace Science LLC	Recombinant Adeno-Associated Virus Serotype 9 Vector Encoding a Codon-optimized Full-length Version of Human NGLY1 (GS-100)	NGLY1 Deficiency
Myrtelle, Inc	Adeno-associated virus containing a self-complementary DNA payload of a codon optimized human ASPA cDNA (rAAV-Olig001-ASPA)	Canavan Disease
Moderna TX	Lipid nanoparticle encapsulated mRNA encoding a normal human MUT Protein (mRNA-3705)	Isolated methylmalonic acidemia due to complete or partial methylmalonyl-coenzyme A mutase deficiency
Neurogene, Inc	Recombinant serotype 9 adeno-associated virus vector MECP2 transgene	Rett Syndrome

RDEA

- Seek to advance rare disease drug development programs by providing a mechanism for sponsors to collaborate with FDA throughout the efficacy endpoint development process.

- Admitted sponsors may request up to 4 meetings with FDA to discuss development of their proposed novel endpoint.

- After completion of four RDEA meetings, the sponsor can request additional input from FDA, as needed, through other formal meeting mechanisms, such as Type B, Type C, Type C Surrogate Endpoint, or Type D meetings.

Thank you & OTP Resources

- Cellular & Gene Therapy Guidance Documents

- OTP Events, Meetings, and Workshops web page
  - Lists upcoming events
  - Links to information and recordings of past OTP events

- Interactions with Office of Therapeutic Products website

- OTP Learn Webinar Series

Contact Information

- **Regulatory Questions:**

  OTP Main Line – 240 402 8190

  Email: OTPRPMS@fda.hhs.gov

- **Interactions with Office of Therapeutic Products website:**

  Interactions with Office of Therapeutic Products | FDA

- **OTP Learn Webinar Series:**

  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

FDA Headquarters

- **CBER website:** www.fda.gov/BiologicsBloodVaccines/default.htm
- **Phone:** 1-800-835-4709 or 240-402-8010
- **Consumer Affairs Branch**: ocod@fda.hhs.gov
- **Manufacturers Assistance and Technical Training Branch**: industry.biologics@fda.hhs.gov