Regulatory Perspectives on Gene Therapies for Rare Diseases

Rare Diseases Forum

Washington, D.C.

October 17, 2018

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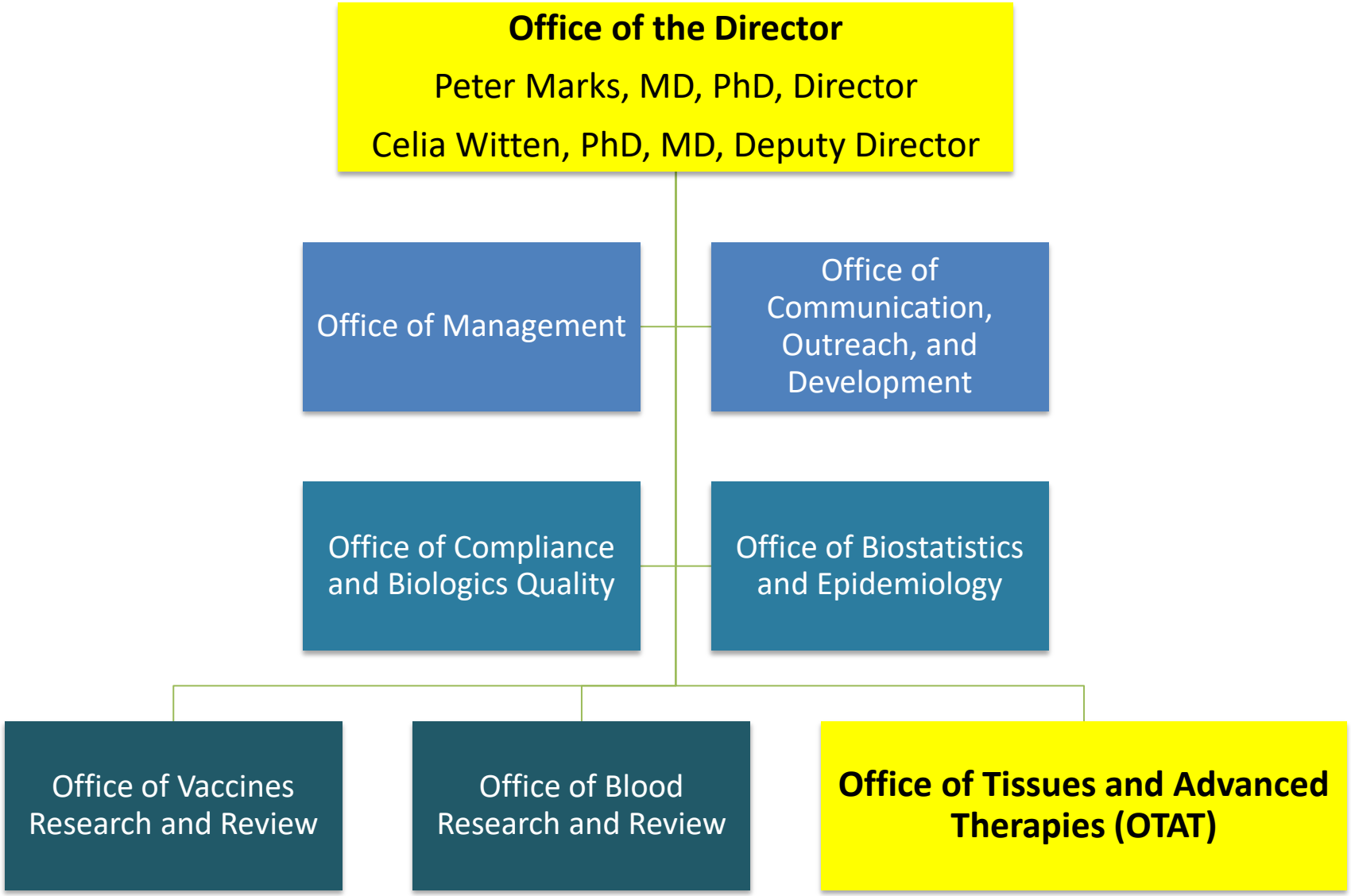
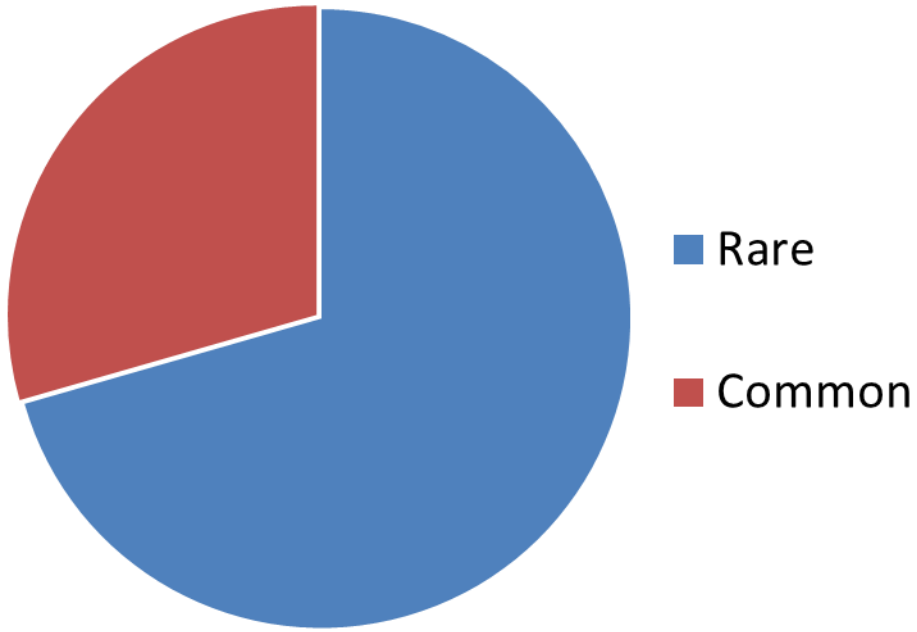
Outline

- Introduction
- Challenges in the field---major outstanding issues
- FDAs Initiative in addressing the Issues
- Overview of new FDA guidance documents
- Summary - cautious optimism for the future of Gene Therapy (GT)

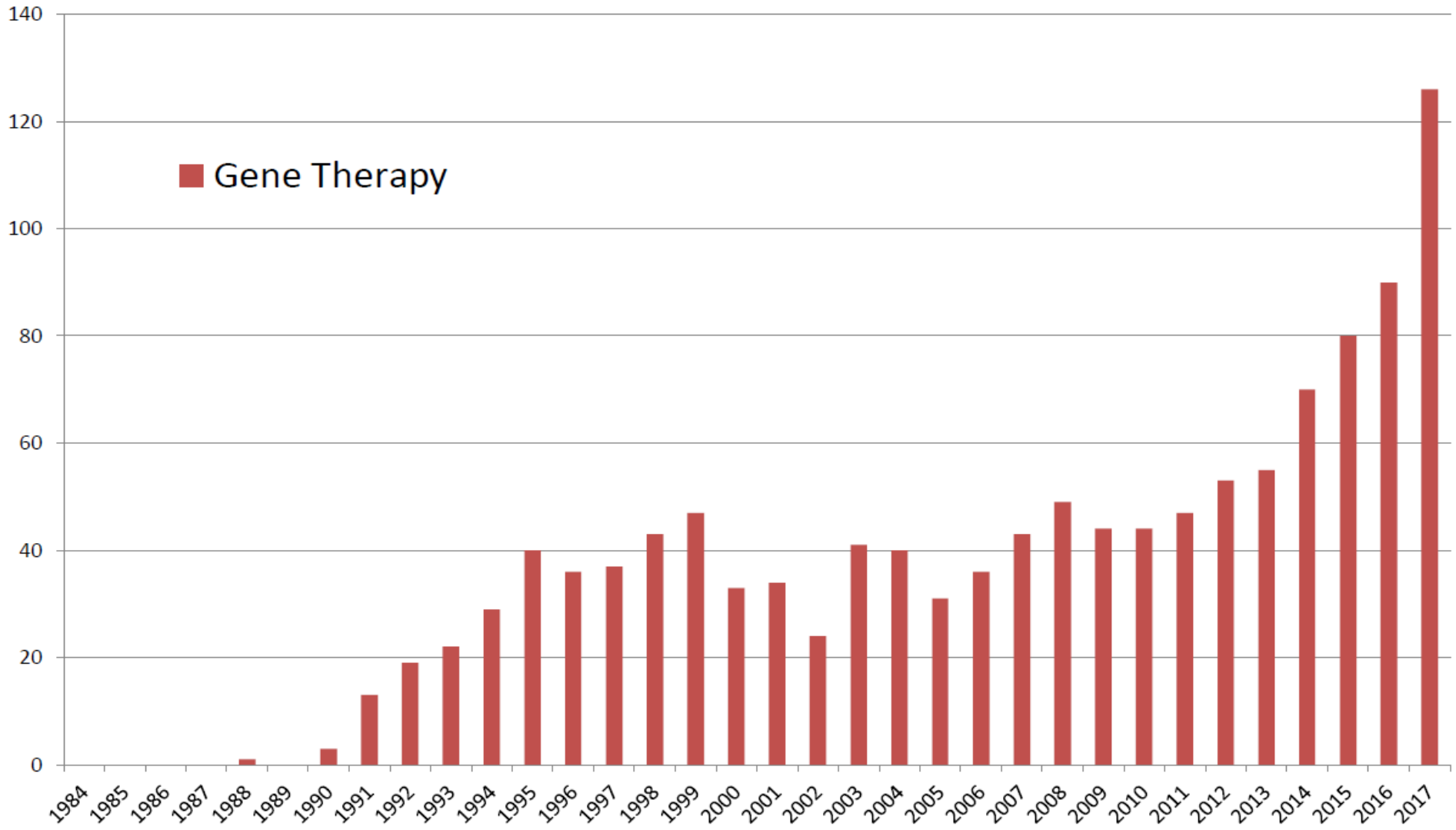
Center for Biologics Evaluation and Research



OTAT Cellular and Gene Therapies Investigational New Drug Applications



Rapid Growth in new GT IND Applications



History of Gene Therapy Product Development

- September 14, 1990 A four-year old girl was treated at the NIH Clinical Center. She had adenosine deaminase (ADA) deficiency, a genetic disease that left her immunosuppressed.
- August 30, 2017 FDA approved the first cell-based gene therapy for leukemia- ***KYMRIAH*** (tisagenlecleucel). The treatment involves removing immune system T-cells from an individual patient and genetically modifying the cells in the laboratory to attack and kill leukemia cells. The genetically-modified cells, also known as CAR-T cells (chimeric antigen receptor T-cells), are then infused back into the patient.
- October 18, 1017 FDA approved ***YESCARTA*** (axicabtagene ciloleucel), a cell-based gene therapy, to treat adult patients with certain types of large B-cell lymphoma who have not responded to or who have relapsed after at least two other kinds of treatment. YESCARTA, a CAR-T cell therapy, is the second gene therapy approved by the FDA and the first for certain types of non-Hodgkin lymphoma (NHL).
- December 19, 2017 FDA approved **LUXTURNA** (*voretigene neparvovec),* the first gene therapy for an inherited disorder, retinal dystrophy, which is a rare condition that causes a progressive form of blindness, usually beginning in childhood. The product is an AAV-2 expressing the human RPE65 gene.

Gene Therapy Challenges

- Clinical trial designs are challenging for studies of rare diseases
- Product manufacturing: quality must be ensured
- "Tweaking" the product is very common during development
  - comparability issues
- Dose exploration is limited by cost and manufacturing capability
- Pre-existing antibody to the GT product may limit its therapeutic potential
- Durability of response should be evaluated in clinical trials
- Delivery of gene therapy product may requires invasive methods
- Dedicated delivery device may need to be developed in conjunction with the gene-therapy product itself; may be considered as a combination product

Gene Therapy Safety Considerations

- Compared to small-molecule drugs, less experience with pharmacokinetics, and relatively low concern with drug-drug interaction, drug metabolism
- Novel safety concerns
  - insertional mutagenesis
  - viral vector shedding
  - immunological reactions to vector or protein product
  - unknown duration of action
- Concerns about new gene-editing techniques: known or unknown off-target effects
- Safety assessments associated with more uncertainty when evaluated in a small study population in a trial of a rare disease

Ethical Issues

- Generally is not acceptable to enroll healthy volunteers into GT studies
- Pediatric studies: consider 21 CFR Subpart D.
- Gene therapy may have acceptable benefit/risk for serious genetic diseases, but what about for less severe conditions?
- Should people be allowed to use gene therapy to enhance basic human traits such as height, intelligence, or athletic ability?
- Very costly. Who pays?

CBER Initiatives

Facilitating additional Interactions with FDA

- INTERACT (**I**nitial **T**argeted **E**ngagement for **R**egulatory **A**dvice on **C**BER product**s**)

➢ **INTERACT** Meetings Program was created for potential sponsors to engage with CBER staff and obtain advice on a specific topic or issue that is critical to early product development.

Email: interact-cber@fda.hhs.gov

- RMAT (**R**egenerative **M**edicine **A**dvanced **T**herapy)

➢ Sponsors of cell and gene therapies are now eligible to obtain an RMAT designation if their product is intended to treat serious or life-threatening diseases and there is preliminary clinical evidence that the product can address unmet medical needs.

➢ Benefits: The RMAT designation gives the sponsor of a new drug opportunities for increased and earlier interactions with the FDA and eligibility for priority review and accelerated approval.

CBER Initiatives *continued*

Six Draft GT guidance documents in 2018

- Three Disease-specific Guidance documents:
  - Treatment of Hemophilia
  - Treatment of Retinal Disorders
  - Treatment of Rare Diseases
- CMC guidance for GT products
- Testing for Replication competent retrovirus (RCR)
- Long term follow-up

Summary

- Genetic basis of human disease is complex. We still have a lot to learn.
- Trial design should consider the study population, endpoints, safety monitoring.
- GT products hold great promise as therapeutic agents for treatment of a wide variety of diseases.
- With the approval of the initial few GT products, there is high expectation for development of future applications of GT.
- Vigilance is essential, and we do not want to forget the lessons learned from past collective clinical experiences with GT products.

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FDA Headquarters

- **OTAT Learn Webinar Series:**

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