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National Organization for Rare Disorders

AMERICAN SOCIETY of GENE & CELL THERAPY

The FDA'S Role in Gene Therapy

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Alone we are rare. Together we are strong.®

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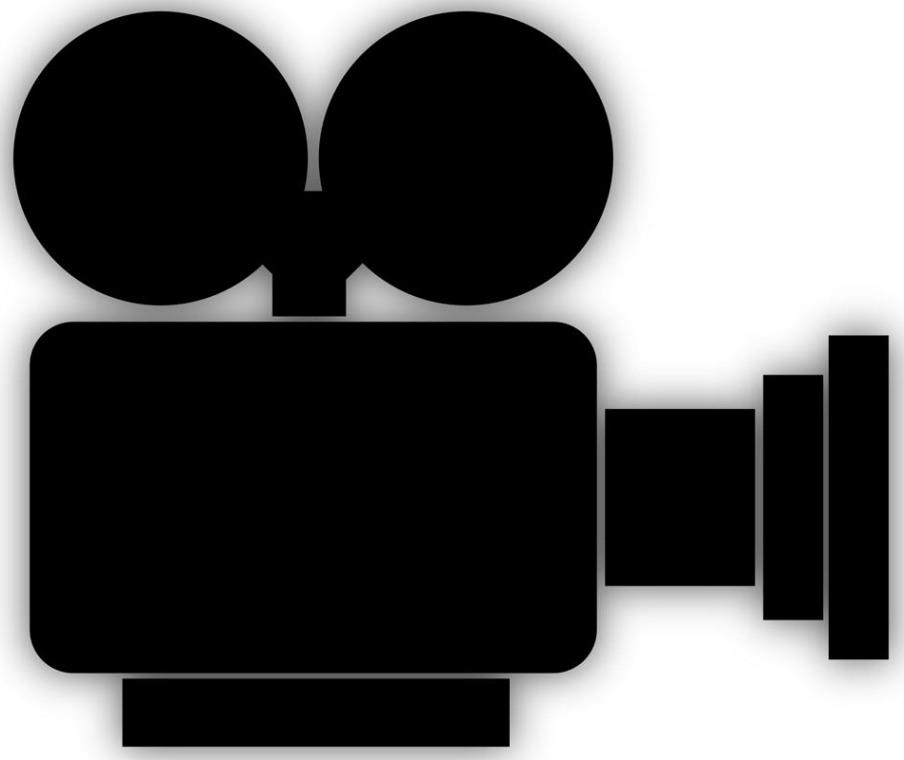

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Question and Answer Session

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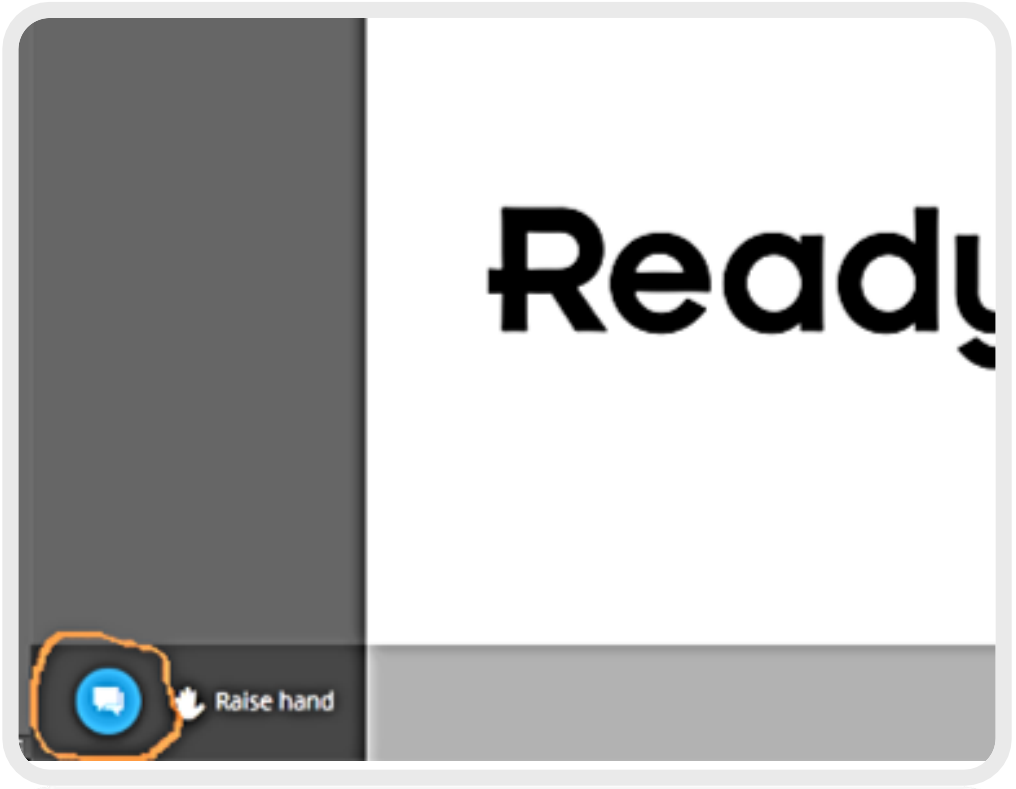

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NORD, an independent nonprofit, is leading the fight to improve the lives of **rare disease patients and families.**

We do this by supporting patients and organizations, accelerating research, providing education, disseminating information and driving public policy.

Gene Therapy Webinar Series

Today's webinar is the third webinar in an exciting five-part series on gene therapy from NORD in collaboration with the American Society for Gene and Cell Therapy (ASGCT.)

Mark your calendar for the rest of the series:

- **Understanding the Gene Therapy Process and Aftercare -** Wednesday, November 20
- **Life After Gene Therapy -** Wednesday, December 18

Dates subject to change

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Learn More

https://rarediseases.org/living-rare-forum/

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Speakers

Peter Marks, MD, PhD
Director, CBER

JulieTierney, JD
Senior Policy Advisor, CBER

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The FDA's Role In Gene Therapy

NORD Webinar

Peter Marks, M.D., Ph.D.
Julie Tierney, J.D.
Center for Biologics Evaluation and Research

October 30, 2019

Agenda

Part 1 (Peter Marks)

- Overview of drug development
- The stages of clinical trials
- Advancing gene therapy

Part 2 (Julie Tierney)

- Orphan product development
- Priority review vouchers
- Expediting product development

Product Development Ecosystem

- FDA is responsible for ensuring that medical products are safe and that they meet a legal standard for efficacy
  - Involved in the process of product development from concept through post-market surveillance

https://www.fda.gov/patients/learn-about-drug-and-device-approvals/drug-development-process

Product Development Ecosystem

- A variety of stakeholders
  - Patients and families
  - Advocacy organizations
  - Researchers and physicians
  - Pharmaceutical and biotechnology companies
  - Trade organizations

https://www.fda.gov/patients/learn-about-drug-and-device-approvals/drug-development-process

Drug Development Milestones

- Discovery
- Preclinical research
- Clinical research
- Regulatory review
- Post-market surveillance

https://www.fda.gov/patients/learn-about-drug-and-device-approvals/drug-development-process

Discovery

- Screening of compounds to find possible beneficial effects on a disease or condition
- Repurposing of existing products to treat a new disease entity
- New insights from research into a disease process allowing rational product design
- New technologies allowing drug delivery or manipulation of genetic material

http://wcms-internet.fda.gov/patients/drug-development-process/step-1-discovery-and-development

Preclinical Research

- Testing a product before it is used in humans to evaluate for toxic effects and to see if has the potential to have beneficial effect on the condition being studied
- Two major types of preclinical research
  - In vitro (in cell or tissue culture)
  - In vivo (animal experiments)
- Computer modeling also can contribute

http://wcms-internet.fda.gov/patients/drug-development-process/step-2-preclinical-research

Further Drug Development

- Absorption, distribution, excretion, metabolism
- Potential benefits and mechanisms of action
- Best dosage
- Best way to give the drug (route of administration)
- Side effects or adverse events
- How it affects different groups of people (such as by gender, race, or ethnicity) differently
- How it interacts with other drugs and treatments
- Effectiveness as compared with similar drugs

http://wcms-internet.fda.gov/patients/drug-development-process/step-1-discovery-and-development

Some Drug Development Tools

- Biomarkers
  - Trial-specific
  - Formal qualification program
- Complex Innovative Trial Designs
  - Bayesian designs
  - Adaptive clinical trials
- Patient-focused Drug Development
- Use of Real-world Evidence

Phases of Clinical Research

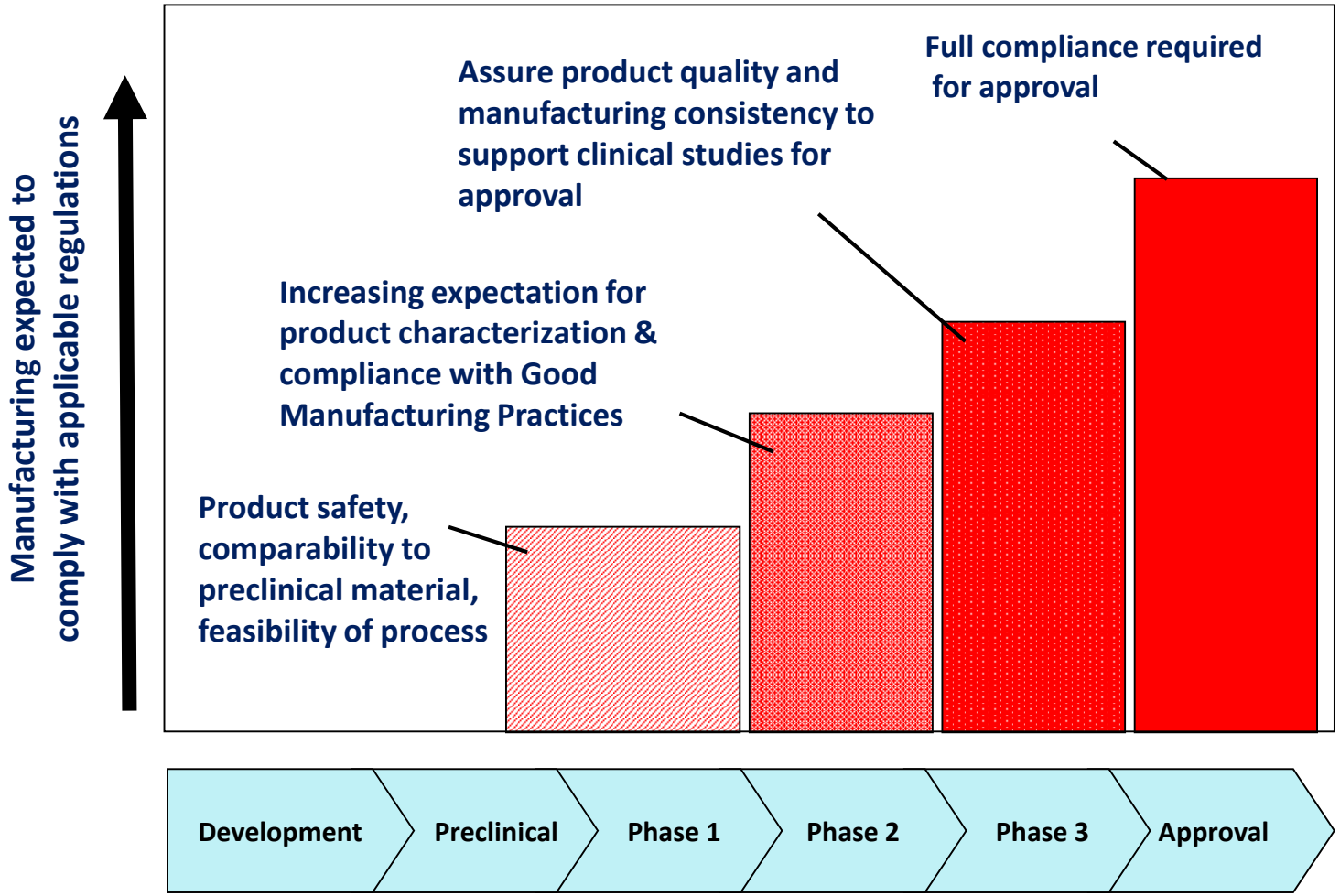
- Phase 1 (typical patient numbers in parentheses)
  - Initial safety and dose-finding trial (10-100)
- Phase 2
  - Initial efficacy and side effects (50-500)
- Phase 3
  - Definitive efficacy and side effects (100-10,000)
- Phase 4
  - Additional efficacy or safety information (1000's)

http://wcms-internet.fda.gov/patients/drug-development-process/step-3-clinical-research

Clinical Research for Rare Diseases

- Clinical trial programs are developed to be fit for purpose and depend on several factors including the strength of the effect and ability to measure outcomes
- Phase 1/2
  - Initial safety and dose-finding, initial efficacy (5-20)
- Phase 2 (Pivotal trial)
  - Further efficacy and side effects (20-100)

Progression of Manufacturing



FDA Application and Review

- A product application contains information on
  - Product composition
  - Product manufacture
  - Non-clinical studies
  - Clinical trials
- FDA reviews the product application, inspects facilities and may consult outside experts prior to approving a product
  - May place conditions on the approval

http://wcms-internet.fda.gov/patients/drug-development-process/step-4-fda-drug-review

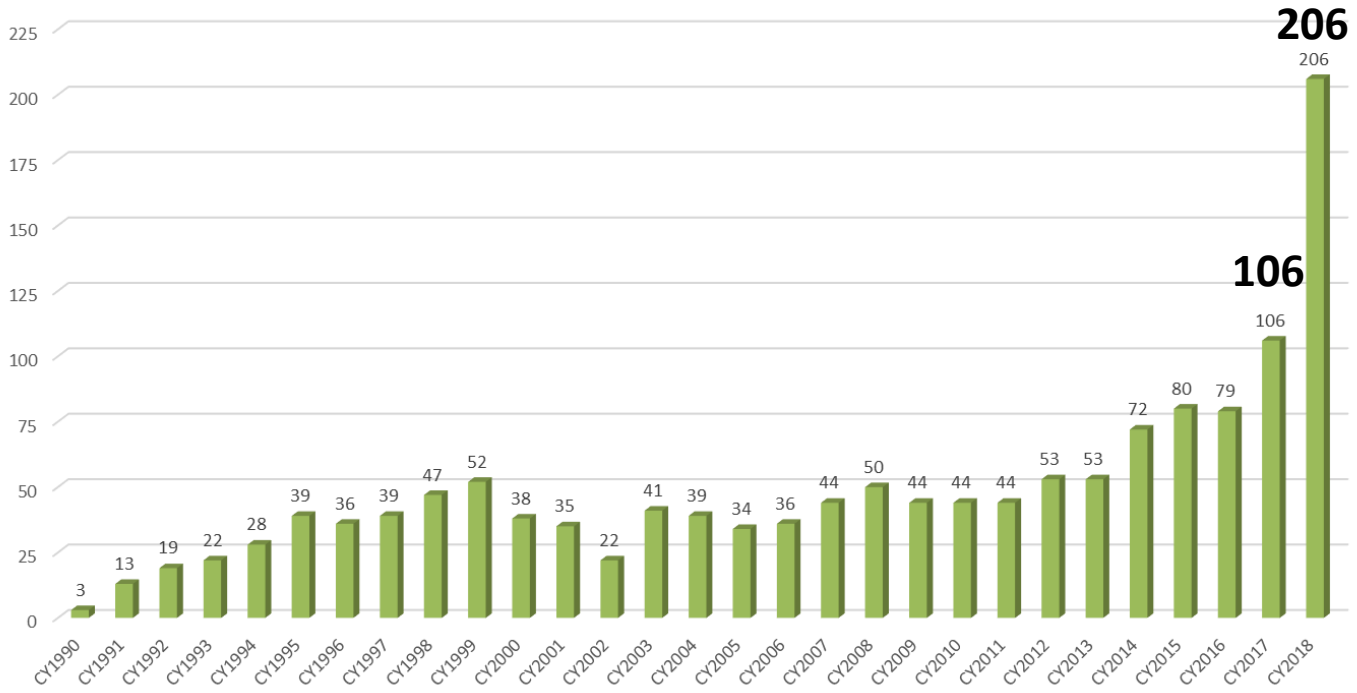
Post-Market Safety Monitoring

- The FDA's role does not end once a product is on the market
- FDA monitors safety through
  - Passive surveillance
    - Patient and provider reporting through MedWatch
  - Active surveillance
    - Sentinel system and others
  - Review of Phase 4 studies conducted by companies

http://wcms-internet.fda.gov/patients/drug-development-process/step-5-fda-post-market-drug-safety-monitoring

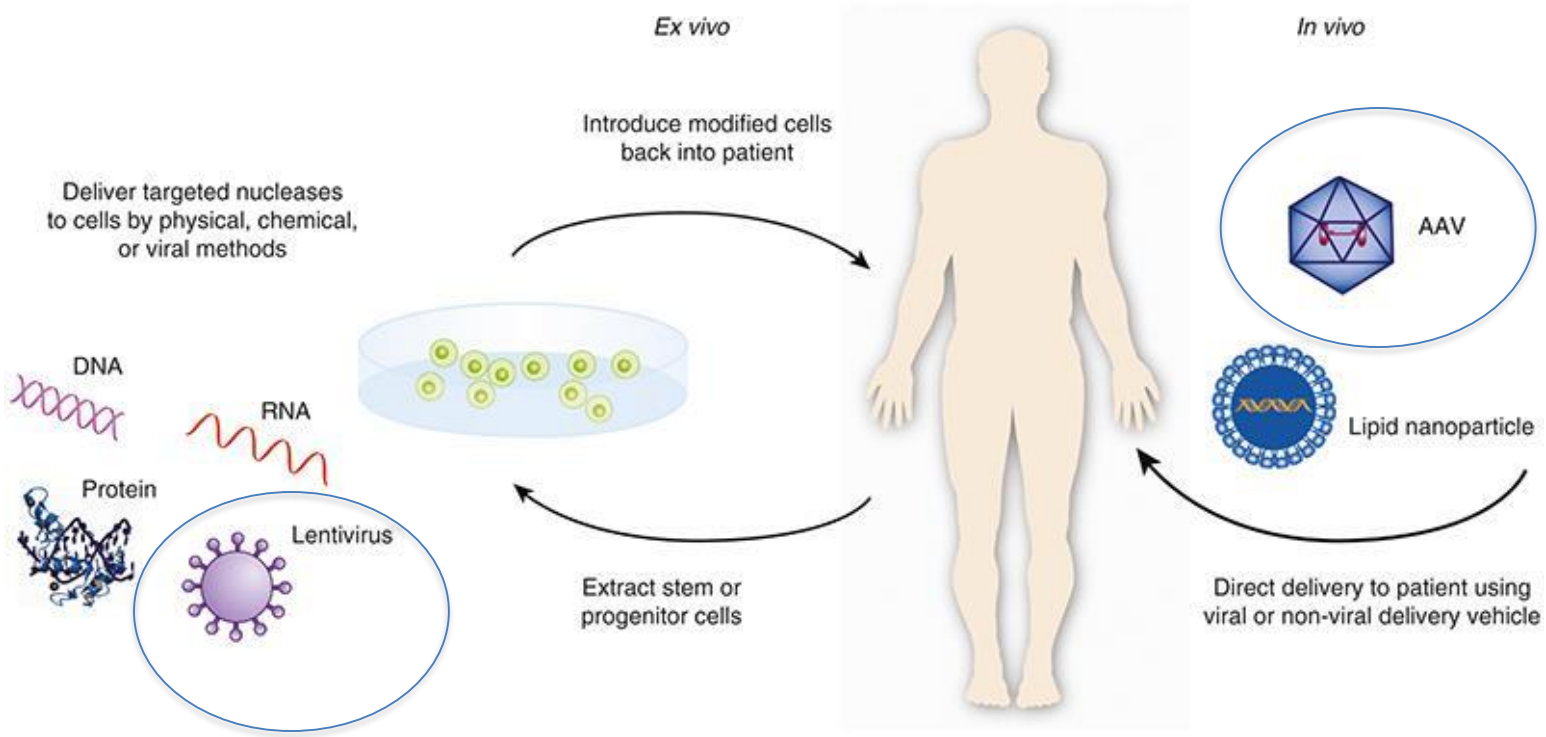
Increased Activity in Gene Therapy

Number of Investigational New Drug (IND) applications to FDA is increasing noticeably



Currently CBER has over 800 active gene therapy INDs

Advances in Gene Therapy



Current Challenges in the Development of AAV Gene Therapy

- Addressing issues of preexisting and elicited immunity to adeno-associated virus (AAV)
- Assessing long-term safety and efficacy
- Implementing efficient clinical development
- Manufacturing of gene therapy products

Promoting Product Development

- An increasingly important part of FDA's mission is to facilitate the development and approval of innovative products that address unmet medical needs
  - User Fee Acts (PDUFA, MDUFA, BsUFA, GDUFA)
  - Orphan Designation
  - Priority Review Vouchers
  - Expedited Development Programs

Promoting Product Development

- In return for the fees charged to sponsors, the Prescription Drug User Fee Act (PDUFA) placed performance metrics on FDA and established programs facilitating the development of certain drugs and certain biologics
- The first five-year PDUFA program was enacted in 1992, now on PDUFA VI
  - MDUFA IV, BsUFA II, GDUFA II

Orphan Product

Designation and/or Exclusivity

- To qualify
  - Drug or biologic intended for safe and effective treatment, diagnosis or prevention of rare diseases affecting less than 200,000 people in the U.S. or if affecting more people, cost recovery is not expected from marketing a treatment drug
- Features
  - Tax credits for qualified clinical testing
  - Exempt from prescription drug user fee
  - If approved, 7 years of marketing exclusivity

Priority Review Voucher Programs

- Neglected Tropical Disease
- Medical Countermeasure
- Rare Pediatric Disease
  - Sponsor who receives an approval for a drug or biologic for a "rare pediatric disease" may qualify for a voucher that can be redeemed to receive a priority review of a subsequent marketing application for a different product

Expedited Development Programs

- Fast Track
- Priority Review
- Accelerated Approval
- Breakthrough Therapy
- Regenerative Medicine Advanced Therapy

These programs may be applicable to drugs or biologics intended to treat serious conditions

Fast Track

For drugs or biologics intended to treat serious conditions

- To qualify
  - Nonclinical or clinical data demonstrate potential to address unmet medical need **OR** drug has been designated a qualified infectious disease product
- Features
  - Actions to expedite development and review
  - Rolling review

Priority Review

For drugs or biologics intended to treat serious conditions

- To qualify
  - Approval would represent significant improvement in safety or effectiveness **OR** pediatric study report supplement **OR** application for drug designated as qualified infectious disease product **OR** application submitted with a priority review voucher
- Features
  - Shorter clock for review of marketing application (6-month compared with 10-month standard review)

Accelerated Approval

For drugs or biologics intended to treat serious conditions

- To qualify
  - Drug or biologic provides a meaningful advantage over available therapies **AND** demonstrates an effect on a surrogate or clinical endpoint that is reasonably likely to predict clinical benefit
- Features
  - Approval based on effect on a surrogate endpoint
  - Confirmatory trial(s) are required to verify the clinical benefit or effect on irreversible morbidity or mortality

Breakthrough Therapy

For drugs or biologics intended to treat serious conditions

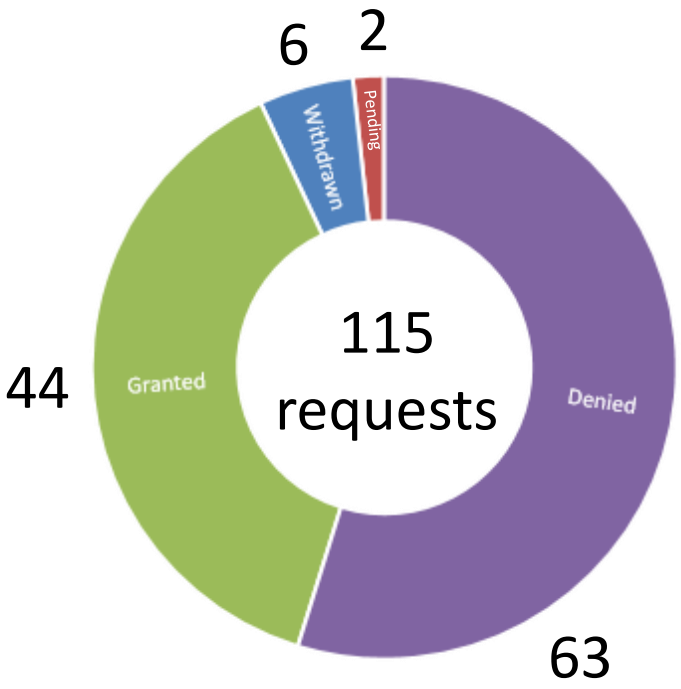
- To qualify
  - Preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint or endpoints over available therapies
- Features
  - Intensive guidance on efficient drug development
  - Organizational commitment
  - Other actions to expedite review (e.g., rolling review)

Regenerative Medicine Advanced Therapy Designation (RMAT)

For drugs or biologics intended to treat serious conditions

- Applies to certain cell and gene therapies, tissue engineering products, human cell and tissue products, combination products
- Designated products are eligible as appropriate for priority review and accelerated approval
- Post-approval requirements can be fulfilled by
  - Clinical studies, patient registries or other sources of real-world evidence such as electronic health records; collection of larger confirmatory datasets; post-approval monitoring of all patients treated

RMAT Designations Granted



Data as of September 30, 2019

- 44 products granted designation
- Majority have Orphan Product designation (27/44)
- Most are cellular therapy products or cell-based gene therapy products

Take Home Messages

- The next decades will see the development of numerous gene therapy products
- Regulatory approaches will need to either be developed or adapted to accommodate the novel nature of some of these entities
- FDA takes a scientific approach to regulation
- As FDA considers innovative technologies it must balance benefits against risks, taking into account uncertainties that exist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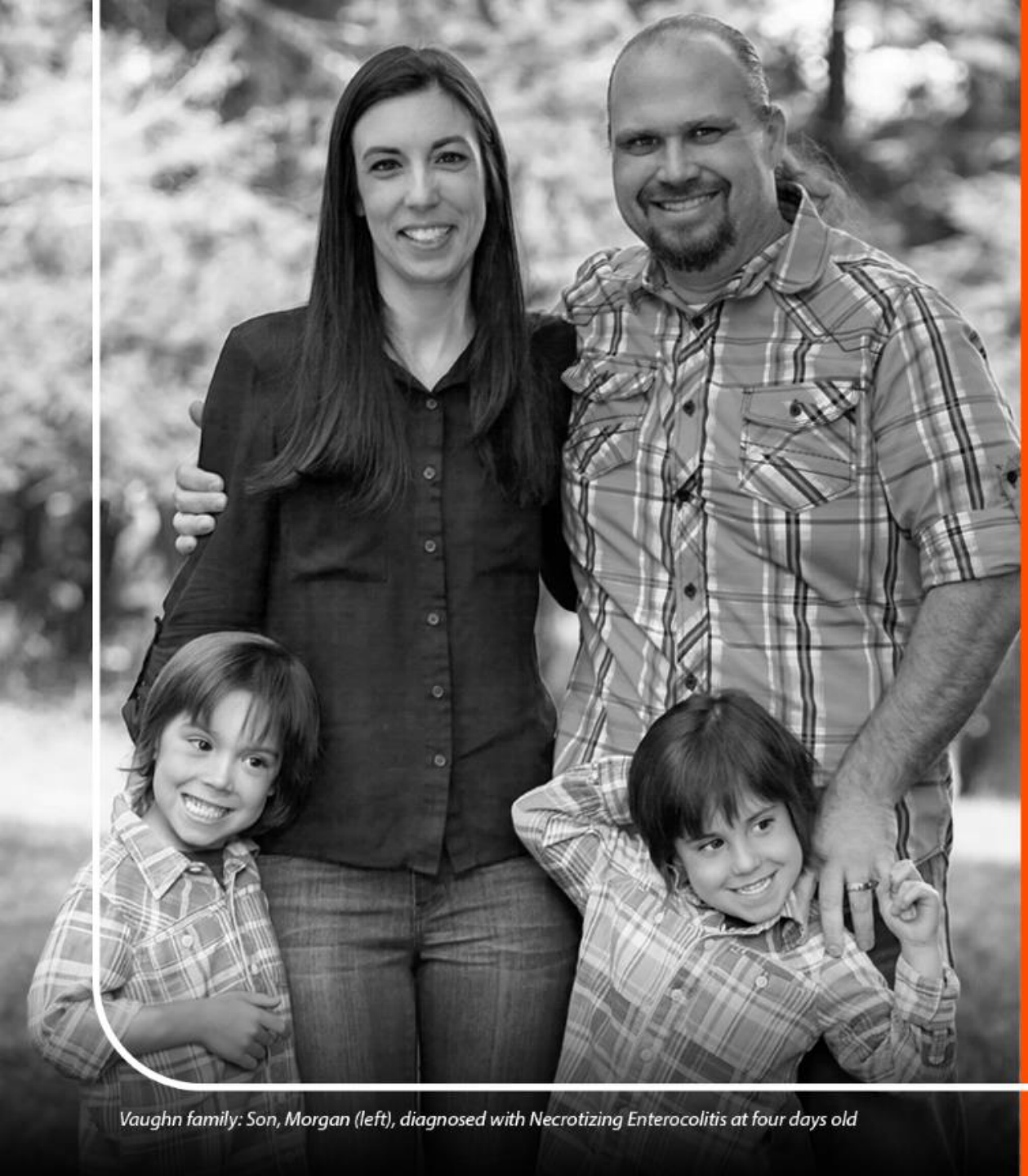
ADMINISTRATION



Vaughn family: Son, Morgan (left), diagnosed with Necrotizing Enterocolitis at four days old

Question and Answer Session

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Questions?

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The presenters will answer them in the order in which they came in and based on relevance to the discussion.

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Resources for Patients and Caregivers

Clinical Trials

Clinicaltrials.gov or asgct.org/clincialtrials

National Institutes of Health

https://ghr.nlm.nih.gov/primer/therapy/genetherapy

Food and Drug Administration

https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products

ASGCT

https://www.asgct.org/education/gene-therapy-basics

NORD

https://rarediseases.org/video-topic/research-science/#watch-39678

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