FDA's Approach to Facilitating the Development of Gene Therapies

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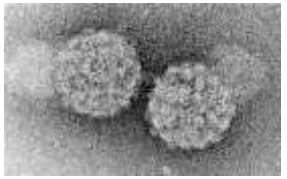
Objectives

- Discuss some definitions
- Review expedited development programs
- Describe challenges in product development
- Note resources for product developers

CBER Regulates Advanced Therapy Medicinal Products (ATMPs)

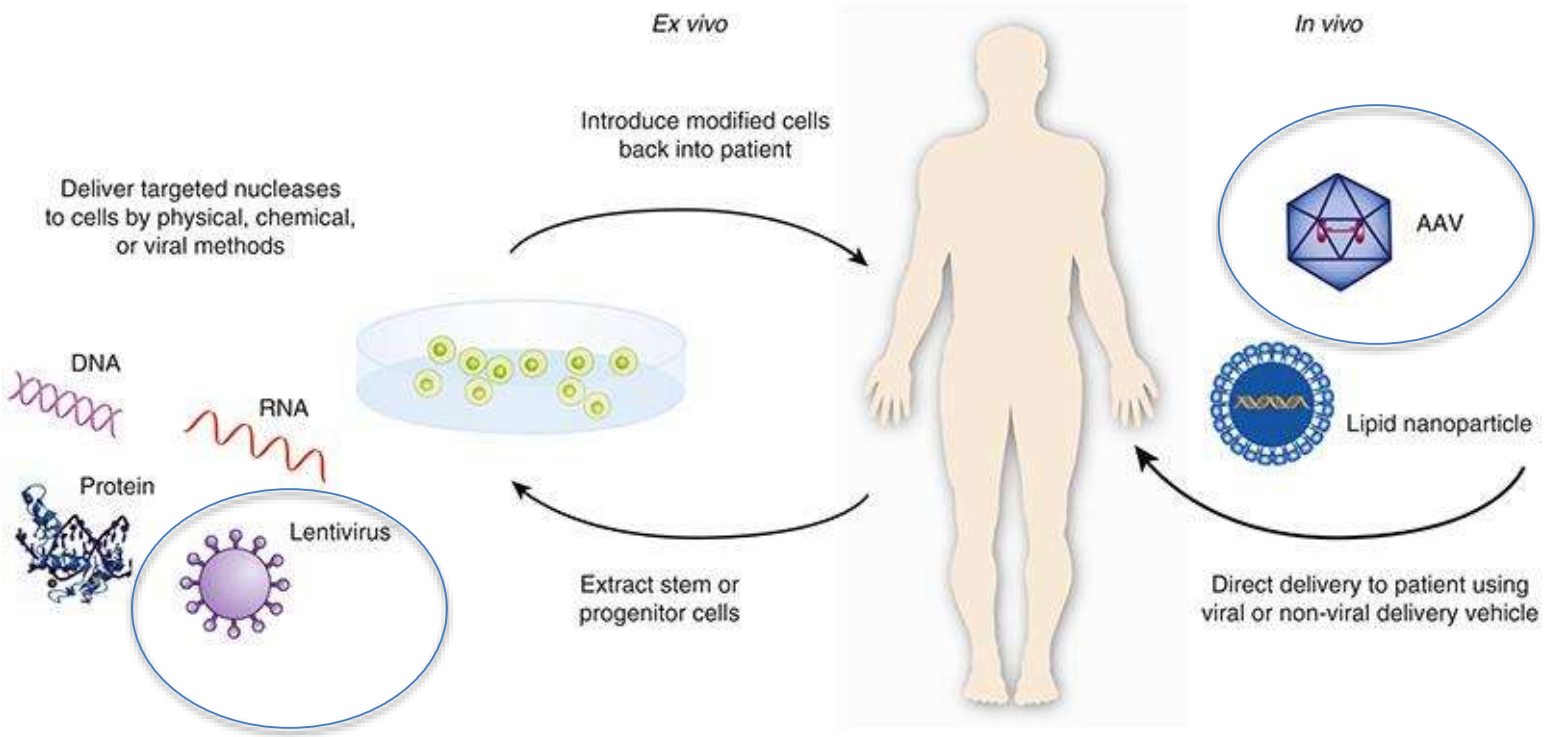


Products included

- Gene therapies
- Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) requiring licensure
- Xenotransplantation products

Clinical benefit comes from having a controlled manufacturing process and understanding critical quality attributes for ATMPs because product quality, safety, and efficacy are inextricably linked

Delivering Gene Therapy



Recent Product Approvals

- **Tisagenlecleucel (KYMRIAH):** for treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) refractory or in second or later relapse [May 1, 2018 addition of relapsed or refractory large B-lymphoma indication]

  First Approved August 30,2017
  https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/ucm573706.htm

- **Axicabtagene ciloleucel (YESCARTA):** for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy

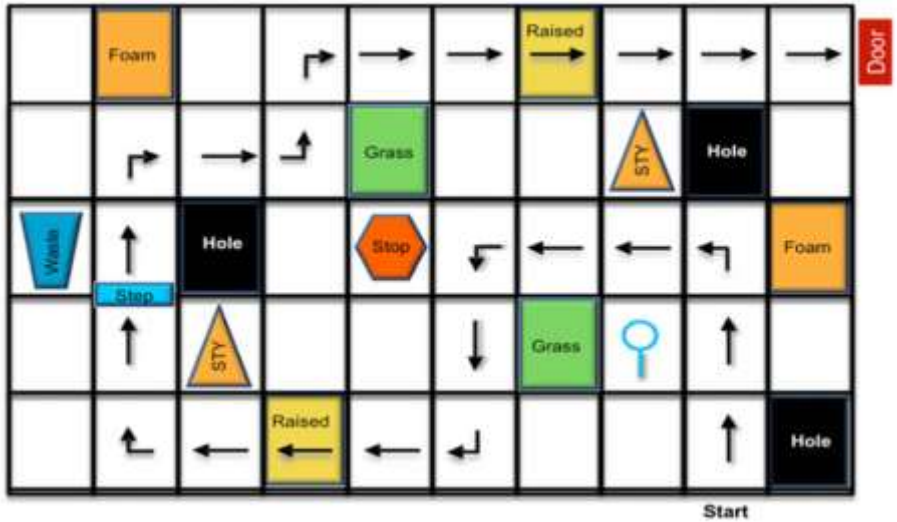
  Approved October 18,2017
  https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/ucm581222.htm

One Directly-Administered Gene Therapy Approved in 2017

- **Voretigene neparvovec-rzyl (LUXTURNA):** for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy in patients with viable retinal cells as determined by the attending physician(s).
  - Novel endpoint used for approval developed by sponsor with input from FDA
    https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/ucm589507.htm

Multi-Luminance Mobility Test

Negotiating a path with obstacles at different light levels



Scoring based on time and accuracy

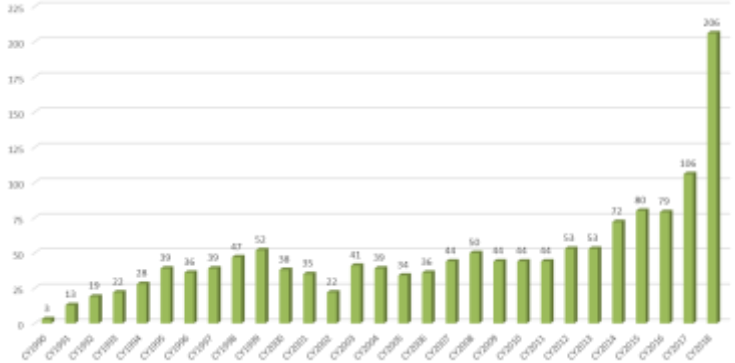
Illuminance (lux)	Luminance (cd/m^2)	Corresponding environment
1	0.32 mesopic vision	Moonless summer night; or indoor nightlight
4	1.3 mesopic vision	Cloudless summer night with half moon; or outdoor parking lot at night
10	3.2 mesopic vision	60 min after sunset in a city setting; or a bus stop at night
50	15.9 photopic vision	Outdoor train station at night; or inside of illuminated office building stairwell
125†	39.8 photopic vision	30 min before cloudless sunrise; or interior of shopping mall, train or bus at night
250‡	79.6 photopic vision	Interior of elevator, library or office hallway
400	127.3 photopic vision	Office environment; or food court

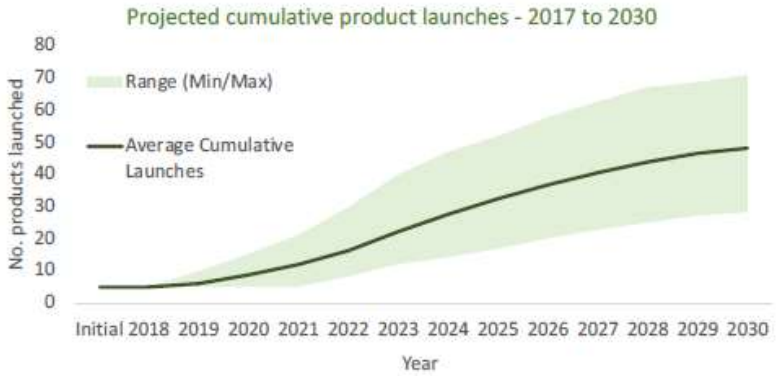
Chung DC et al., Clin Exp Ophthalmol, 20182018; 46:247–259

Predicted Growth of Gene Therapy

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

Number of IND Applications Received by FDA





Correlates with prediction by MIT of 40 to 60 product launches and more than 500,000 treated by 2030

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

Expedited Development Programs

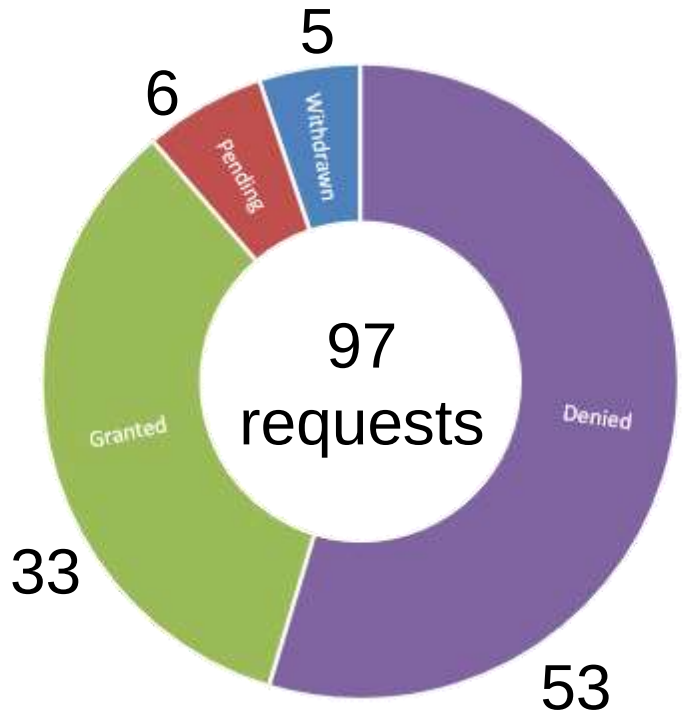
- Fast Track
- Priority Review
- Accelerated Approval
- Breakthrough Therapy
- Regenerative Medicine Advanced Therapy

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

Regenerative Medicine Advanced Therapy Designation (RMAT)

- Products must be intended for serious or life-threatening diseases or conditions
- Preliminary clinical evidence must indicate potential to address unmet medical needs
- Designated products are eligible as appropriate for priority review and accelerated approval
- Expanded range of options for fulfilling post approval requirements of accelerated approval

RMAT Designations Granted



- 33 products granted designation
- Majority have Orphan Product designation (20/33)
- Most are cellular therapy products or cell-based gene therapy products

Data as of April 1, 2019

Advancing the Development of Cell and Gene Therapy

- Guidance documents
- Reduction of administrative burden
- Clinical development initiatives
- Standards
- Manufacturing initiatives

Suite of Gene Therapy Draft Guidance Documents – July 2018

1. Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)
2. Testing of Retroviral Vector-Based Gene Therapy Products for Replication Competent Retrovirus (RCR) during Product Manufacture and Patient Follow-up
3. Long Term Follow-up After Administration of Human Gene Therapy Products
4. Human Gene Therapy for Hemophilia, on gene therapy products intended for treatment of hemophilia
5. Human Gene Therapy for Retinal Disorders
6. Human Gene Therapy for Rare Diseases

https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/default.htm

Revitalizing the RAC, Standards Development, and Research

- FDA and NIH collaborating to reduce regulatory burden while enhancing the value added provided by the Recombinant DNA Advisory Committee (RAC)
- CBER is working with NIH and National Institute of Standards and Technology (NIST) and others to facilitate the development of standards for use in cell and gene therapy
- CBER laboratory research programs and collaborations with academic and public private partners to advance field

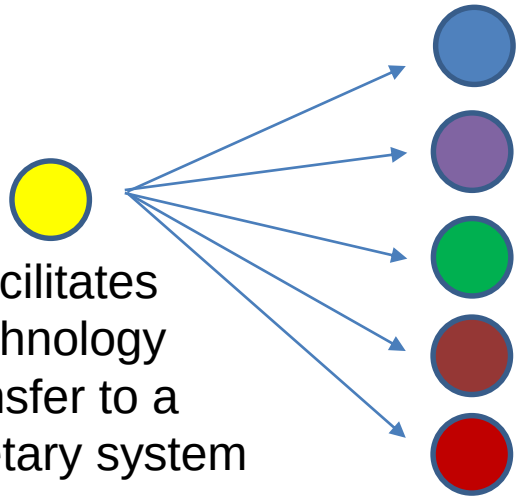
Challenges in the Development of Cell and Gene Therapies

- Need novel approaches to clinical development
  - Application of advanced statistical methodologies
  - Potential use of appropriate surrogate endpoints
- Transition from pilot scale to commercial manufacturing can be challenging for gene therapies
  - Consider scalable manufacturing processes

Concept for Facilitating More Efficient Technology Transfer

Manufacturers' proprietary gene therapy vectors

Common transfer vector and production protocol for use by academic investigators in early phase development



Facilitates technology transfer to a proprietary system

Advantages

- Streamline preclinical evaluation required for first in human trials
- Makes technology more accessible to academic innovators addressing both rare and common diseases
- Increases value of asset both to investigators and industry

Potential Challenges

- Agreement on vectors
- Prework needed to develop vector and protocols
- Vector and protocol distribution

INTERACT Program

INitial Targeted Engagement for Regulatory Advice on CBER producTs

- To further encourage early interaction with sponsors and replace the pre-pre-IND meeting process across the Center regarding preclinical, manufacturing and, clinical development plans

https://www.fda.gov/BiologicsBloodVaccines/ResourcesforYou/Industry/ucm611501.htm

Summary

- FDA is committed to advancing the development and evaluation of cell and gene therapies
  - Helping to individualize product development
  - Working to overcome limitations in manufacturing
  - Providing input and collaboration on novel endpoints
  - Encouraging innovative clinical trial designs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