Center for Biologics Evaluation and Research (CBER)

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Center for Biologics Evaluation and Research (CBER) Update

Peter Marks, MD, PhD

FDLI Meeting

May 2, 2019

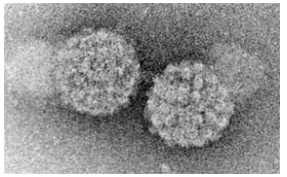
Overview

- Describe products regulated by CBER
- Explain challenges of biological products
- Review recent approvals
- Discuss expediting development of advanced therapies
- Overview strategic priorities for the coming year

Products Regulated by CBER

- Allergenics
- Blood and Blood Components
- Blood Derivatives
- Devices Related to Biologics
- Gene Therapies
- Human Tissues and Cellular Products
- Vaccines (preventative and therapeutic)
- Live Biotherapeutic Products
- Xenotransplantation Products

Definition of 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 a controlled manufacturing process and understanding critical quality attributes because product quality, safety, and efficacy are inextricably linked

Challenges of Biological Products

- Manufacturing
  - Made from living cells, tissues, or organisms or complex mixtures not easily characterized
  - Tend to be heat sensitive and susceptible to microbial contamination
  - Complexity of manufacturing facilities/materials, processes and products
- Clinical Development
  - Products may be intended to prevent relatively rare events or used in very small populations
  - May be impossible to clinically observe whether the product is effective in practice
  - Long term safety/efficacy data may be required
- Regulatory
  - Scientific basis underlying efficacy of products is not always clear
  - Ensure adequate control of manufacturing process without being excessive
  - Lack of regulatory precedent in some areas

Major Product Approvals – FY18

- **ANDEXXA** (Coagulation factor Xa (Recombinant) inactivated-zhzo)
  - Indicated for patients treated with rivaroxaban and apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. (approved May 3, 2018)

https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/andexxa-coagulation-factor-xa-recombinant-inactivated-zhzo

Major Product Approvals – FY18

- **Imugen Babesia microti Arrayed Fluorescent Immunoassay (AFIA) and Babesia microti Nucleic Acid Test (NAT)**
  - First donor screening tests for detection of antibodies to Babesia microti (B microti) in human plasma samples (AFIA), and B. microti DNA in human whole blood samples (NAT) (approved March 6, 2018)
  - Babesiosis is caused by babesia transmission by Ixodes scapularis ticks
  - B. microti is the main species that causes infection in the United States
  - Transfusion-transmitted babesiosis can be fatal in immunocompromised individuals

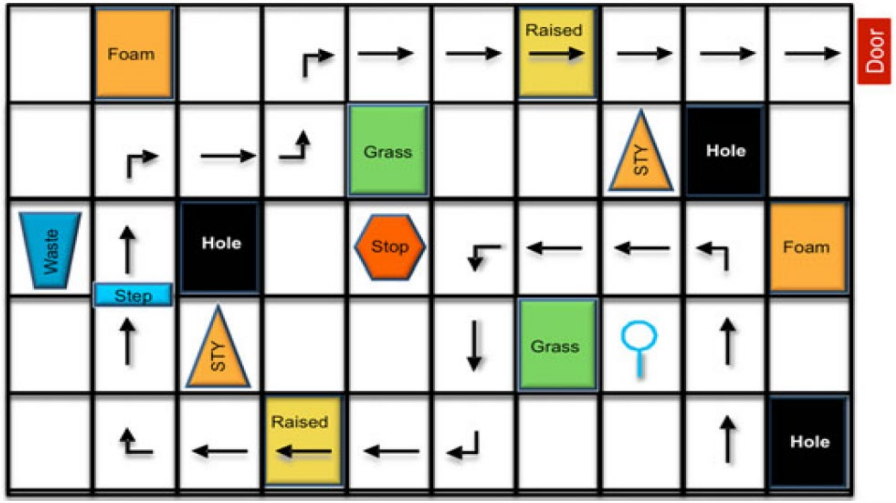
Major Product Approvals – FY18

- **Voretigene neparvovec-rzyl (LUXTURNA)**
  - Indicated 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 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

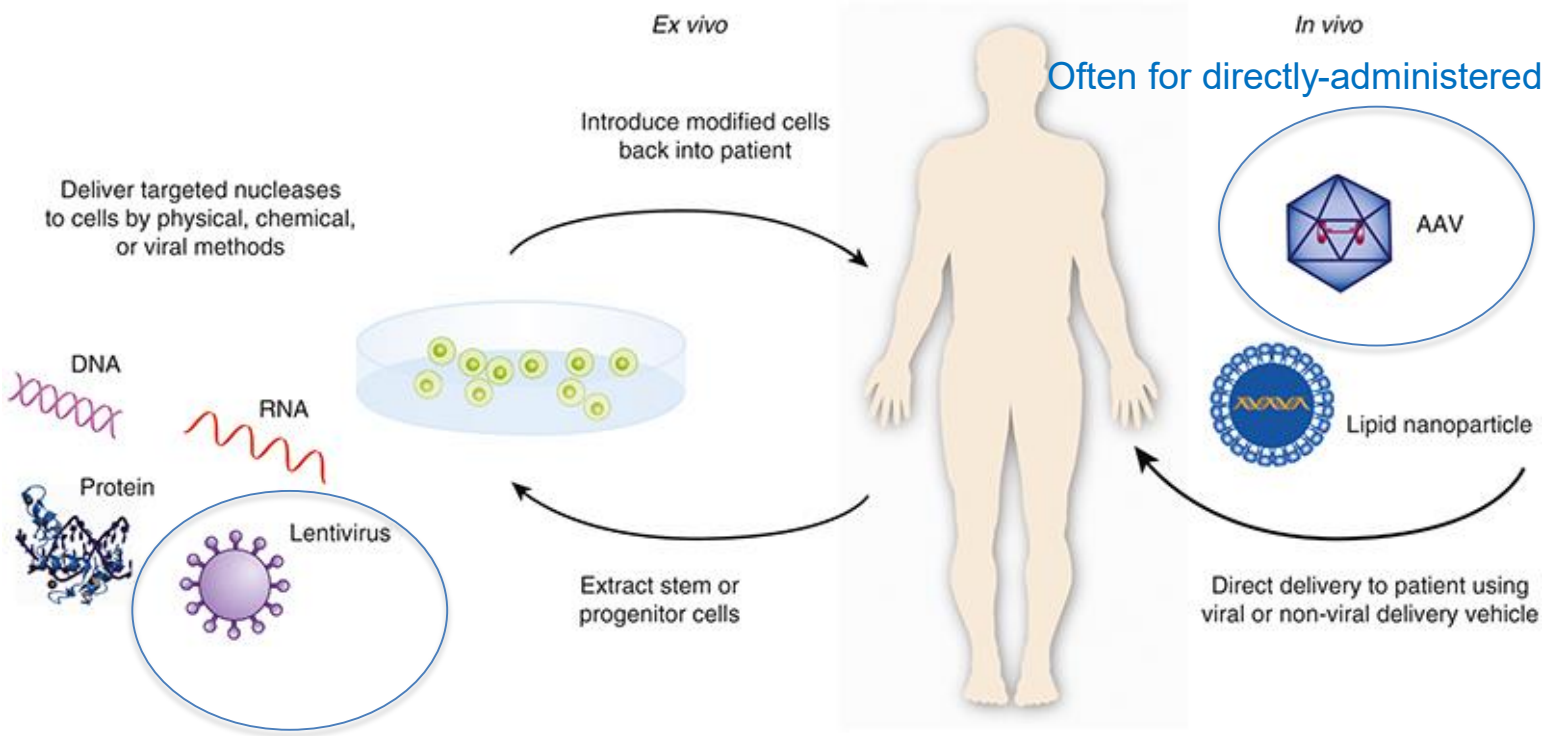


Scoring based on time and accuracy

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

Delivering Gene Therapy



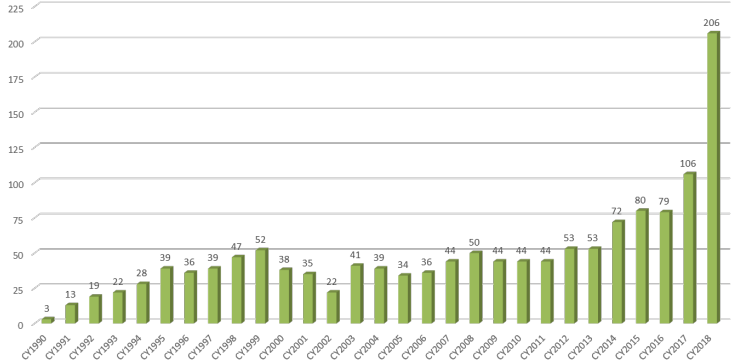
Often for directly-administered products

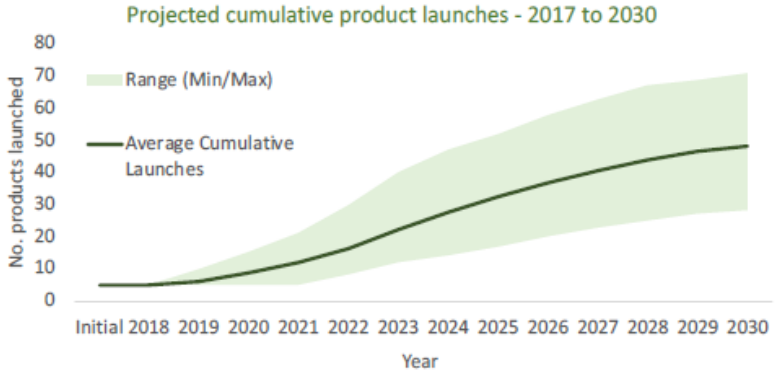
Often used for CAR-T cells

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 of 40 to 60 product launches and more than 500,000 treated by 2030

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

Expedited Development Programs

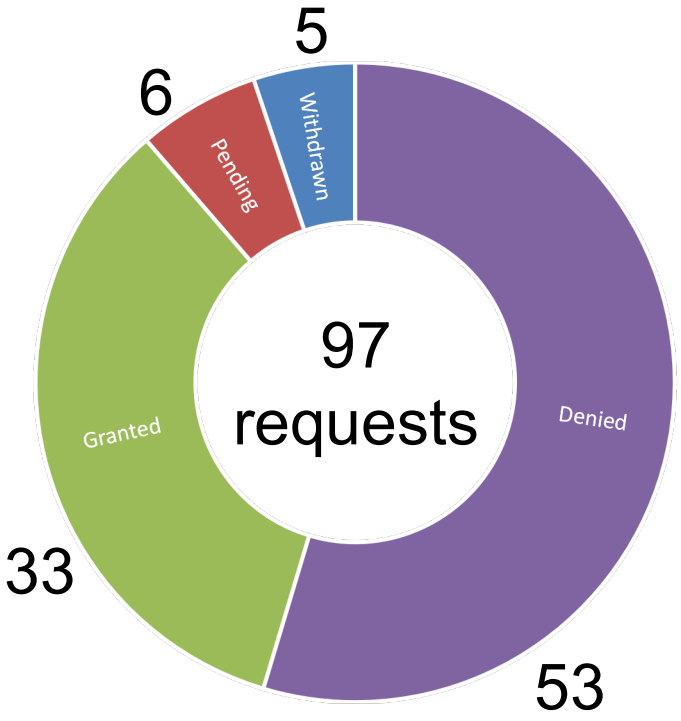
- Fast Track
- Priority Review
- Accelerated Approval
- Breakthrough Therapy
- Regenerative Medicine Advanced Therapy

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 (ATMPs)

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

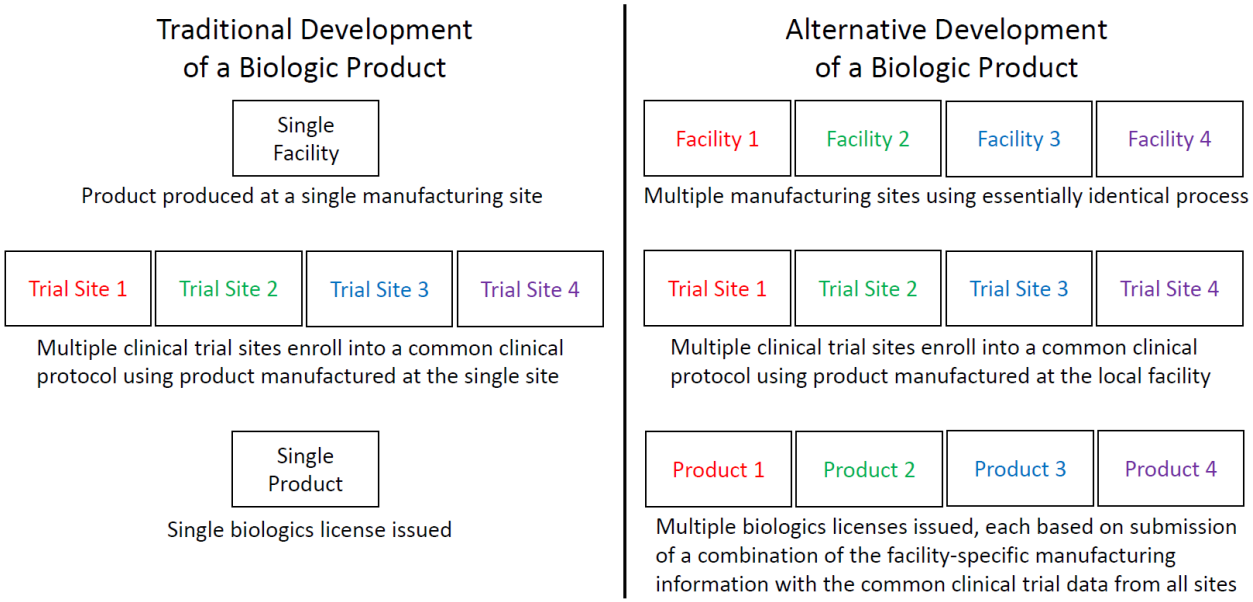
Revitalizing the RAC, Standards Development, and Research

- 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

Research at CBER

- Applied scientific research supporting product development
  - About 80 principal investigators
  - 300 to 400 staff involved in either part time or full time research
  - WHO Collaborating Center, reference reagent preparation, lot release testing
- Planned or Ongoing scientific initiatives
  - Advanced manufacturing of gene therapy vectors
  - Advanced manufacturing of vaccines
  - Pathogen reduction for whole blood
  - Use of natural language processing and AI

Innovative Development Program for Regenerative Medicine Products



https://www.nejm.org/doi/full/10.1056/NEJMsr1715626

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

CBER Strategic Priorities FY2019

- Timely regulatory approvals for novel products
- Cell and gene therapy guidance documents
- Compliance and enforcement plan for cell therapies
- Regulatory framework for live biotherapeutic products
- Advanced manufacturing for biologic products
- Recruitment and retention of critical staff

Summary

- CBER is committed to advancing the development of complex biological products through applied scientific research
  - Working to overcome limitations in manufacturing
  - Providing input and collaboration on endpoints
  - Encouraging innovative clinical trial designs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ADMINISTRATION

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