Center for Biologics Evaluation and Research (CBER)

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Moderated by Neil Di Spirito, Member of the Firm, Epstein Becker & Green, PC
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

www.fda.gov
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

Chung DC et al., Clin Exp Ophthalmol, 2018; 46:247–259
Delivering Gene Therapy

Often used for CAR-T cells

Often for directly-administered products
Predicted Growth of Gene Therapy

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

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
5. Human Gene Therapy for Retinal Disorders
6. Human Gene Therapy for Rare Diseases

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

Traditional Development of a Biologic Product

- Single Facility
- Product produced at a single manufacturing site
- Multiple clinical trial sites enroll into a common clinical protocol using product manufactured at the single site
- Single Product
- Single biologics license issued

Alternative Development of a Biologic Product

- Facility 1
- Facility 2
- Facility 3
- Facility 4
- Multiple manufacturing sites using essentially identical process
- Trial Site 1
- Trial Site 2
- Trial Site 3
- Trial Site 4
- Multiple clinical trial sites enroll into a common clinical protocol using product manufactured at the local facility
- Product 1
- Product 2
- Product 3
- Product 4
- Multiple biologics licenses issued, each based on submission of a combination of the facility-specific manufacturing information with the common clinical trial data from all sites


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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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