Regulatory Flexibilities for Cell and Gene Therapies for Rare Diseases

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Overview

- Introduction to FDA CBER OTP
- Select cell and gene therapy approvals
- International collaboration

Diversity of OTP Regulated Products

- **Gene Therapies**
  - Ex vivo genetically modified cells, non-viral vectors (e.g., plasmids), replication-deficient viral vectors (e.g., adenovirus, adeno-associated virus, lentivirus), replication-competent viral vectors (e.g., measles, adenovirus, vaccinia), microbial vectors (e.g., Listeria, Salmonella)
- **Stem cell and stem cell-derived products**
  - Hematopoietic, mesenchymal, cord blood, embryonic, induced pluripotent stem cells (iPSCs)
- **Terminally-differentiated cell therapies**
  - Pancreatic islets, chondrocytes, myoblasts, keratinocytes, hepatocytes
- **Therapeutic vaccines and other antigen-specific active immunotherapies**
  - Cancer vaccines and immunotherapies, such as dendritic cells, lymphocyte-based therapies, cancer cell-based therapies, peptides, proteins; non-infectious disease therapeutic vaccines, such as peptides, proteins, small molecules
- **Blood- and Plasma-derived products**
  - Purified and recombinant proteins for hematology (e.g., coagulation factors)
- **Human Tissues**
- **Devices**

Gene Therapies Holds Great Promise

80% of rare diseases have a genetic basis.

FDA has approved **17 gene therapy products**, most of which are for rare disorders.

OTP currently oversees more than **2,600** active investigational products; **more than half** of these are gene therapy products.

Collaboration and flexibilities are critical in development of gene therapy products

Regulatory Flexibilities for Approved Gene Therapies for Rare Diseases

Luxturna:

- Ex-vivo genetically modified autologous CD34+ hematopoietic progenitor cells
- For the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy

Trial Design

Control

Novel Endpoint

Zolgensma:

- Directly administered adeno-associated virus (AAV) vector that delivers SMN gene
- For the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the *survival motor neuron 1 (SMN1)* gene

Trial Design

Control

Efficacy Analysis

Regulatory Flexibilities for Approved Gene Therapies for Rare Diseases, Cont'd.

Syksona original approval:

- Ex-vivo genetically modified autologous CD34+ hematopoietic progenitor cells
- To slow the progression of neurologic dysfunction in boys 4-17 years of age with early, active cerebral adrenoleukodystrophy (CALD)

Accelerated Approval

Trial Design

Efficacy Analysis

Casgevy original approval:

- Ex vivo, autologous hematopoietic progenitor cells, modified by genome editing using CRISPR/Cas9
- Treatment of sickle cell disease (SCD) in patients 12 years and older with recurrent vaso occlusive crises (VOCs)

Trial Design

Control

Efficacy Analysis

Collaboration on **Gen**e **T**herapies Global (CoGenT Global) Pilot

- Initial participation by Standing Regulatory Members of ICH
- Partners may participate in internal regulatory meetings and meetings that include the sponsor
- Specific regulatory reviews are shared and discussed with partners
- All meetings conducted and information shared under strict confidentiality agreements
- Goal is to increase the efficiency of the regulatory process, reducing time and cost for agencies and sponsors

International Collaboration, Cont'd.

- **International Conference of Harmonization**
  - Cell and Gene Therapy Discussion Group, 2023
  - Guidelines on virus and vector shedding, oncolytic viruses, and addressing risk of inadvertent germline integration with GT vectors

- **International Pharmaceutical Regualtors Programme**
  - Global regulatory framework for cell, tissue, and gene therapies
  - Reflection papers on long term follow up for cell therapy trials and biodistribution of GT products

- **Discussion Clusters**
  - Mutliateral (FDA, EMA, others)
  - Product-focused (ATMP, Blood)
  - Indication-specific (rare disease, pediatric, oncology)

- **Informal Discussions**

Contact Information

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- **Interactions with Office of Therapeutic Products website:**

  Interactions with Office of Therapeutic Products | FDA

- **OTP Learn Webinar Series:**

  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

FDA Headquarters

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