FDA’s Efforts to Facilitate the Development of Cell and Gene Therapies

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CASSS Meeting on Cell and Gene Therapy Products
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Disclosures

• I am a full-time employee of the United States government and have no relevant relationships with commercial interests to disclose
Overview

• Discuss FDA’s efforts to facilitate development of cell and gene therapies
• Describe the importance of manufacturing
• Review the applicable regulatory framework
• Provide some resources for product developers
Bottom Line Up Front

• FDA is committed to advancing the development of cell and gene therapies for populations of all sizes
  – Helping to individualize product development
  – Providing input and collaboration on novel endpoints
  – Encouraging innovative clinical trial designs
Growth in Cell and Gene Therapy

Original Investigational New Drug Applications (INDs)

- Excluding expanded access requests

IND Amendments

- Including expanded access requests

www.fda.gov
U.S. Approved Gene Therapies

- Kymriah (2017)
- Yescarta (2017)
- Luxturna (2017)
- Zolgensma (2019)
- Tecartus (2020)
- Breyanzi (2021)
- Abecma (2021)
- Carvykti (2022)
Cell-Based Gene Therapy
Potential Advantages to Use of Genetically-Modified Cellular Therapies

• Appropriate methods can be used to address the issue of location of genomic integration
  – Ability to select appropriately transduced cells for administration to recipients
  – Use of newer technologies such as CRISPR possible
  – Control of effector function is possible, if necessary
• Possibility to provide therapeutic benefit with an extended duration of effect
Challenges in the Development of CAR-T Cell Therapies

• Transition from pilot scale to commercial manufacturing can be challenging
  – Centralized versus distributed manufacturing

• Need novel approaches to clinical development
  – Use of complex and innovative clinical trial designs
  – Advanced planning for clinical trials seamlessly transitioning from phase 1 to pivotal (licensure) trial
CAR-T Manufacturing Systems
CAR-T Cells for Solid Tumors

- Several challenges have hindered the development of CAR-T cells for solid tumors
  - Targeting of the CAR-T cell to the tumor’s location
  - Overcoming immunosuppressive microenvironment
  - Achieving optimal CAR-T cell function over time
  - Relative paucity of highly specific tumor antigens
Allogeneic CAR-T Cells

• Molecular biology, including genome editing, allows the development of cells deficient in MHC class I molecules (multiple methods)

• Potentially facilitates off the shelf product
  – Promotes manufacturing consistency
  – Available immediately for those in need
  – May ultimately reduce cost of therapy
Novel CAR-T Cell Constructs

Broadening Antigen Targeting  Narrowing Antigen Targeting

Adapted from: Walsh Z, Yang Y, Kohler ME. Immunological Reviews 2019;290:100-113
Directly-Administered Gene Therapy
FDA Approved Systemic Directly-Administered Gene Therapy

• **Onasemnogene abeparvovec-xioi (Zolgensma):** for the treatment of patients less than two years of age with spinal muscular atrophy (SMA) with confirmed biallelic mutations in the *survival motor neuron 1 (SMN1)* gene
  
  – SMA Type 1 commonly presents with muscle weakness that is evident at birth or within the first few months of life

Onasemnogene Clinical Results

Clinical trial results: patients with infantile-onset SMA that are untreated do not develop a CHOP INTEND score (a test for neuromuscular disorders) greater than 40.

Evelyn with documented SMA1 treated with onasemnogene, now age 3 running around, something never seen in untreated children.

Mendell JR et al. NEJM 2017; 377:1713-1722
Importance of Therapies for Disorders that are Very Rare

• Out of thousands of rare hereditary and acquired diseases there are hundreds of disorders affecting one to a few dozen per year that could be addressed with novel therapies
  – Addressing molecular defects may reduce some more common diseases to very rare diseases
Personalized medicine
Finding the right drug on the shelf to treat the patient
versus
Individualized medicine
Creating the right drug to treat the patient
Individualized medicine
Creating the right drug to treat the patient

Customized Products
- Same indication
- Same mode of action

Example:
Personalized vaccine for pancreatic cancer using dendritic cells pulsed with an individualized peptide mixture

Created Products
- Different indication
- Different mode of action

Example:
Gene therapies for two different hemoglobin mutations using same vector back bone
Challenges of Individualized Therapies

• Manufacturing
• Nonclinical development
• Clinical development
• Product access
Current manufacturing platforms limit gene therapy production

Approximate Treatment Population Per Year

Viability? (Cost) | Sweet Spot | Viability? (Technology)
---|---|---
1-100 | >100-10,000 | >10,000

Leveraging validated processes can potentially facilitate the development of new products
Manufacturing

Will the gene therapy manufacturing platform of the future be a device?
Concepts in Development

• “Cookbook” for the development and manufacturing of bespoke therapeutics

• Leveraging of nonclinical and manufacturing data from one application to another
  – Concept of originator and offshoot products leveraging information on file and focusing on distinguishing attributes of offshoot products
Develop a Bespoke GT “Cookbook”
Premise

• In appropriate situations, non-clinical data and manufacturing information from one product may be able to be leveraged to another
All results from treatments are reported back to the consortium for iterative learning.

Bespoke Gene Therapy Consortium

Foundation for the National Institutes of Health (FNIH)
Non-profit umbrella organization

FDA streamlining of regulatory requirements: master files/templates

Vector generation
Manufacture of therapeutic
Clinical ability to treat patients

Standard vector menu
Standard process menu
Standard delivery menu

Therapies for patients

Idea for Gene Therapy Target

www.fda.gov
FDA’s Regulatory Role
FDA Organization

Office of the Commissioner

National Center for Toxocologic Research

Office of Regulatory Affairs

Center for Biologics Evaluation and Research
Center for Drug Evaluation and Research
Center for Devices and Radiologic Health
Center for Food Safety and Nutrition
Center for Veterinary Medicine

Medical Product Centers
Regulatory Framework for Biologics

• Constitution
• Laws/Statutes
  • Public Health Service Act
    • Section 351
    • Section 361
  • Federal Food Drug and Cosmetic Act
• Regulations/Rules
• Guidance
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
Objectives of Suite of Regenerative Medicine Guidance Documents

• Clarify existing regulations to make it simpler for sponsors to determine if they need to obtain premarket authorization for their products

• Expedite the development and approval of safe and effective innovative regenerative medicine therapies and associated devices
Suites of Regenerative Medicine Final Guidance Documents

1. Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception
2. Regulatory Considerations for Human Cell, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use
3. Evaluation of Devices Used with Regenerative Medicine Advanced Therapies
4. Expedited Programs for Regenerative Medicine Therapies for Serious Conditions
Expedited Programs for Regenerative Medicine Therapies

• Describes FDA’s considerations for the Regenerative Medicine Advanced Therapy Designation (RMAT) to expedite product development and review
  – Applies to certain cell therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products
  – Genetically modified cell therapies and gene therapies producing durable effects included
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
- FDA replies to designation requests within 60 days
- Designated products are eligible as appropriate for priority review and accelerated approval
CBER Breakthrough Therapy Designation & Regenerative Medicine Advanced Therapy Designation - Cumulative Requests and Designations

- 170 BTDs Requested
- 172 RMAT Designations Requested
- 64 RMAT Designations Granted
- 55 BTDs Granted

Timeline:
- 2013
- 2014
- 2015
- 2016
- 2017
- 2018
- 2019
- 2020
- 2021
RMAT Requests and Actions

CBER Has Granted 68 RMAT Designations Since Program Inception

- 96 of the 180 RMAT Requests are Cell Therapy products
- 32 of the 68 RMAT Granted products have Orphan Product designation
- 22 of the 68 RMAT Granted products have Fast Track designation

Data as of March 1, 2022
Recent Guidance – March 2022

• Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Therapies; Draft Guidance for Industry

• Human Gene Therapy Products Incorporating Human Genome Editing; Draft Guidance for Industry
CATT Meetings

CBER Advanced Technology Team

• Provides an interactive mechanism for discussion of advanced technologies or platforms needed for the development of CBER-regulated biologics products

• CATT allows access to early and ongoing interactions with CBER before filing of a regulatory submission

https://www.fda.gov/vaccines-blood-biologics/industry-biologics/cber-advanced-technologies-team-catt
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

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