The FDA’s Regulatory Framework for Chimeric Antigen Receptor-T Cell Therapies

Peter Marks, MD, PhD
ASCPT Workshop on CAR-T Cells
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Outline

• Product categorization
• Applicable regulatory framework
• Challenges in product development
• Facilitating agency interactions
Chimeric Antigen Receptor (CAR-T) Cell Therapy

A CAR-T cell (pink) attacking a cancer cell (yellow)

Patient

Patient may receive pre-conditioning chemotherapy prior to infusion
Sometimes cytokine support (IL-2) post-infusion

Gene modified T cell Infusion

Dose formulation Product testing

Expand in culture CD3/CD28 beads ± IL-2 / IL-15

T cell activation and transduction with gene transfer vector

Apheresis Product

Chimeric antigen receptor structure

www.fda.gov
CAR-T Cells are a Form of *Ex vivo* Gene Therapy
CAR-T Cells are Considered a Type of Regenerative Medicine

A field with great promise that includes a variety of innovative products

• Cell and gene therapies
• Therapeutic tissue engineering products
• Human cell and tissue products
• Combination products

Many of the products fall into the category known by European regulatory authorities as advanced therapy medicinal products (ATMPs)
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 efficacy flows from an understanding of critical quality attributes and a controlled manufacturing process for ATMPs because product quality and efficacy are inextricably linked
Suite of Regenerative Medicine Guidance Documents – November 2017

1. Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception – Final

2. Regulatory Considerations for Human Cell, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use – Final

3. Evaluation of Devices Used with Regenerative Medicine Advanced Therapies – Draft

4. Expedited Programs for Regenerative Medicine Therapies for Serious Conditions – Draft

Suite of Gene Therapy Draft Guidance Documents – July 2018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

Regenerative Medicine Advanced Therapy Designation (RMAT)

• To expedite the development and review of regenerative medicine advanced therapies
  – 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
- 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

- 31 products granted designation
- Majority have Orphan Product designation (19/31)
- Most are cellular therapy products or cell-based gene therapy products

Data as of March 1, 2019
Challenges in the Development of Cell and Gene Therapies

• Transition from pilot scale to commercial manufacturing can be challenging for both cellular and gene therapies
  – Consider scalable manufacturing processes
• Need novel approaches to clinical development
  – Limited patient populations for clinical trials
  – Potential use of appropriate surrogate endpoints
  – Advance planning for clinical trials
Solutions on the Horizon: Closed Manufacturing Systems

- Partially automated closed manufacturing systems
Solutions on the Horizon: Modular Manufacturing Facilities

• Scalable pre-built biotechnology centers
Advancing the Development of Cell and Gene Therapies

- 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 regenerative medicine

- Plans for CBER laboratory research programs and collaborations with academic and public private partners to advance field
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 biologics license issued

Alternative Development of a Biologic Product:
- Facility 1, Facility 2, Facility 3, Facility 4
- Multiple manufacturing sites using essentially identical process
- Multiple clinical trial sites enroll into a common clinical protocol using product manufactured at the local facility
- 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 interaction with sponsors and replace the pre-pre-IND meeting process across the Center

• Existing webpage on the INTERACT program will be updated in the next months

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

• FDA is committed to advancing the development and evaluation of CAR-T cells and similar potentially life-saving products
  – Helping to individualize product development
  – Working to overcome limitations in manufacturing
  – Providing input and collaboration on novel endpoints
  – Encouraging innovative clinical trial designs