Regulatory Considerations for Cell-Based Immunotherapies

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ACDRS-NIH Workshop: Cell-Based Immunotherapy
January 22, 2019
Overview

• Cell-based immunotherapy overview
• Relevant regulatory guidance and pathways
• Remaining product development challenges
• Agency resources
Cellular Immunotherapies

• Products have been in development for a number of years and now are maturing to reach the market
• Chimeric antigen receptor-T cells (CAR-T cells) represent a genetically-modified cellular therapy with potential applications to multiple diseases
  – Hematologic malignancies
  – Solid tumors
  – Infectious disease
  – Autoimmune disease
Two Cellular Immunotherapies Approved in 2017

• **Tisagenlecleucel (KYMRIAH):** for treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) refractory or in second or later relapse [May 2018 addition of relapsed or refractory large B-lymphoma indication]

• **Axicabtagene ciloleucel (YESCARTA):** for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy
Potential Advantages to Use of Genetically-Modified Cellular Therapies

• Possibility to provide therapeutic benefit with an extended duration of effect

• Appropriate methods can be used to address the issue of location of genomic integration
  – Ability to select appropriately transduced cells for administration to recipients
  – Control of effector function is possible, if necessary, through use of various approaches
Potential Challenges to Use of Genetically-Modified Cellular Therapies

• Process must be developed to consistently manufacture and characterize cells

• Logistics of manufacturing for autologous cells can be challenging
  – Though an allogeneic product may be preferable, there are developmental challenges to overcome

• Administration of therapies may be associated with various short and longer term side effects
• 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
Regenerative Medicine Guidance Documents

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
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

- 30 products granted designation
- Majority have Orphan Product designation
- Most are cellular therapy products or cell-based gene therapy products

Data as of January 18, 2019
Issues in the Manufacture of Cellular Immunotherapies

• Limitations in materials needed for production
  – Media, serum
  – Lentiviral vectors

• Challenges of developing and validating manufacturing processes
  – Transfer from academic to commercial production

• Need for standards for reproducible production
Potential Solutions on the Horizon for Manufacturing

- Partially automated closed manufacturing systems
Potential Solutions on the Horizon for Manufacturing

• Scalable pre-built biotechnology centers
Improving the Manufacture of Cellular Therapies

• 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
  – Improved cell lines for vector production
Simplifying Agency Interactions for Gene Therapy Products

- Gene therapy protocol sponsors interact with both the Recombinant DNA Advisory Committee (RAC) at NIH and the FDA for approval and reporting of adverse events.
- Given recent advances in gene therapy, FDA and NIH reviewed the utility of the existing framework.
- FDA and NIH are collaborating on a proposal to reduce regulatory burden while enhancing the value added provided by the RAC.
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 4
- Multiple manufacturing sites using essentially identical process
- Multiple clinical trial sites enroll into a common clinical protocol using product manufactured at the single site
- 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

NEJM 2018; 378: 954-959
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
• Details of requesting a meeting at: https://www.fda.gov/BiologicsBloodVaccines/ResourcesforYou/Industry/ucm611501.htm
Summary

• FDA is committed to advancing the development and evaluation of cellular immunotherapies
  – Helping to individualize product development
  – Working to overcome limitations in manufacturing
  – Encouraging innovative clinical trial designs
  – Decrease regulatory burden