FDA U.S. FOOD & DRUG ADMINISTRATION

Regulatory Considerations for Cell- Based Immunotherapies

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ACDRS-NIH Workshop: Cell-Based Immunotherapy

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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

Regenerative Medicine Guidance Document Suite – November 2017

- 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

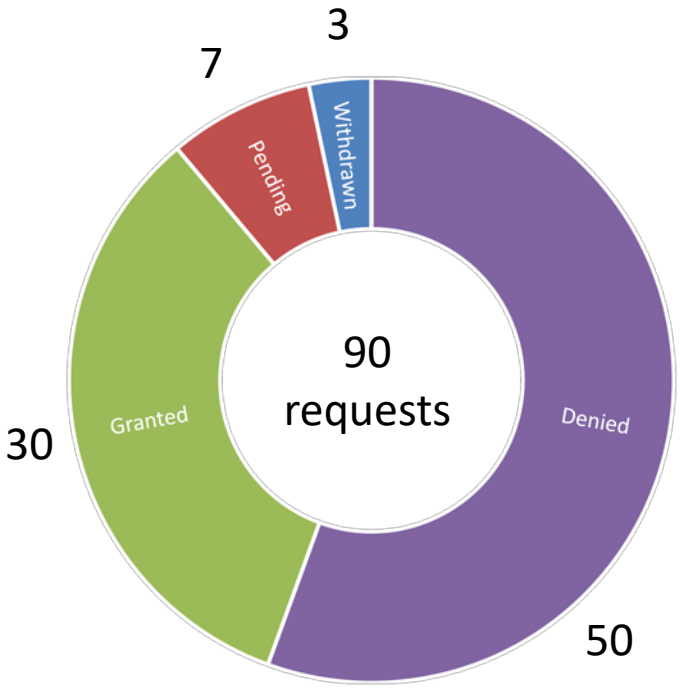
Regenerative Medicine Advanced Therapy Designation (RMAT)

- 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



Data as of January 18, 2019

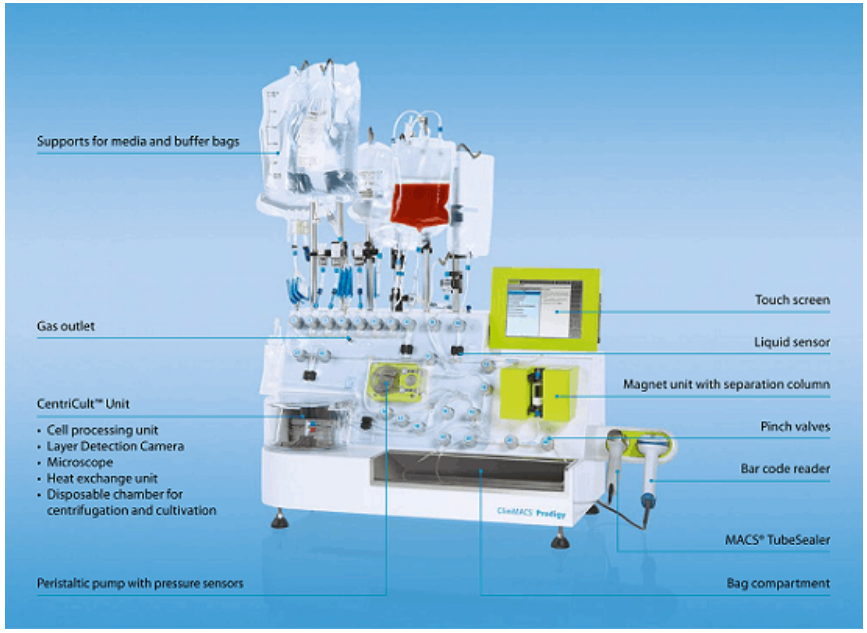
- 30 products granted designation
- Majority have Orphan Product designation
- Most are cellular therapy products or cell-based gene therapy products

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

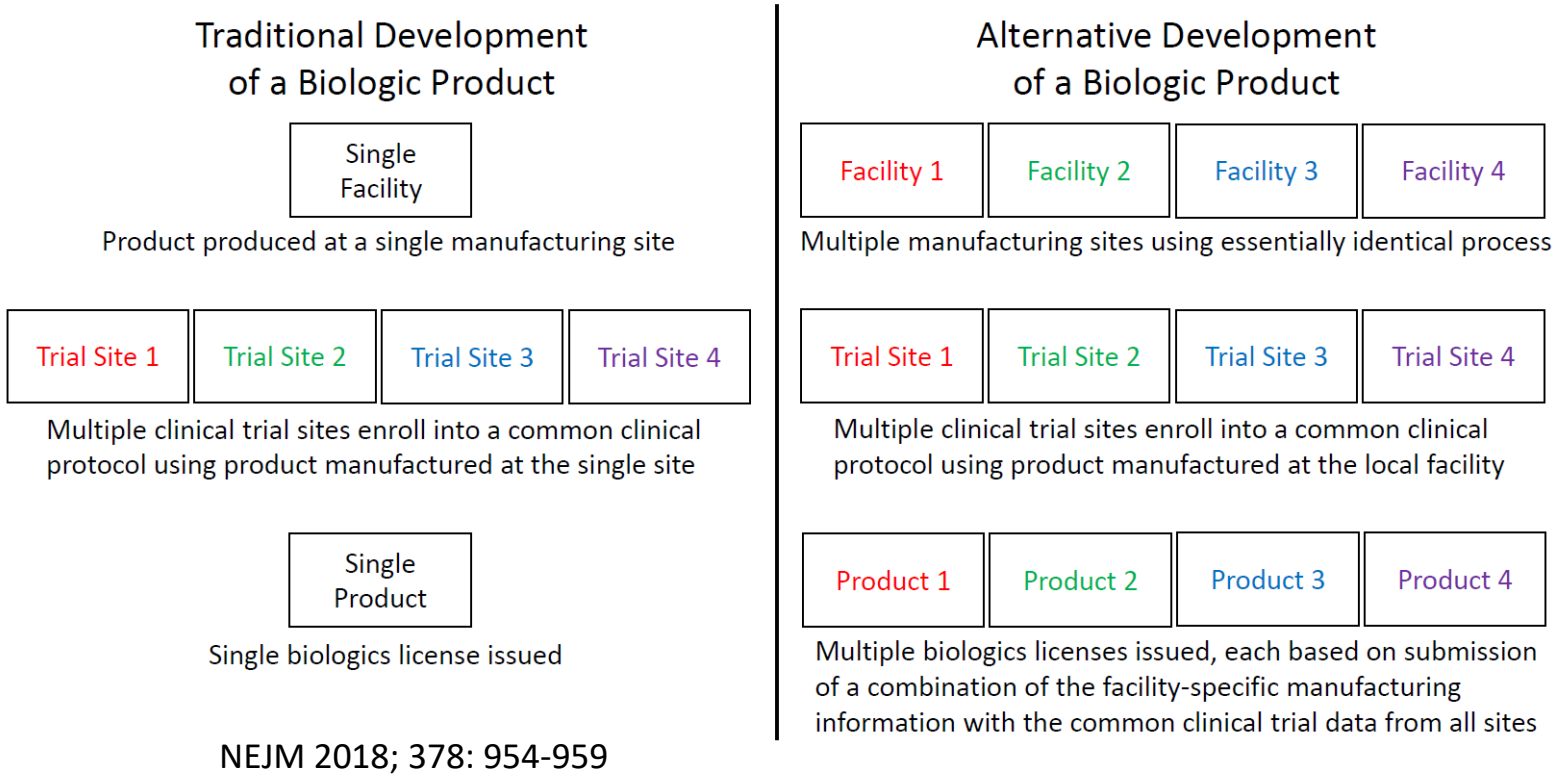
Improving the Manufacture of Cellular Therapies

- 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



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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