U.S. FOOD & DRUG ADMINISTRATION

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

Peter Marks, MD, PhD

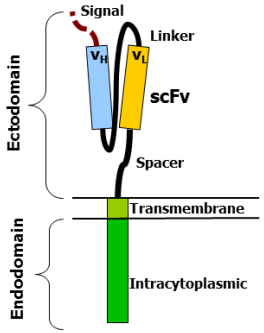
ASCPT Workshop on CAR-T Cells

March 14, 2019

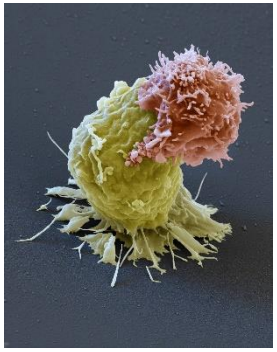
Outline

- Product categorization
- Applicable regulatory framework
- Challenges in product development
- Facilitating agency interactions

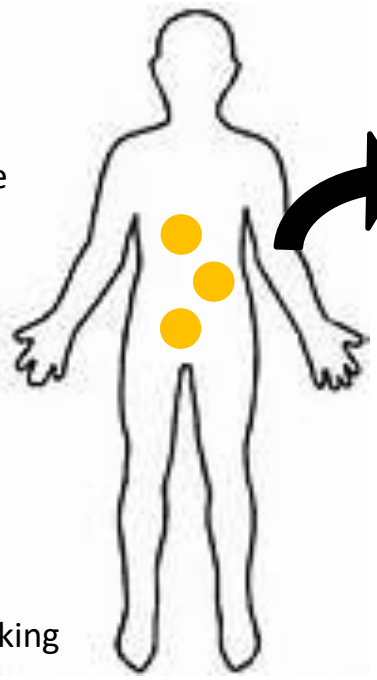
Chimeric Antigen Receptor (CAR-T) Cell Therapy



Chimeric antigen receptor structure



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



Patient

T cell activation and transduction with gene transfer vector

Apheresis Product

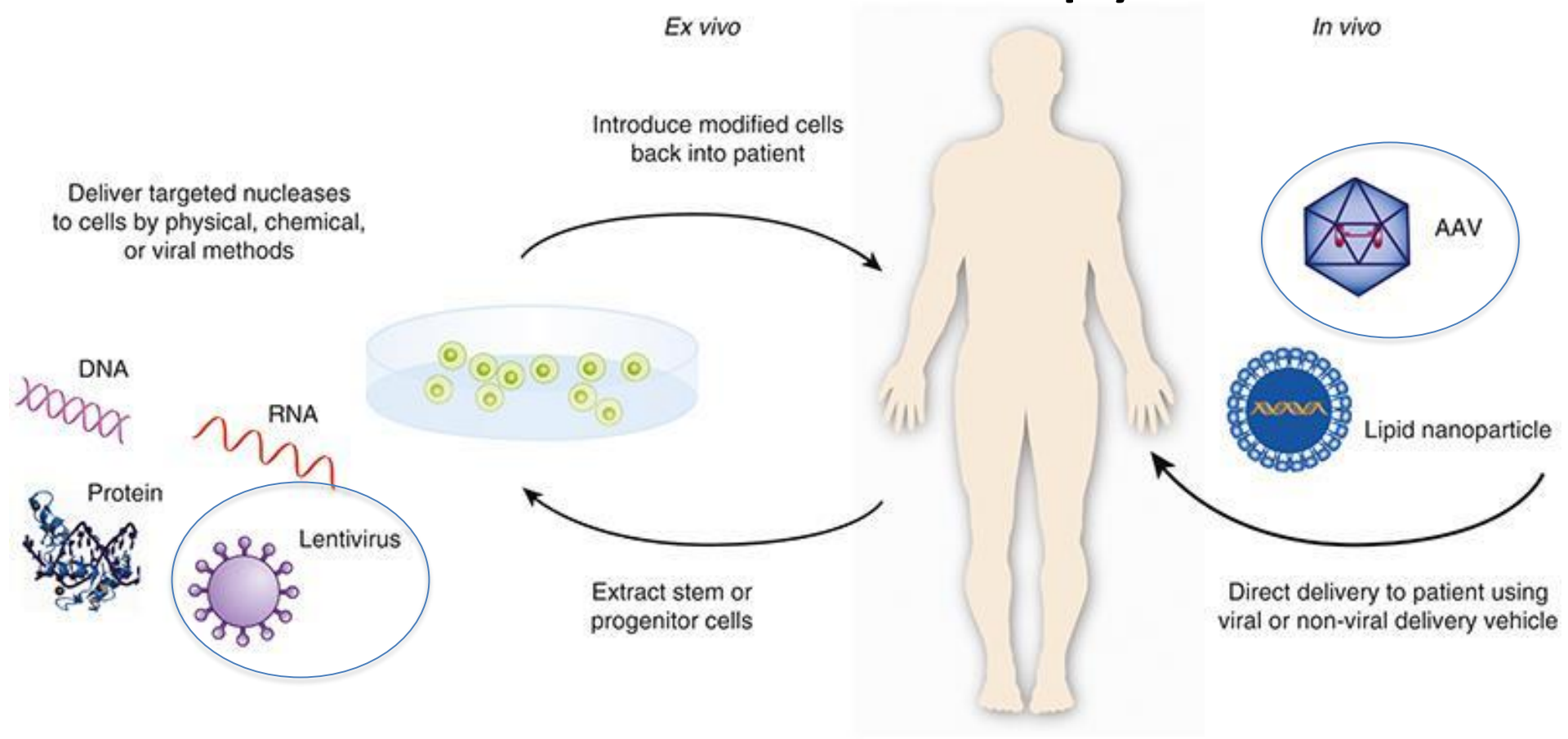
Expand in culture CD3/CD28 beads ± IL-2 / IL-15

Dose formulation Product testing

Gene modified T cell Infusion

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

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

1. https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM419926.pdf
2. https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM585403.pdf
3. https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM585414.pdf
4. https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM585417.pdf

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
4. Human Gene Therapy for Hemophilia, on gene therapy products intended for treatment of hemophilia
5. Human Gene Therapy for Retinal Disorders
6. Human Gene Therapy for Rare Diseases

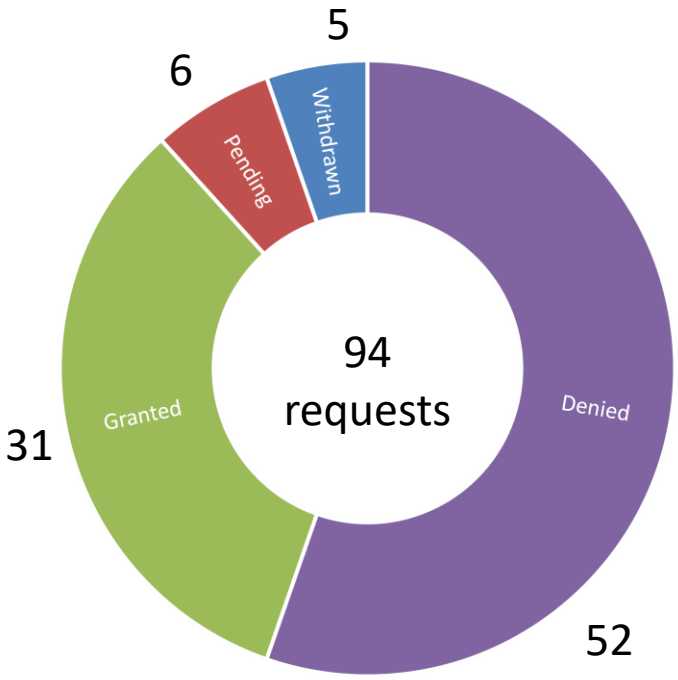
Regenerative Medicine Advanced Therapy Designation (RMAT)

- 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



Data as of March 1, 2019

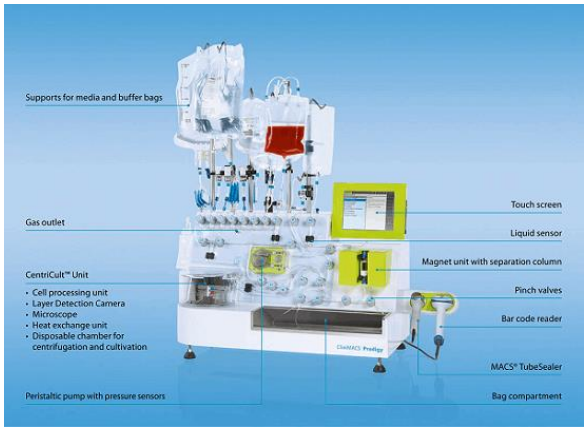
- 31 products granted designation
- Majority have Orphan Product designation (19/31)
- Most are cellular therapy products or cell-based gene therapy products

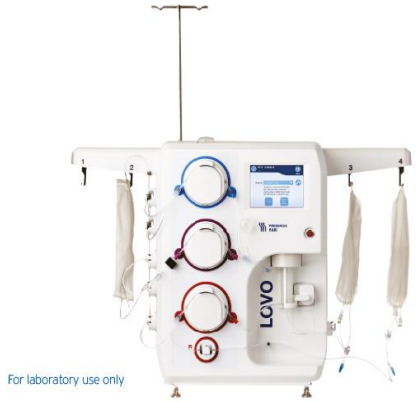
Challenges in the Development of Cell and Gene Therapies

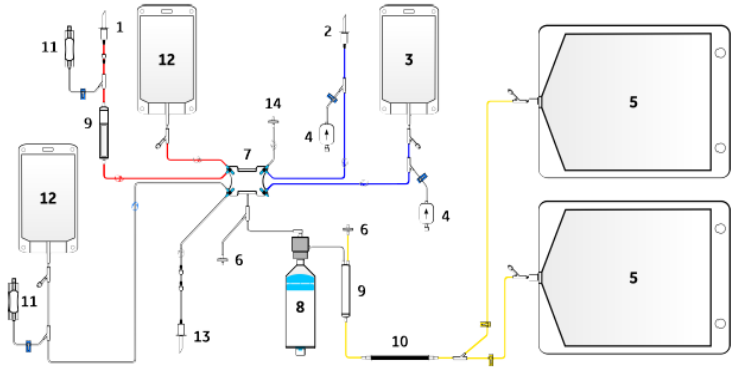
- Transition from pilot scale to commercial manufacturing can be challenging for both cellular and gene therapies
  - Consider scalable manufacturing processes
- Need novel approaches to clinical development
  - Limited patient populations for clinical trials
  - Potential use of appropriate surrogate endpoints
  - Advance planning for clinical trials

Solutions on the Horizon: Closed Manufacturing Systems

- Partially automated closed manufacturing systems

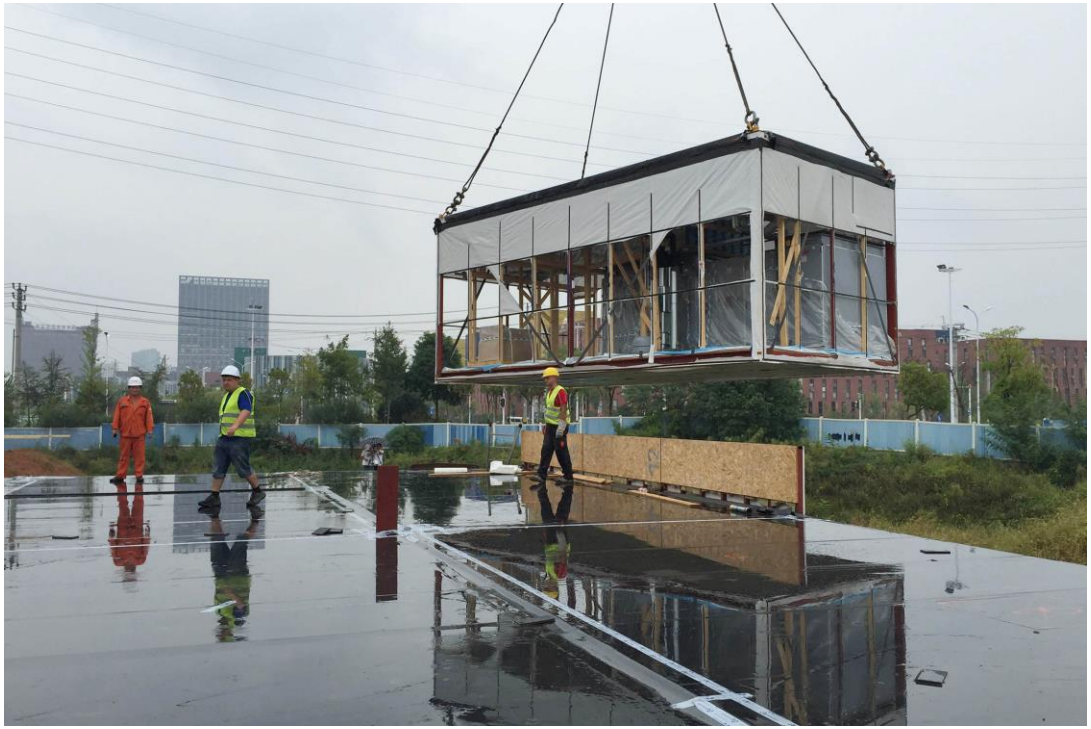






Solutions on the Horizon: Modular Manufacturing Facilities

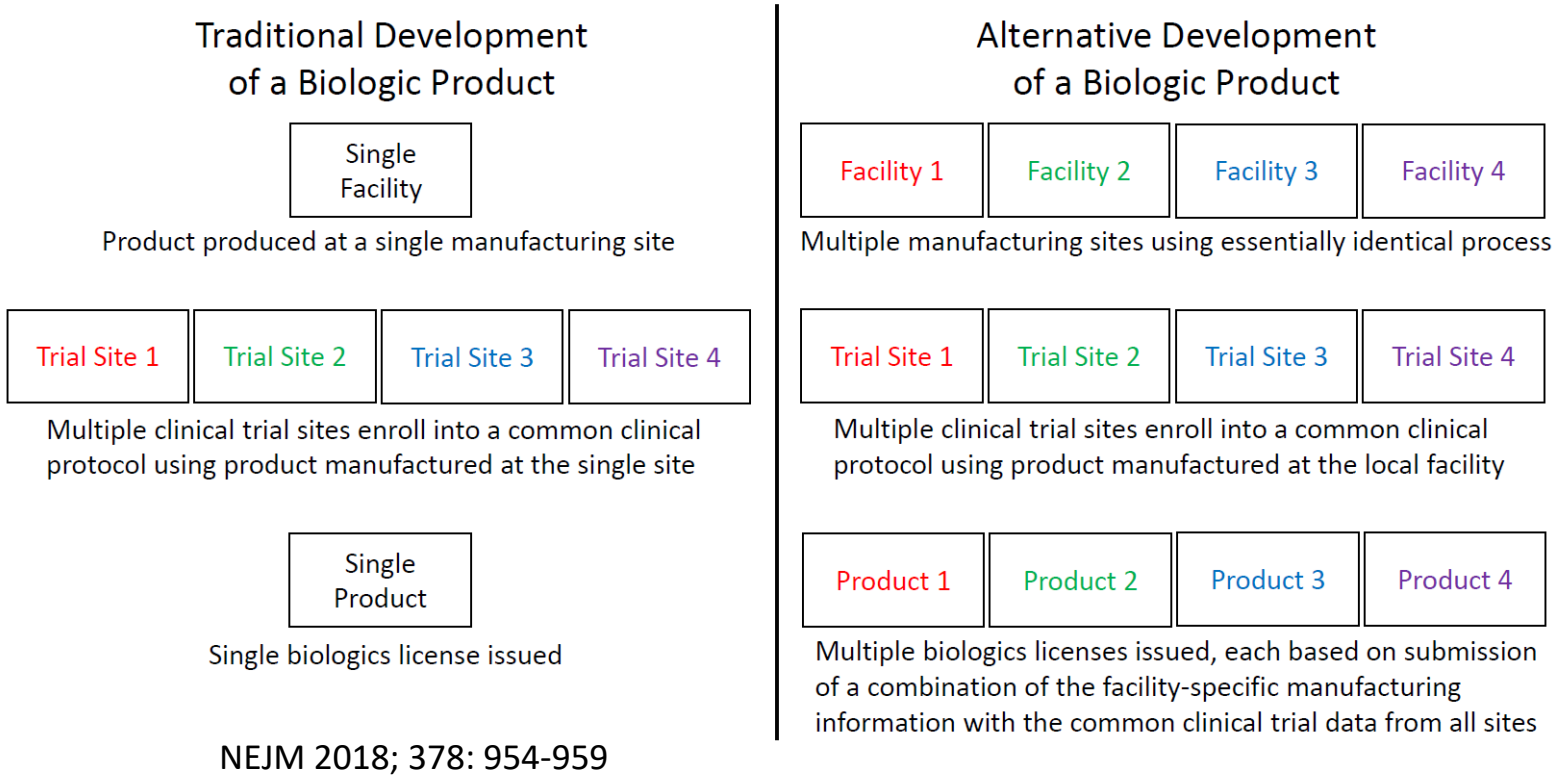
- Scalable pre-built biotechnology centers



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



NEJM 2018; 378: 954-959

https://www.nejm.org/doi/full/10.1056/NEJMsr1715626

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


FDA
U.S. FOOD & DRUG
ADMINISTRATION