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

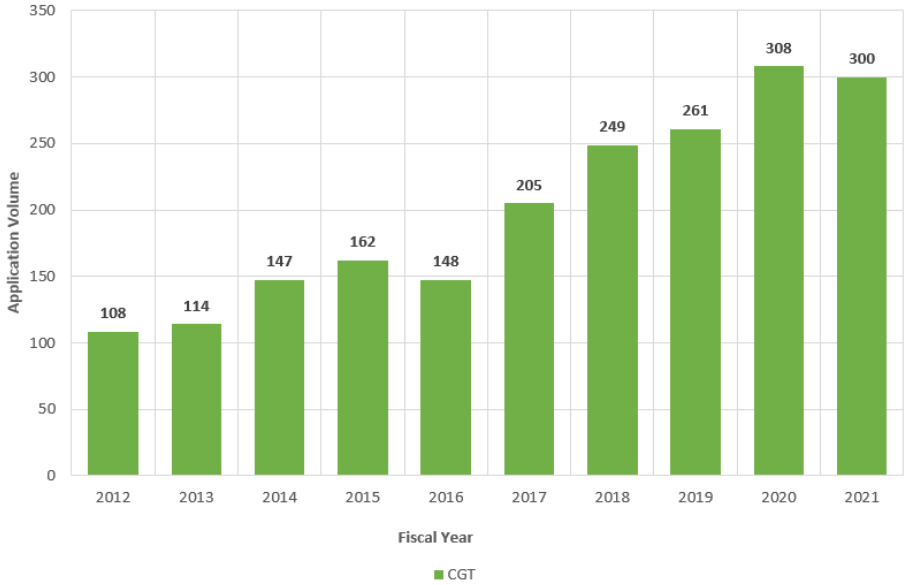
- Discuss FDA's efforts to facilitate development of cell and gene therapies
- Describe the importance of manufacturing
- Review the applicable regulatory framework
- Provide some resources for product developers

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

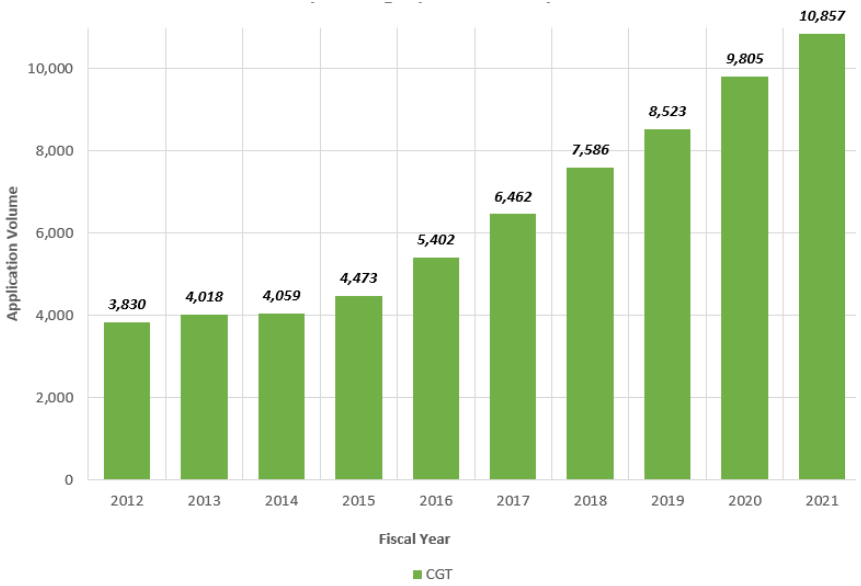
Growth in Cell and Gene Therapy

Original Investigational New Drug Applications (INDs)



Excluding expanded access requests

IND Amendments



Including expanded access requests

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

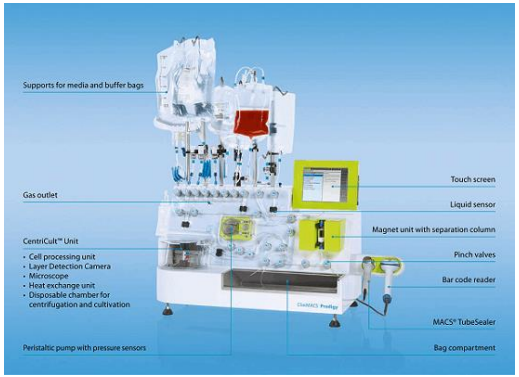
Potential Advantages to Use of Genetically-Modified Cellular Therapies

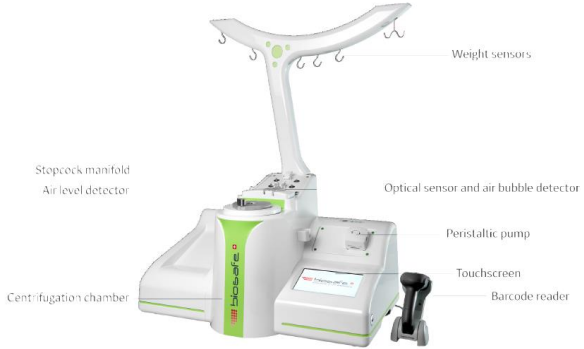
- Appropriate methods can be used to address the issue of location of genomic integration
  - Ability to select appropriately transduced cells for administration to recipients
  - Use of newer technologies such as CRISPR possible
  - Control of effector function is possible, if necessary
- Possibility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

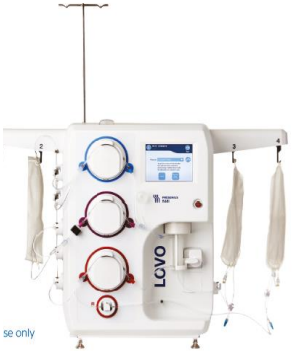
Challenges in the Development of CAR-T Cell Therapies

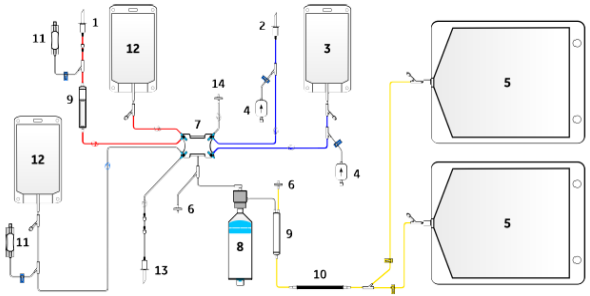
- Transition from pilot scale to commercial manufacturing can be challenging
  - Centralized versus distributed manufacturing
- Need novel approaches to clinical development
  - Use of complex and innovative clinical trial designs
  - Advanced planning for clinical trials seamlessly transitioning from phase 1 to pivotal (licensure) trial

CAR-T Manufacturing Systems









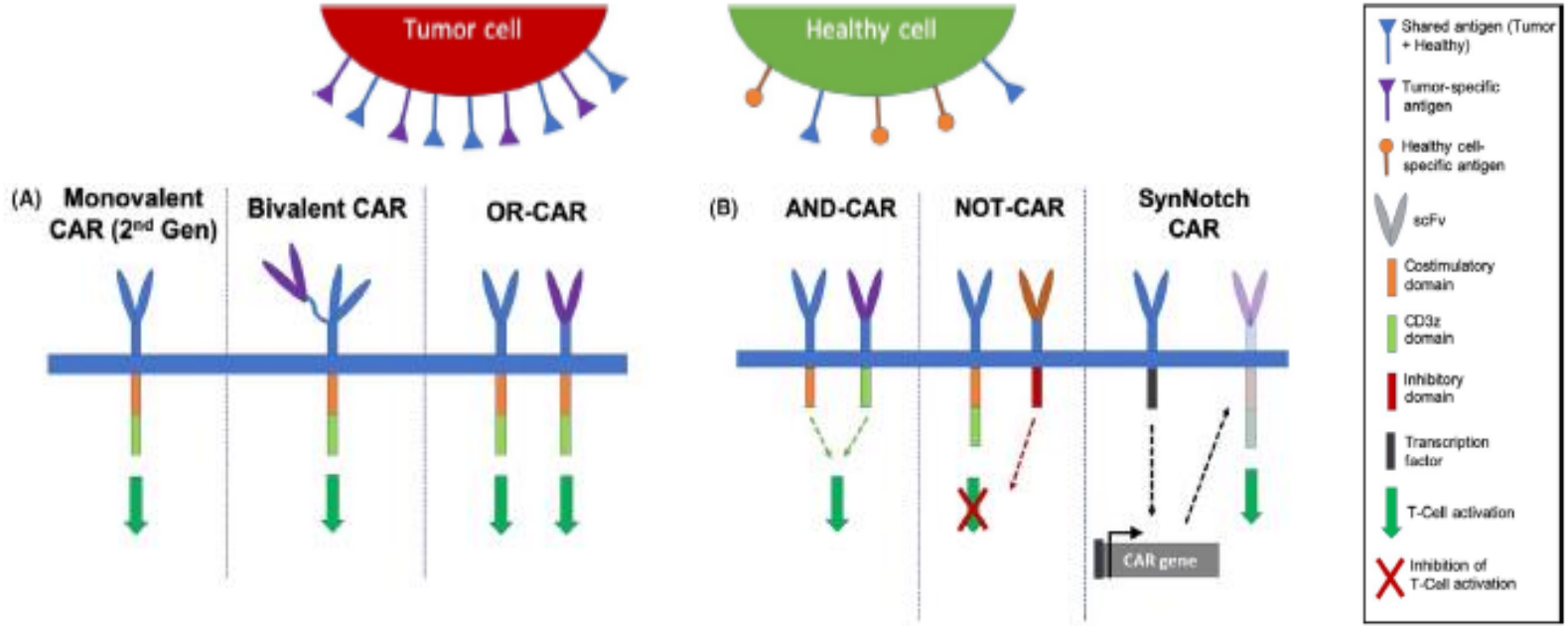
CAR-T Cells for Solid Tumors

- 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

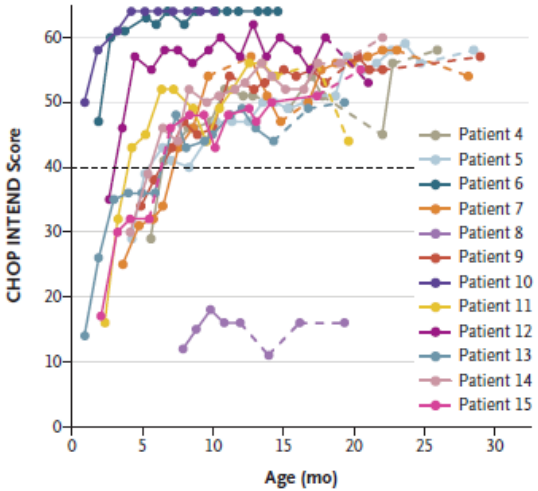
FDA Approved Systemic Directly-Administered Gene Therapy

- **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

https://www.fda.gov/news-events/press-announcements/fda-approves-innovative-gene-therapy-treat-pediatric-patients-spinal-muscular-atrophy-rare-disease

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



Mendell JR et al. NEJM 2017; 377:1713-1722

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

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

Ready to Wear

Made to Measure

Bespoke

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

Manufacturing

Current manufacturing platforms limit gene therapy production

Approximate Treatment Population Per Year	1-100	>100-10,000	>10,000

Leveraging validated processes can potentially facilitate the development of new products

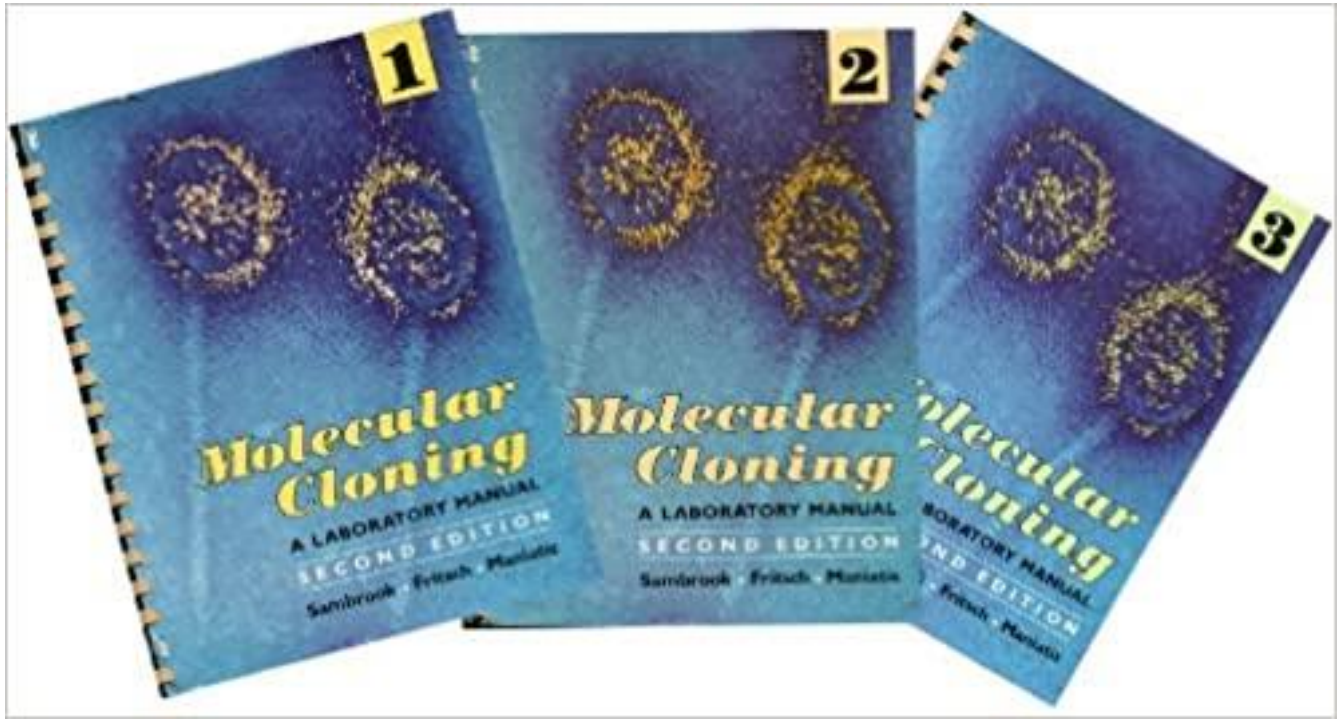
Manufacturing

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

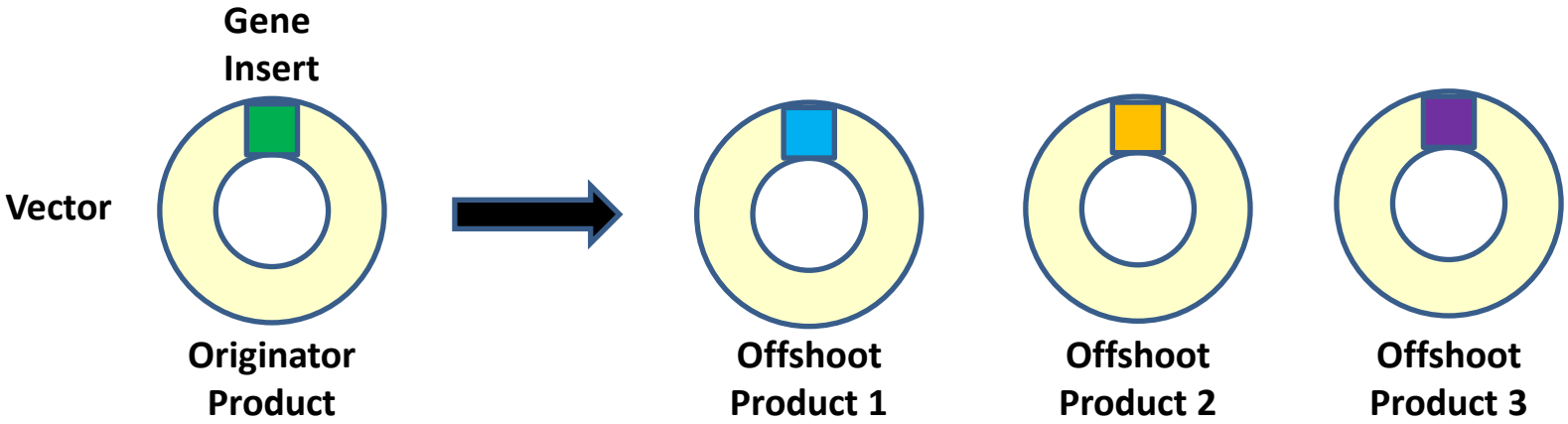
Concepts in Development

- “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”



Bespoke Therapies



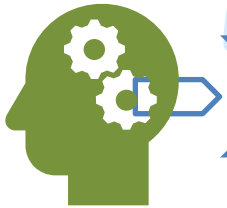
Premise

- In appropriate situations, non-clinical data and manufacturing information from one product may be able to be leveraged to another

Bespoke Gene Therapy Consortium

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

FDA streamlining of regulatory requirements: master files/templates



Idea for Gene Therapy Target

Vector generation

Standard vector menu

Manufacture of therapeutic

Standard process menu

Clinical ability to treat patients

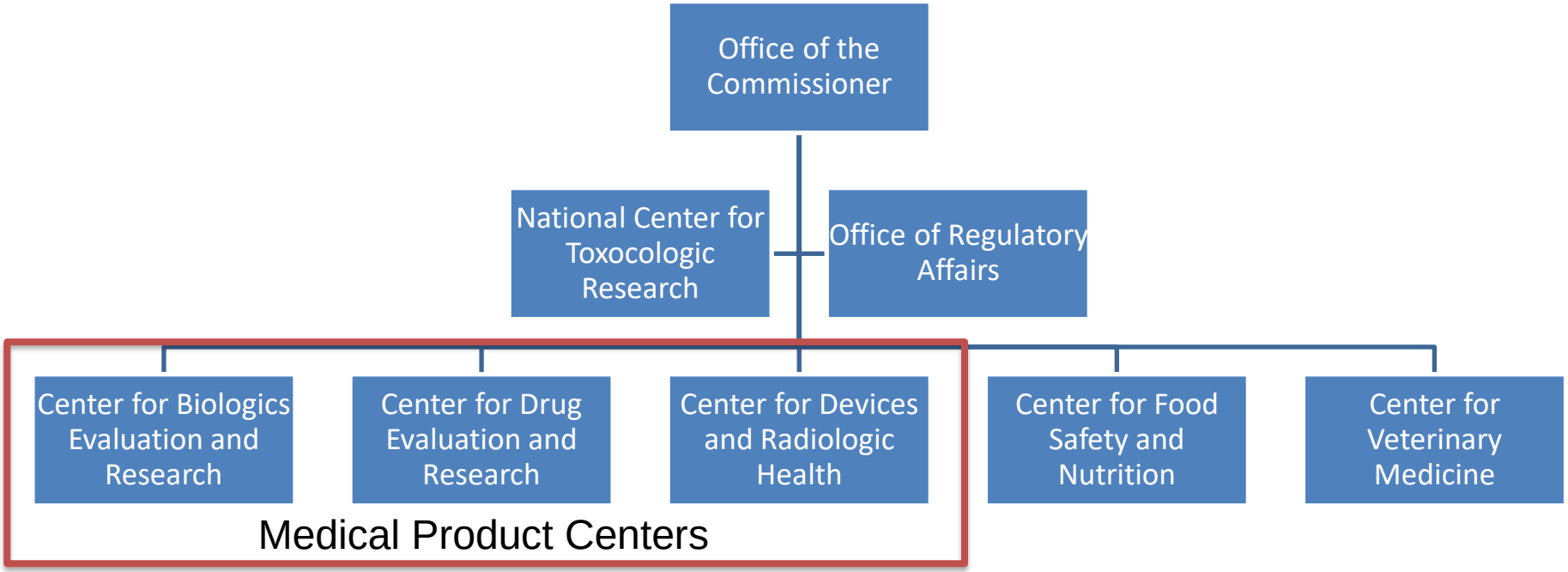
Standard delivery menu

Therapies for patients

All results from treatments are reported back to the consortium for iterative learning

FDA's Regulatory Role

FDA Organization



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

Suite of Regenerative Medicine Final Guidance Documents

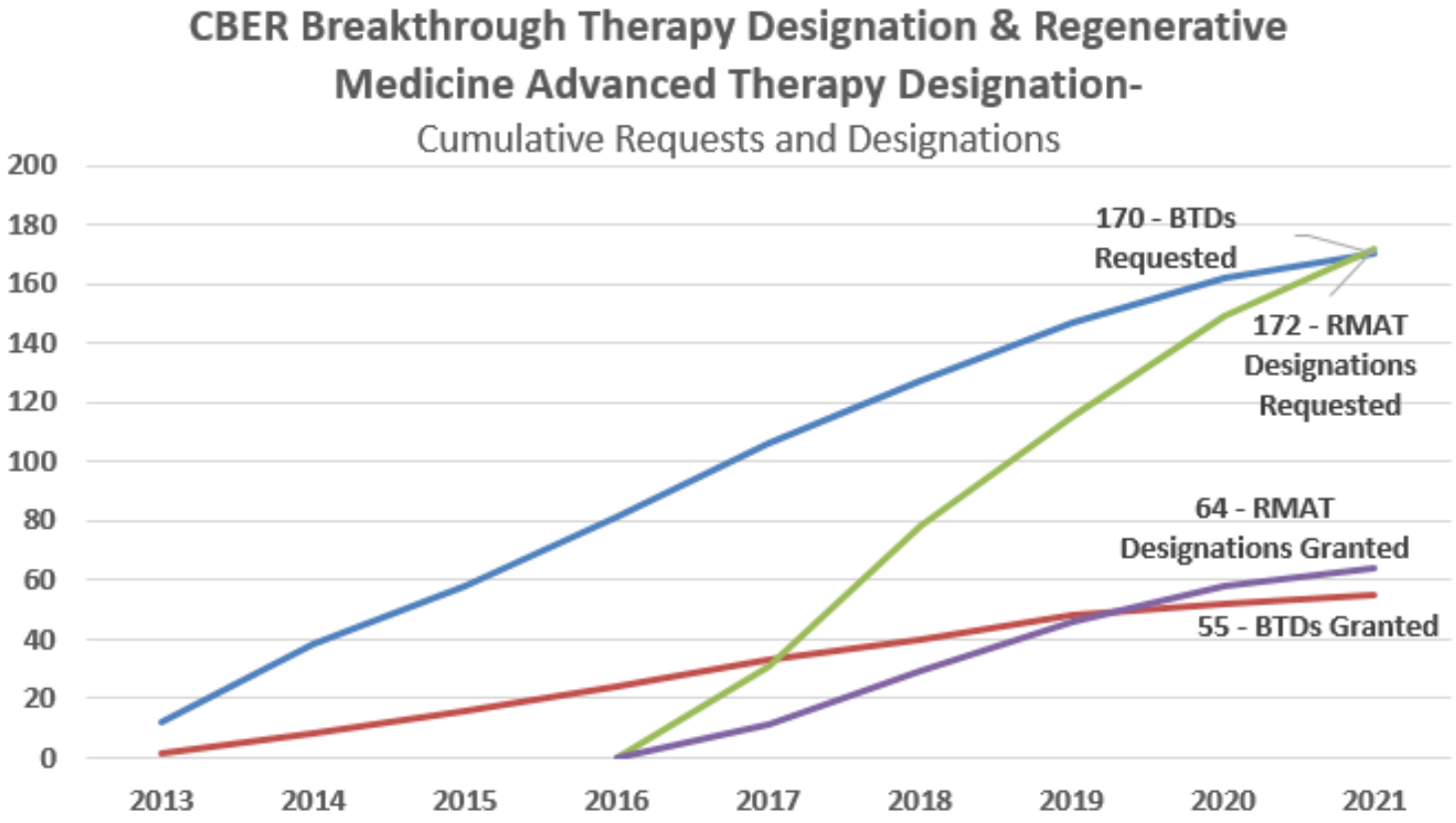
1. Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception
2. Regulatory Considerations for Human Cell, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use
3. Evaluation of Devices Used with Regenerative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

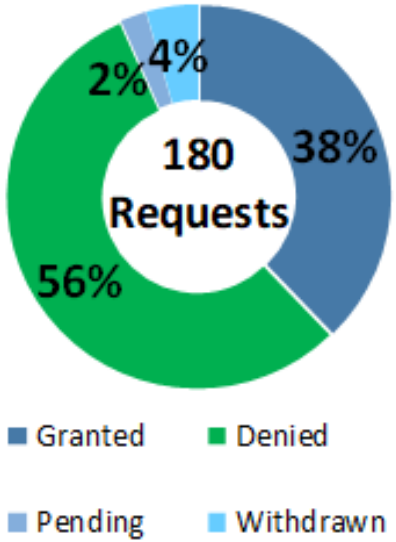
Regenerative Medicine Advanced Therapy Designation (RMAT)

- 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 with 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
200
180
160
140
120
100
80
60
40
20
0
2013
2014
2015
2016
2017
2018
2019
2020
2021
170 - BTDs Requested
172 - RMAT Designations Requested
64 - RMAT Designations Granted
55 - BTDs Granted

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

- 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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