U.S. FOOD & DRUG ADMINISTRATION

FDA Approval Pathways for Innovative Cell & Gene Cancer Therapies

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Office of Tissues and Advanced Therapeutics (OTAT)
Center for Biologics Evaluation and Research (CBER)

Cancer Drug Development Forum (CDDF)
Multi-stakeholder Workshop: Gene and Cell Therapies in Oncology
Session 2: How to Develop a Gene and Cell Cancer Killer: The Clinical Trials

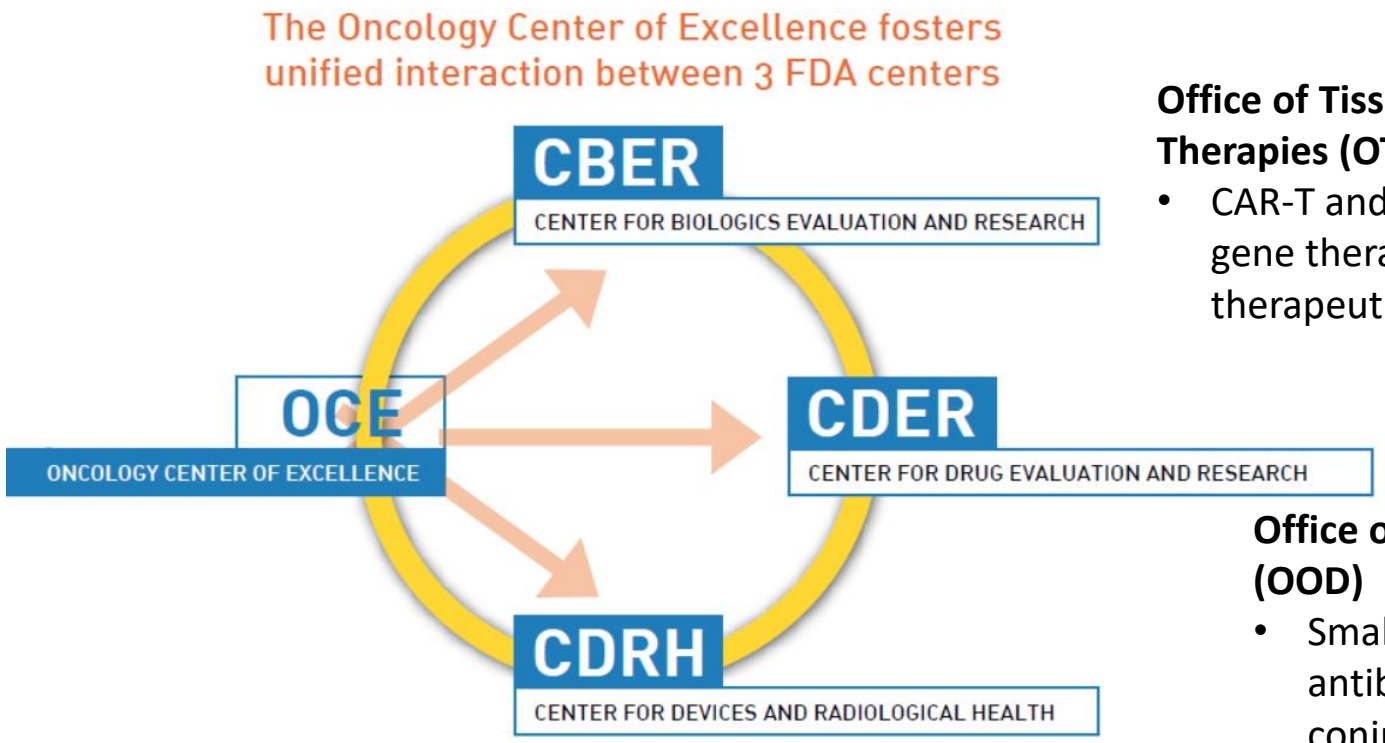
November 12, 2021

I have no financial relationships to disclose.
My comments are an informal communication and represent my own best judgment.
These comments do not bind or obligate FDA.

Outline

- Overview of FDA Regulation of Oncology Therapies
- Considerations for Studies for Cell and Gene Therapies in Cancer
- Overview of FDA Meetings on Cell and Gene Therapies
- Updates on FDA Expedited Programs
- CBER Guidance
- Summary

FDA Regulation of Oncology Products



Office of Tissues and Advanced Therapies (OTAT)

- CAR-T and other cellular therapies, gene therapies, oncolytic viruses, therapeutic vaccines, and microbiome

Office of Oncologic Diseases (OOD)

- Small molecules, monoclonal antibodies, antibody-drug conjugates

Office of Invitro Diagnostics and Radiological Health

- Companion and complementary diagnostics, surgical and delivery devices and therapeutic devices

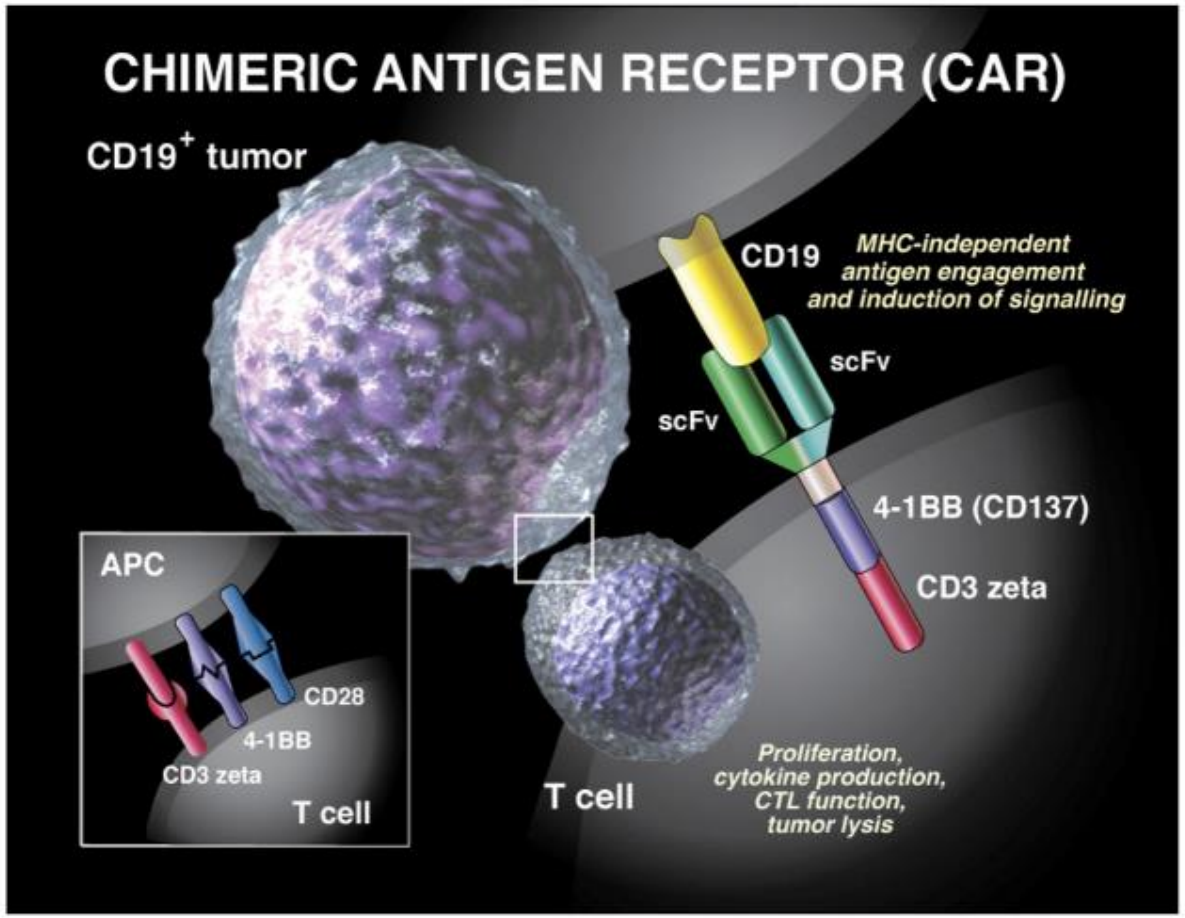
Examples of CBER OTAT-Regulated Products

- **Stem cells/stem cell-derived**
  - Hematopoietic, neural, mesenchymal
  - Placental, umbilical cord blood
  - Fetal, embryonic
  - Induced pluripotent stem cells (iPSCs)
- **Somatic cells**
  - Retinal pigment epithelial cells
  - Pancreatic islet cells
  - Chondrocytes
- **Gene therapies**
  - Genetically-modified cells
  - Replication-competent vectors
  - Non-viral vectors
  - Viral vectors
  - Genetically modified organisms
- **Cancer Vaccines/Cellular Immunotherapies**
  - Peptides
  - Protein-based products
- **Blood products**
  - Coagulation factors
  - Fibrin sealants
  - Fibrinogen
  - Thrombin
  - Plasminogen
  - Immune globulin
  - Snake venom antisera
- **Devices**
- **Tissues**
- **Combination products**
  - Tissue-engineered and regenerative medicine products

CBER Approved Oncology Products

- Provenge (sipuleucel-T) – Dendreon
- TICE® BCG (Intravesical) – Merck, Sharpe and Dohme Corp.
- Imlygic (talimogene laherparepvec) – Amgen
- HPC (hematopoietic progenitor cells), Cord Blood
  - Hemacord – NY Blood Center
  - Clinimmune labs, University of Colorado Cord Blood Bank
  - Ducord – Duke University
  - LifeSouth Community Blood Centers, Inc.
  - Allocord - SSM Cardinal Glennon Children's Medical Center
  - Bloodworks
  - Clevecord – Cleveland Cord Blood Center
  - MD Anderson Cord Blood Center

CAR T Cells: A Novel Way to Treat Cancer



Shannon L. Maude et al. Blood 2015

CTL, cytotoxic T lymphocyte; MHC, major histocompatibility complex

CBER Approved Oncology Gene Therapy Products

- Tisagenlecleucel (Kymriah) *
  - Refractory B-cell ALL, 2017; Refractory DLBCL and high-grade FL, 2018
- Axicabtagene ciloleucel (Yescarta) *
  - Refractory DLBCL, 2017; Refractory FL, 2021
- Brexucabtagene autoleucel (Tecartus) *
  - Refractory Mantle cell lymphoma, 2020; Refractory B-cell ALL, 2021
- Lisocabtagene maraleucel (Breyanzi) *
  - Refractory B-cell NHL, 2021
- Idecabtagene vicleucel (Abecma) ^
  - Refractory multiple myeloma, 2021

*CD19-directed CAR-T cells; ^ BCMA(CD269)-directed CAR T cells

Cellular Immunotherapies for Cancer

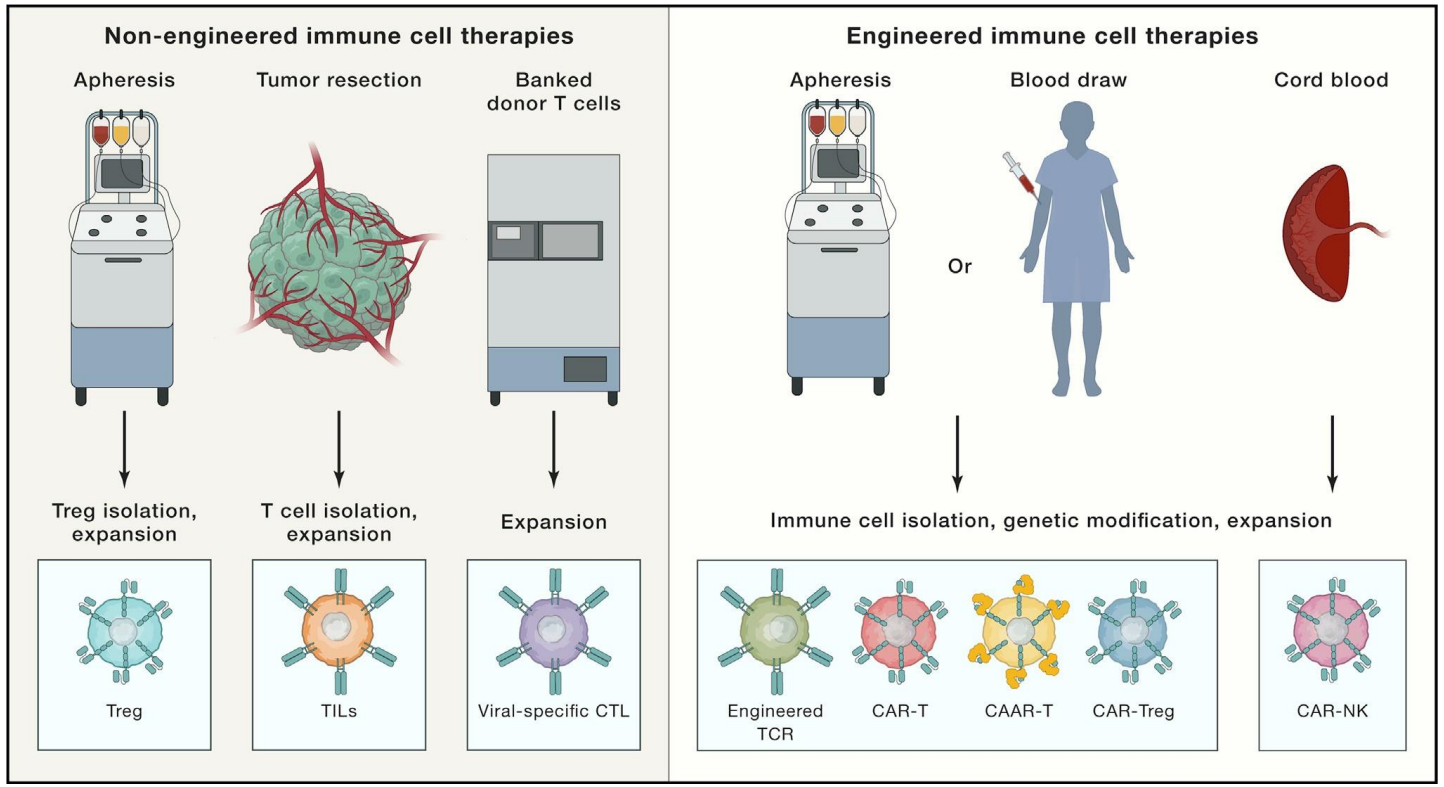
Types of immune cell therapies

Non-engineered cells

- Dendritic cells
- Tumor infiltrating lymphocytes (TILs)

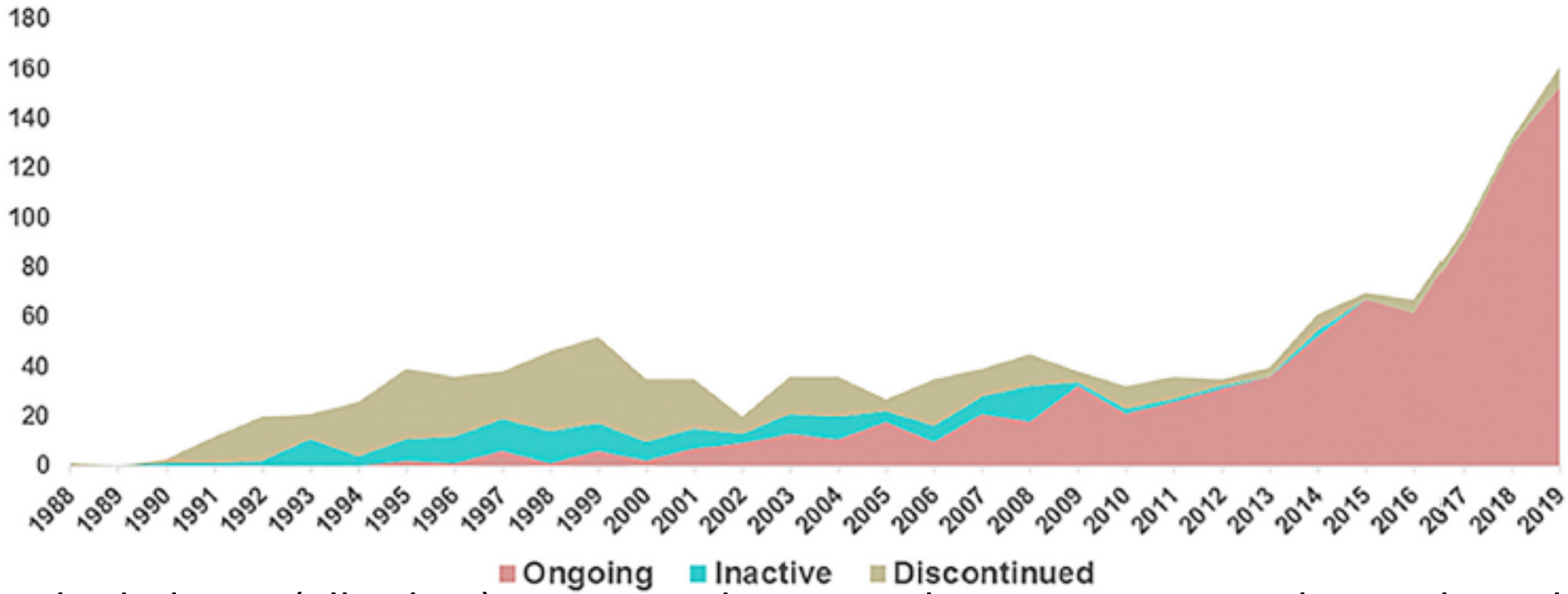
Engineered cells

- Engineered T cell receptor (TCR)
- Chimeric antigen receptor (CAR) T cells
- Chimeric autoantibody receptor (CAR) T cells
- CAR-regulatory T cells (CAR-Treg)
- CAR-expressing Natural Killer cells (CAR-NK)



Weber EW et al. Cell 2020;181:46-47

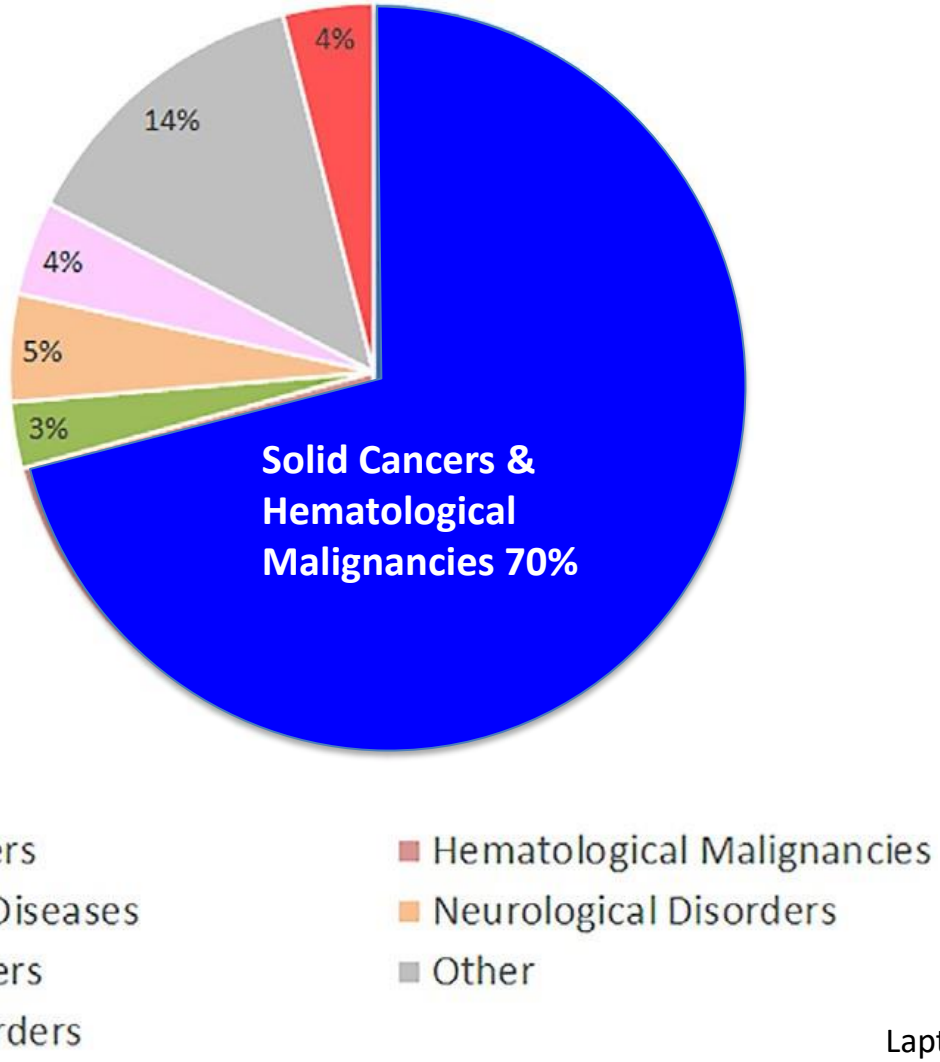
IND Applications for Gene Therapy Products Trends in FDA Submissions



The shaded area (all colors) corresponding to each year represents the total number of IND applications with gene therapy product development programs submitted that year.

Lapteva L et al. Mol Therapy 2020;19:387-397

Majority of IND Applications are in Solid Cancers and Hematological Malignancies



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Considerations for Designing FIH Cellular and Gene Therapy Studies for Cancer

- Cellular Therapies
  - Secondary tumor formation
  - Migration to non-target sites
- Gene Therapies
  - Immune response to vector and/or transgene
  - Insertional mutagenesis
- Invasive procedures may be required
  - Associated procedural risks
- Cells or genes may persist for extended period or produce sustained effect
  - Intensify or prolong adverse reactions
  - Challenges of establishing a standardized approach for defining and capturing toxicities, such as cytokine release syndrome (CRS)

Early Phase/First in Human Cancer Cell Therapy Trials: Objectives

- Safety - primary objective
- Dose exploration - varies according to different products
  - Maximum tolerated dose
  - Feasible dose
  - Optimal dose
- Feasibility assessment of manufacturing
- Activity assessment and preliminary clinical efficacy

Study Design Issues

- Single arm studies should generally focus on unmet needs
  - Relapsed/Refractory to available therapies
  - Potential for Accelerated Approval based on response
  - Contribution of effects a challenge for combinatorial studies
- Specific targets may require a companion diagnostic (CDx)
  - Antigenic targets (CDRH)
  - HLA restrictions (CBER OBRR)
- CDx Assays may require a Study Risk Evaluation (protocol-specific) assessing
  - Are subjects forgoing standard of care?
  - Are anticipated toxicities of proposed regimen acceptable?
- Significant Risk devices require investigational device exemptions (IDE)

Endpoints

- Single-arm trial
  - Safety, dose finding
  - Tumor response rate, duration of responses
  - Time-to-event analyses (overall survival, progression-free survival) difficult to interpret in this setting
    - Historical controls may be unreliable
- Randomized controlled trial – later stage development
  - Time-to-event analyses (overall survival, progression-free survival)
  - Appropriate control required – discuss with FDA
  - May not be feasible for these products in a refractory population
- Potential confounding impact of concurrent treatments
  - Lymphodepletion
  - Addition of checkpoint inhibitors

Dosing / Dose Escalation

- Starting dose for first in human (FIH) study
  - May be based on toxicology data
  - Prior human experience with similar construct
  - Dose should be based on transduced cells per unit weight (or BSA)
- Dose escalation scheme
  - Anticipated cell expansion in vivo
  - Anticipated toxicities
  - Half-log increments for biological drugs (log escalation is generally considered aggressive)
  - Typically employ a 3+3 design
  - Continual reassessment escalation designs may be considered such as Bayesian adaptive designs
  - Intra-patient dose escalation not recommended
  - Staggering of treatment between subjects / dose cohorts
- Provide justification for the plan and the starting dose based on clinical or preclinical data

Dose Limiting Toxicity (DLT)

- Protect subjects and identify optimum biological/recommended phase 2 dose
- Confounded by toxicities of conditioning lymphodepletion regimens
- Context important
  - Some CRS may be expected
  - Severe CRS requiring ICU admission is generally considered a DLT
  - Monitor for off-target toxicities (cardiac, neurological, etc.)
- Ensure *clear* definitions
  - Grading of CRS is evolving – CTCAE may not be adequate
    - ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells [1]

Examples of cancer cell therapy study DLTs:

- Any treatment-emergent Grade 4 or 5 CRS
- Any treatment-emergent Grade 3 CRS that does not resolve to ≤ Grade 2 within 7 days
- Any treatment-emergent autoimmune toxicity ≥ Grade 3
- Grade 3 and greater allergic reactions related to the cell infusion
- Grade 3 and greater major organ toxicities, not pre-existing or not due to the underlying malignancy and occurring within 30 days of cell infusion

[1]Lee DW et al. Biol Blood Marrow Transplant 2019;25:625-638

Management of Toxicities (CRS)

- For suspected CRS, include an algorithm for assessment and management
- Rule out other causes of fever (sepsis, drug reactions)
- Management of toxicity
  - Tocilizumab (blocks IL-6 receptor) – now approved to treat CRS
  - Steroids – Potential interference with T cell activity/expansion
- Provide specific indication(s) for supportive care, fluids, ICU, vasopressors
- Specify cytokine sampling requirements
- If subjects are discharged to outpatient care, they should remain in reasonable proximity to the treating institution in case of delayed toxicities

[1]Reagan PM & Neelapu SS. J Clin Oncol 2021;39(5):456-466
[2]Lee DW et al. Biol Blood Marrow Transplant 2019;25:625-638

Study Stopping Rules

- Temporary pause in enrollment and treatment of additional subjects to limit the number of study subjects being exposed to excess risk
  - Death
  - Increased incidence of unexpected toxicity
- Specify conditions (e.g., type and number of adverse events) for temporary suspension of enrollment and dosing until a safety assessment can be completed
- Based on the outcome of the safety assessment, protocol revision may be warranted
  - Eligibility criteria, dose, monitoring plan
- Not intended to terminate a study

Safety Monitoring

- Duration of monitoring for adverse events
  - Sufficient to cover expected duration of effect
  - Depends on information from preclinical studies, and experience with related products

- Long term follow-up may be required for certain cellular and gene therapies
  - e.g., 15 years of follow-up for integrating viral vector-based products
  - Clinical development can continue while long term follow-up ongoing

FDA Guidance: Long Term Follow-up After Administration of Human Gene Therapy Products (2020)
https://www.fda.gov/media/113768/download

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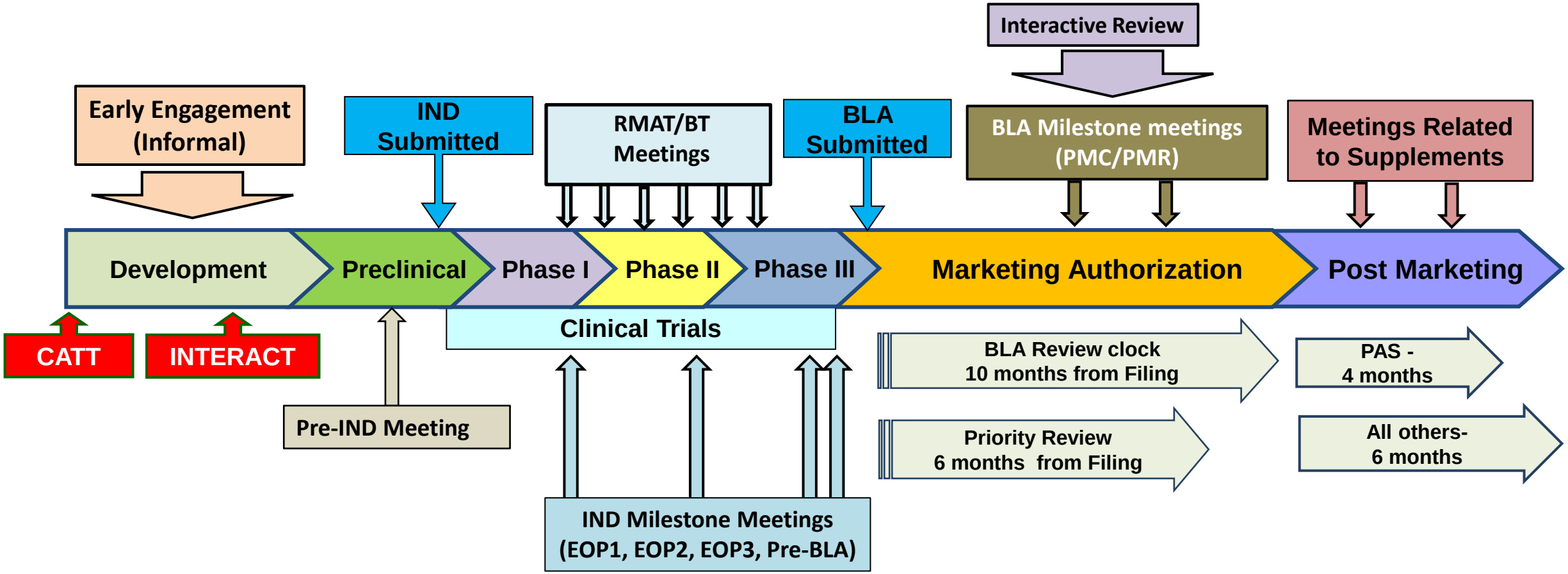
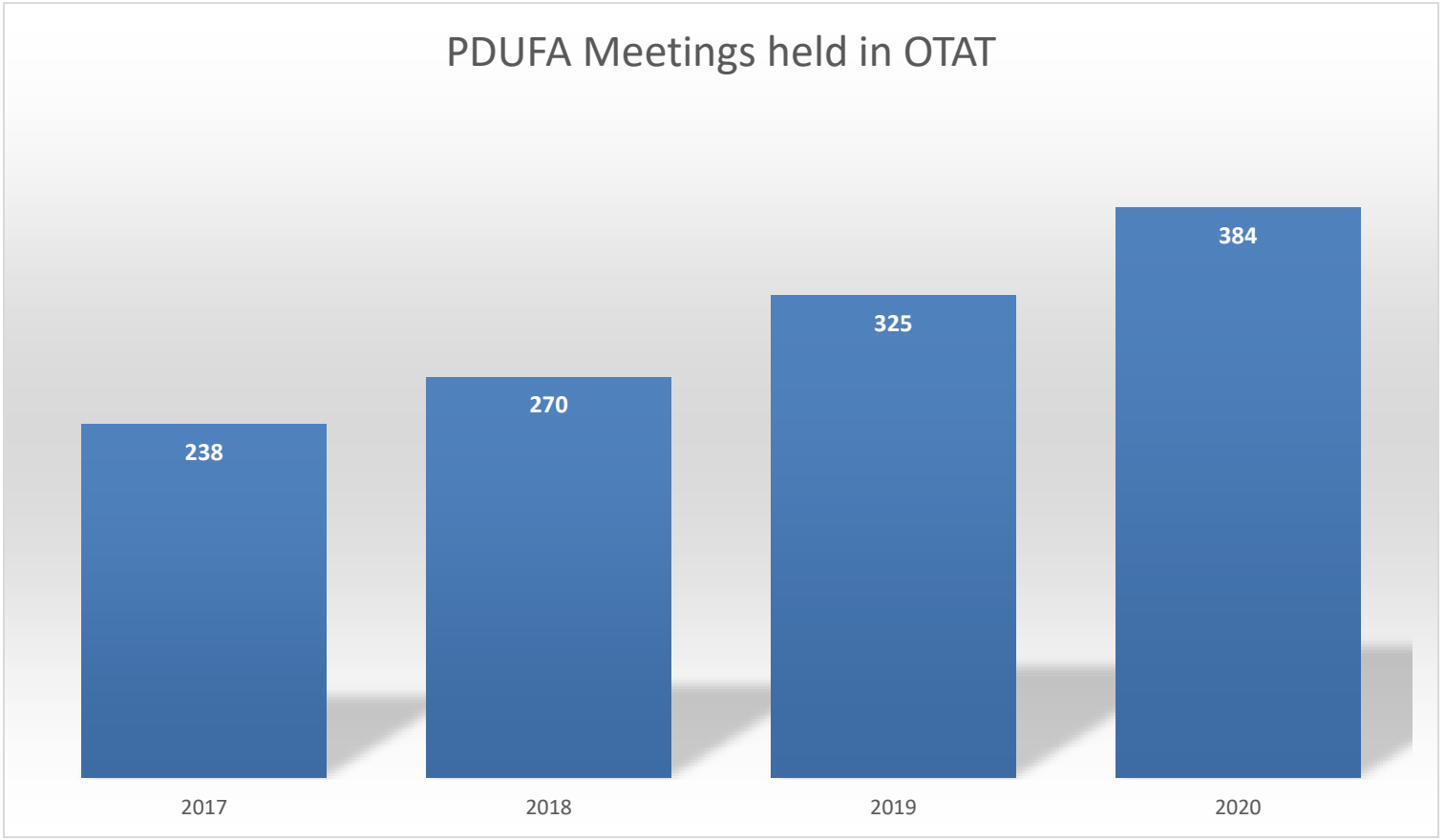
Interaction with CBER/OTAT



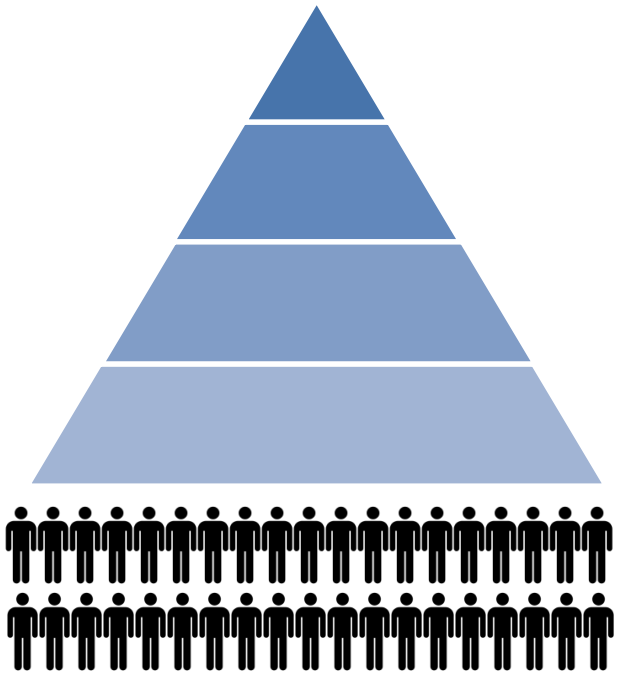
OTAT Meetings with Sponsors



Cell/Gene Therapy Product Development: Different Manufacturing Paradigm

Conventional Drug/Biologic

1 product lot



Many patients

Unique issues for CGT products

Advanced manufacturing

Advanced QC technologies

Scale up/scale out

Comparability

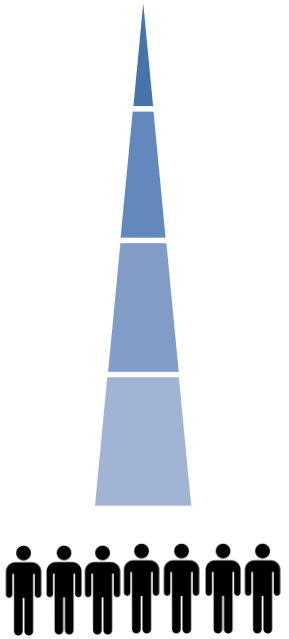
Raw materials

Distribution

Impact of manufacturing failure

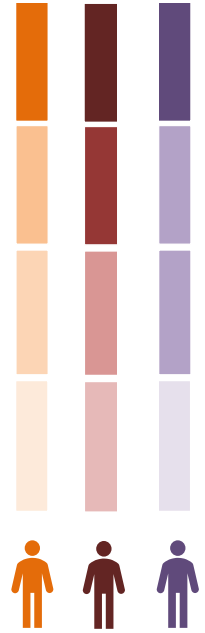
Cell & Gene Therapy Products

1 product lot



Few patients

1 product lot



Single patient

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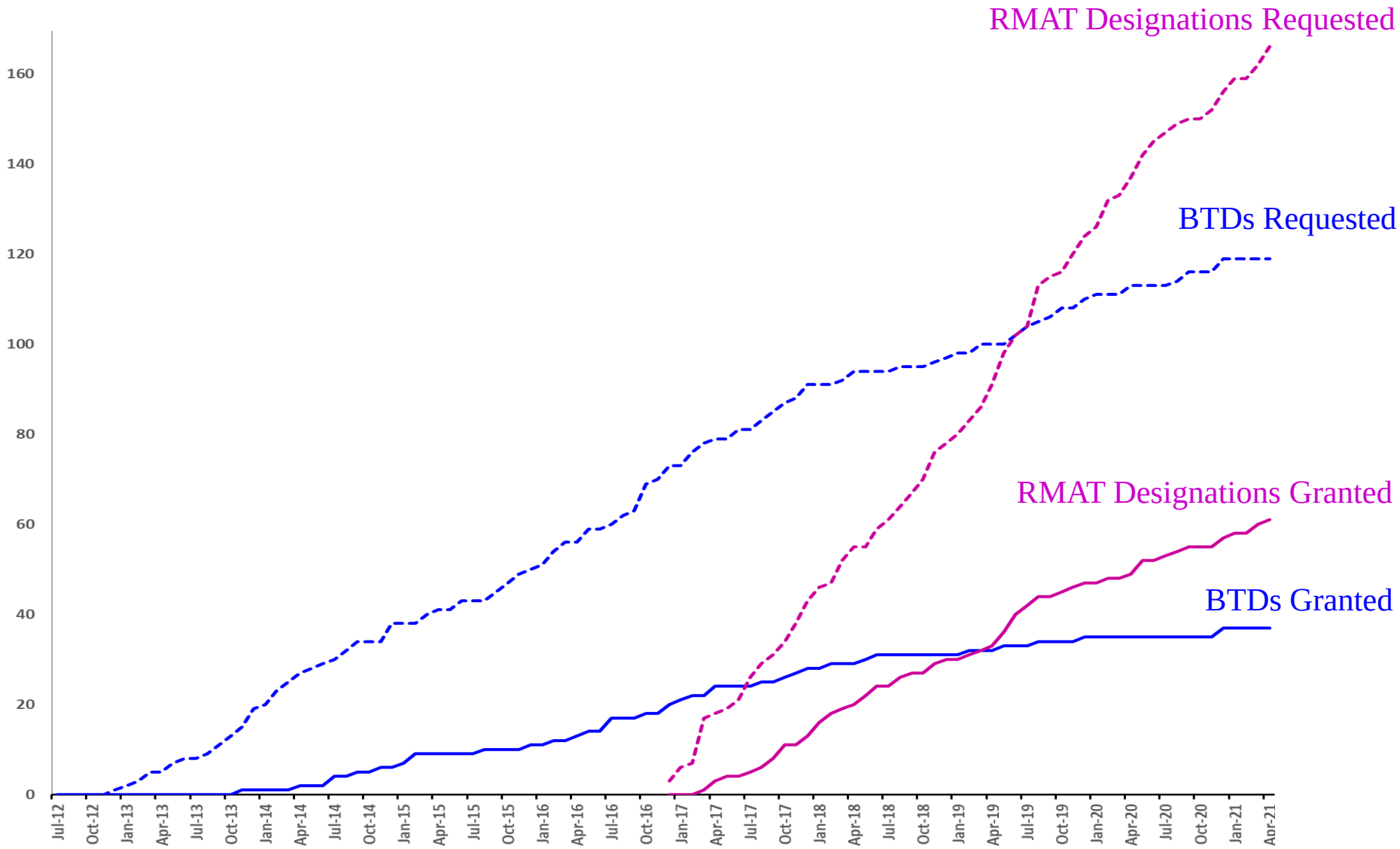
Overview of FDA Expedited Programs

- **Accelerated Approval Regulations: 1992**
  Section 506(c) of Food, Drug & Cosmetic Act (FD&C Act)
- **Priority Review Designation: 1992**
  Prescription Drug User Fee Act
- **Fast Track Designation (FTD): 1997**
  Section 506(b) of FD&C Act, as added by section 112 of the Food and Drug Administration Modernization Act
- **Breakthrough Therapy Designation (BTD): 2012**
  Section 506(a) of the FD&C Act, as added by section 902 of the Food and Drug Administration Safety and Innovation Act
- **Regenerative Medicine Advanced Therapy (RMAT): 2016**
  Section 506(g) of the FD&C Act, as added by section 3033 of the 21st Century Cures A

Regenerative Medicine Advanced Therapy (RMAT)

- **21st Century Cures Act: Title III, Section 3033**
  - Signed into law in 2016
  - Creates pathway for designation as a regenerative medicine advanced therapy
- **Definition of Regenerative Medicine Therapy:**
  - Cell therapy, therapeutic tissue engineering products, human cell and tissue products, or any combination product using such therapies or products
  - Combination product can be eligible for RMAT designation when the biological component provides the greatest contribution to the overall intended effects of the combination product
  - FDA interpretation of Section 3033 of the 21st Century Cures Act adds: “Gene therapies, including genetically modified cells, that lead to a sustained effect on cells or tissues”

Cumulative Overview of BTD and RMAT Designation Requests (excludes withdrawn and pending requests)



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Gene Therapy Guidances

FINAL GUIDANCES

- Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations
- Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)
- Testing of Retroviral Vector-Based Gene Therapy Products for Replication Competent Retrovirus (RCR) during Product Manufacture and Patient Follow-up
- Long Term Follow-Up After Administration of Human Gene Therapy Products
- Human Gene Therapy for Hemophilia
- Human Gene Therapy for Retinal Disorders
- Human Gene Therapy for Rare Diseases

DRAFT GUIDANCE

Studying Multiple Versions of a Cellular or Gene Therapy Product in an Early-Phase Clinical Trial; Draft Guidance for Industry

https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances

COVID-19 and CBER-Regulated Biologics

- **Letter to Sponsors, Applicants and Regulated Entities on COVID-19 (https://www.fda.gov/media/136501/download)**
  - In person meetings with industry converted to teleconferences
  - Processing of incoming documents and CBER responses
  - Extension of response due dates for device marketing application currently on hold

- **COVID-19 related guidance documents relevant to biologics (https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders)**
  - FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency
  - Resuming Normal Drug and Biologics Manufacturing Operations During the COVID-19 Public Health Emergency
  - Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency Questions and Answers
  - Good Manufacturing Practice Considerations for Responding to COVID-19 Infection in Employees in Drug and Biological Products Manufacturing

(https://www.fda.gov/vaccines-blood-biologics/industry-biologics/coronavirus-covid-19-cber-regulated-biologics)

Summary

- Continue to facilitate oncology product development
- Recognize that modifications may be required in product development
- Continue to process Expanded Access requests for investigational product
- Continue to review applications for expedited programs such as Fast Track, Breakthrough Therapy designation, Regenerative Medicine Advanced Therapy designation
- Continue outreach activities with stakeholders

Useful FDA Information

- References for the Regulatory Process for the Office of Tissues and Advanced Therapies (OTAT) http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/ucm094338.htm

- OTAT Learn Webinar Series: http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

FDA WO Campus: Atrium of Building 71/75

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FDA Headquarters

- **OTAT Learn Webinar Series:**

  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

- **CBER website:** www.fda.gov/BiologicsBloodVaccines/default.htm
- **Phone:** 1-800-835-4709 or 240-402-8010
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