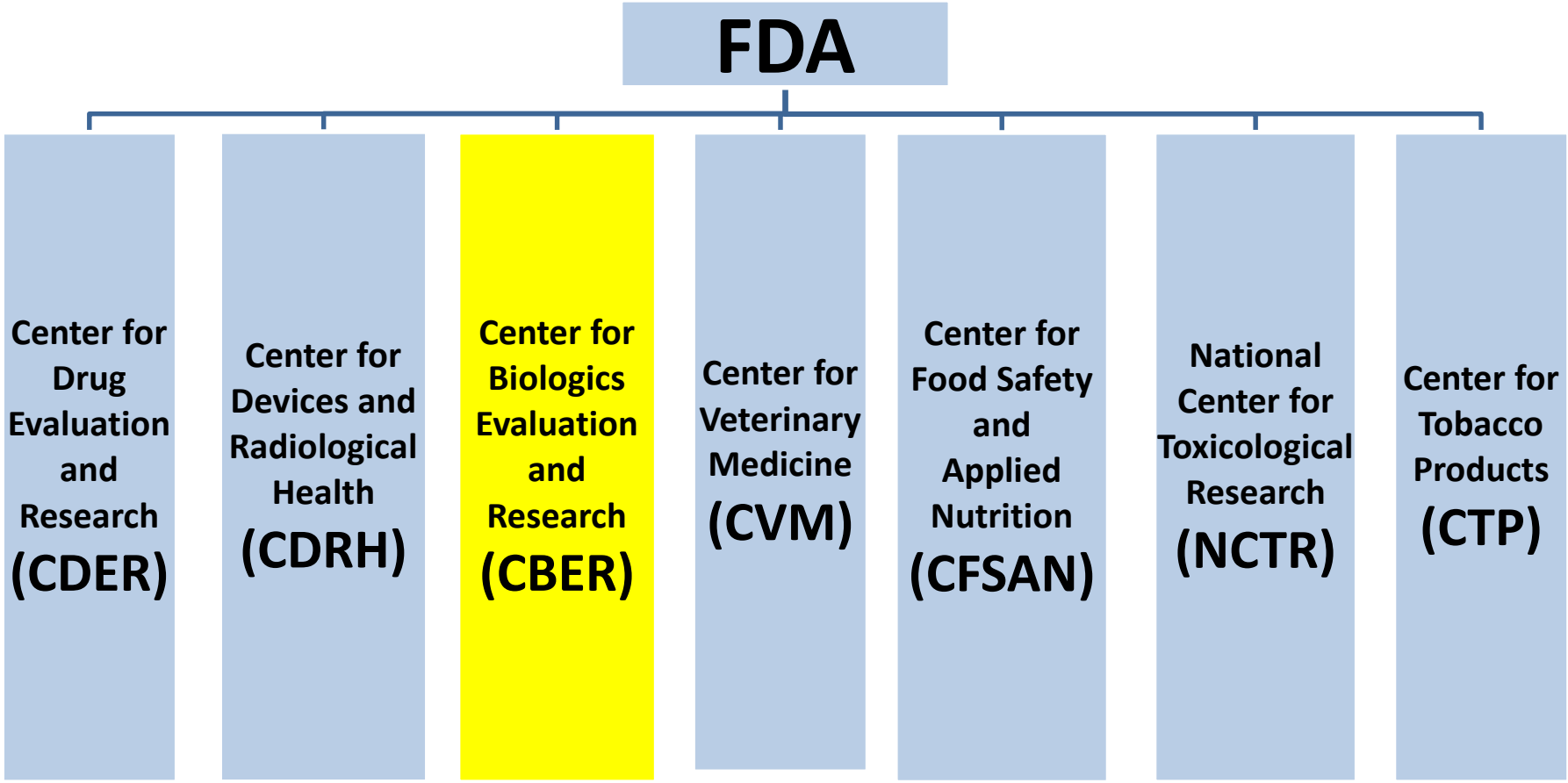
FDA Regulatory Updates: Cell and Gene Therapies

Society for Immunotherapy of Cancer (SITC) 33rd Annual Meeting

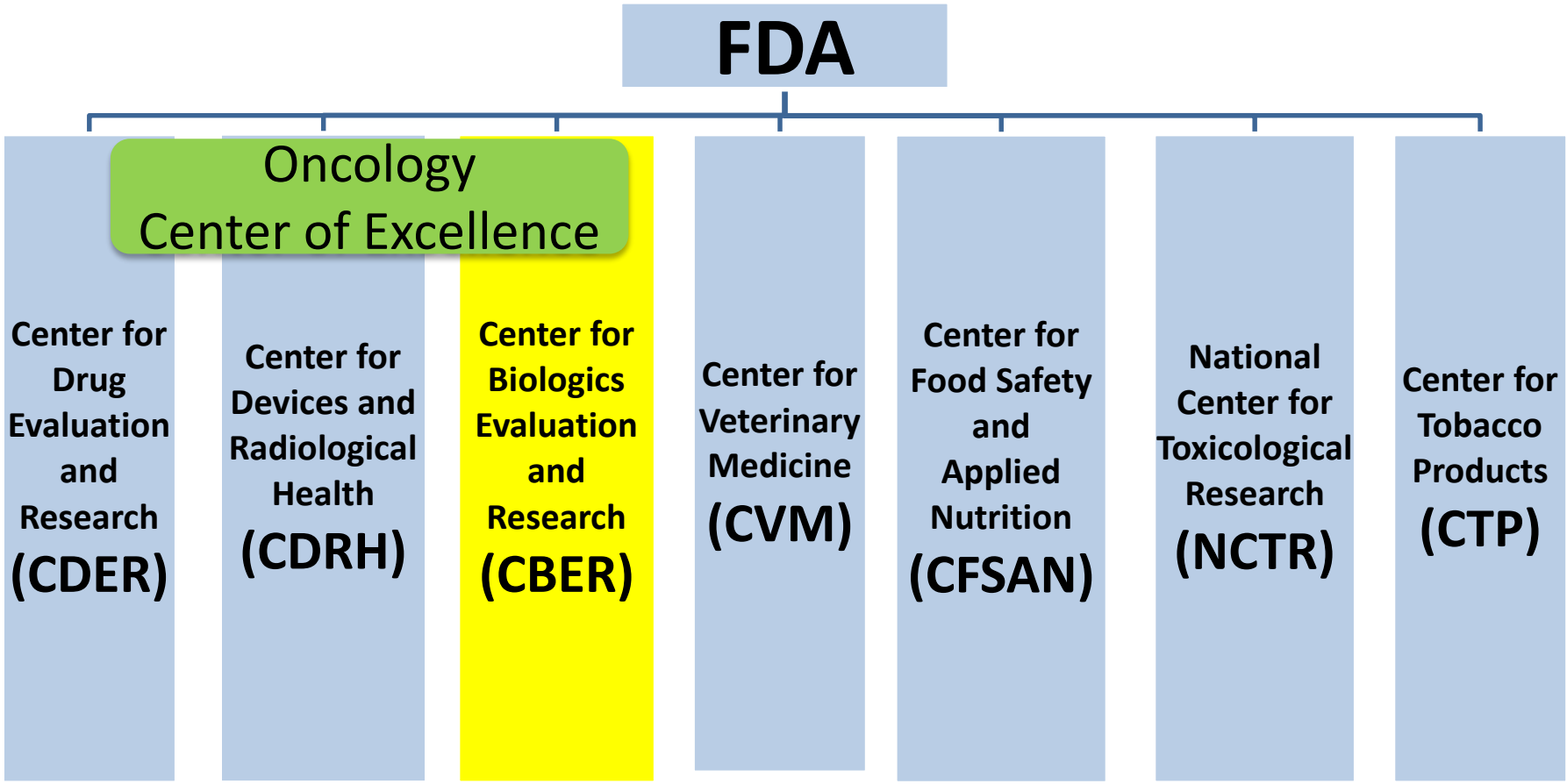
Raj K. Puri, M.D., Ph.D.
Director, Division of Cellular and Gene Therapies
Office of Tissues and Advanced Therapeutics (OTAT)
Center for Biologics Evaluation and Research (CBER)

Date: November 9, 2018
Time: 8:20 AM to 8:35 AM
Location: Walter E. Washington Convention Center, Washington DC

FDA Organization

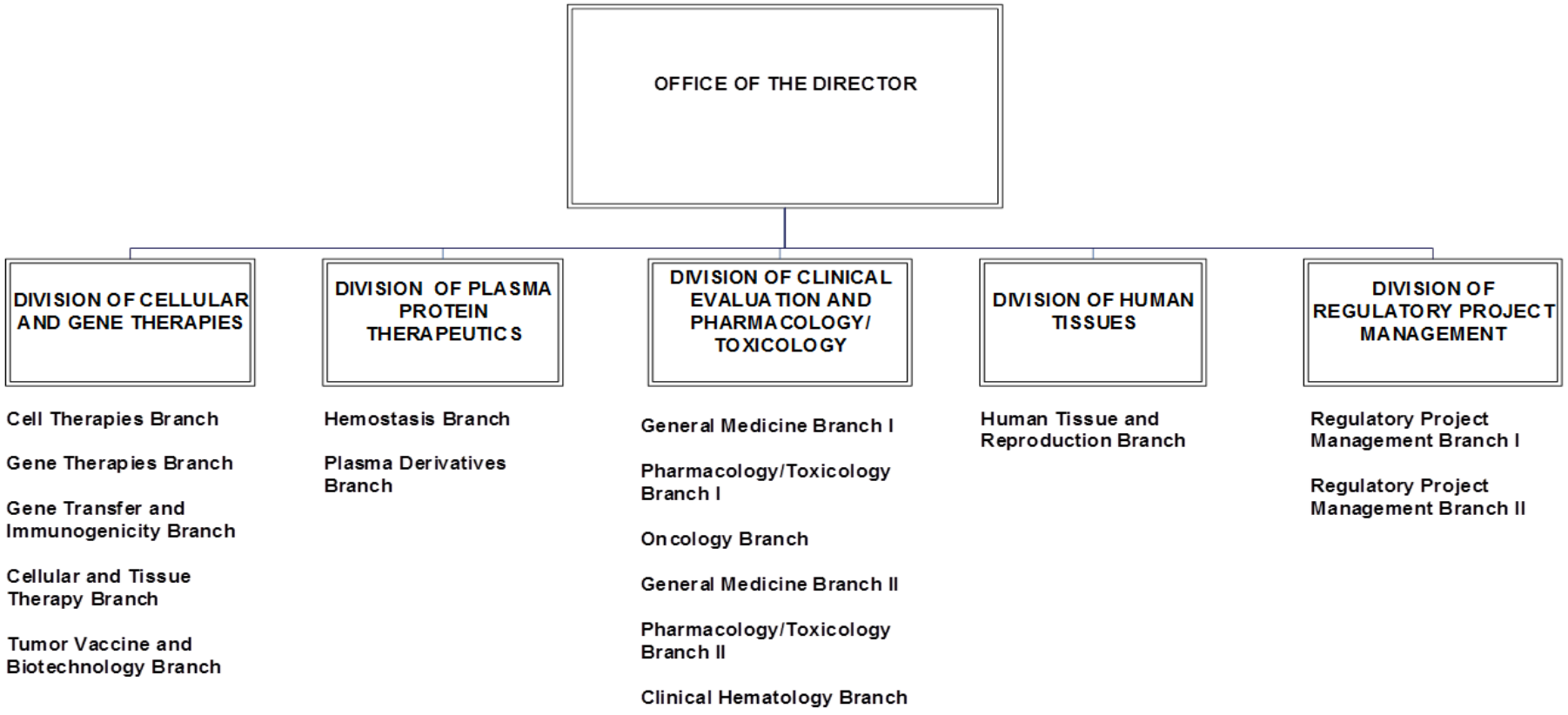


FDA Organization



Office of Tissues and Advanced Therapies

Previously Office of Cellular, Tissue and Gene Therapies (OCTGT)



Examples of 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

FDA Regulation of Oncology Products

- Office of Hematology and Oncology Drug Products (OHOP), CDER
  - Drugs (small molecules)
  - Biologics, including Monoclonal Antibodies, Therapeutic Proteins, Cytokines
- Office of Tissues and Advanced Therapeutics, (OTAT) CBER
  - Cell therapies
  - Gene Therapies
  - Oncolytic viruses
  - Therapeutic vaccines and cellular immunotherapies
  - Microbiome based therapies
- Center for Devices and Radiological Health (CDRH):
  - Devices
    - Companion Diagnostics
    - Surgical and Delivery devices
    - Therapeutic devices

CBER Approved Oncology Products

- Provenge (sipuleucel-T) – Dendreon
- BCG Live (Intravesical) - TheraCys, Sanofi Pasteur Limited
- 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

Oncology Product Approvals in 2017

- Kymriah (tisagenlecleucel)
  - CD19-directed genetically modified autologous T cell immunotherapy
  - For treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse

- Yescarta (axicabtagene ciloleucel)
  - CD19-directed genetically modified autologous T cell immunotherapy
  - Indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Expedited Development of Promising Treatments for Serious Conditions

- **Expedited Programs**
  - Fast Track (FT) (1997)
  - Breakthrough Therapy (BT) (2012)
  - Regenerative Medicine Advanced Therapy (RMAT) (2016)
  - Priority Review (1992)
  - Accelerated Approval (1992)

FDA Guidance: Expedited Programs for Serious Conditions – Drugs and Biologics (2014)

Breakthrough Therapy Designation Request (BTDR)

- Intent is to expedite the development and review of a drug that is:
  - Intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition *AND*
  - Preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints

BT Designations by Disciplines*

Indications	Requests	Granted
Oncology (Solid Tumor)	35	6
Hematology (Malignant and Benign)	26	16
Non-Onco/Hema	33	8

*Excluding withdrawn and pending requests
As of November 6, 2018

BT Designations by Product Types*

Products	Requested	Granted
Gene Therapy	48	23
Cell Therapy	26	3
Others	20	4

*Excluding withdrawn and pending requests

21st Century Cures Act Regenerative Medicine Therapies (RMT)

December 13, 2016

- RMT defined in Section 3033:
  - Cell therapies
  - Therapeutic tissue engineering products
  - Human cell and tissue products
  - Combination products associated with the above
- FDA interpretation by guidance*
  - Includes gene therapies, including genetically modified cells, that lead to a durable modification of cells or tissues

* Expedited Programs for Regenerative Medicine Therapies for Serious Conditions: Draft Guidance for Industry

Section 3033: Regenerative Medicine Advanced Therapy (RMAT) Designation

- Creates program for designation of regenerative medicine advanced therapies
- A drug is eligible for designation if:
  - It is a regenerative medicine therapy
  - The drug is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; and
  - Preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition

Process for RMAT Designation

- Sponsor can make a request with a new IND submission or as an amendment to an existing IND

- Website with information about administrative process: http://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm537670.htm

Process for RMAT Designation

- Request for designation should describe:
  - How the drug meets the definition of regenerative medicine therapy
  - How the drug meets the criterion that it is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition, and
  - The preliminary clinical evidence that indicates that the drug has the potential to address unmet medical needs for such disease or condition

Process for RMAT Designation

- FDA has 60 calendar days to determine if designation criteria are met
  - FDA will provide written response
  - If not granted, FDA will provide a written description of the rationale

Benefits of RMAT Designation

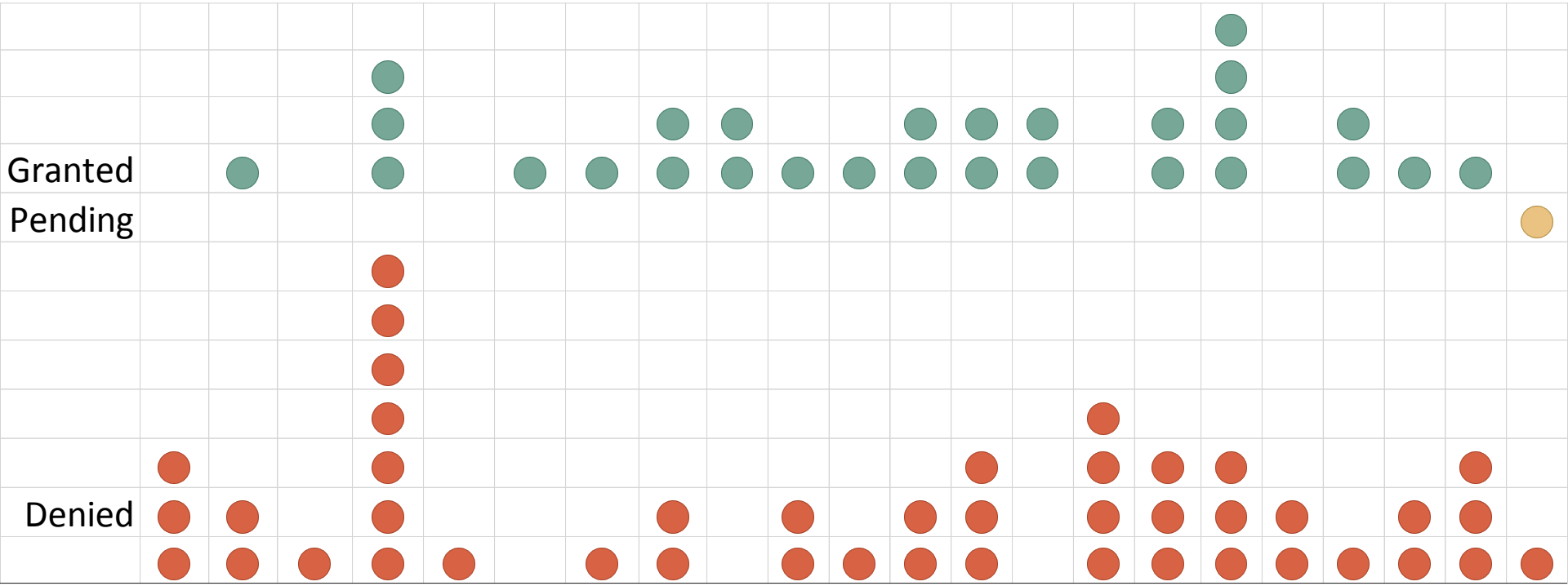
- Interactions with FDA to expedite development and review of regenerative medicine advanced therapies
  - Benefits available to breakthrough therapies
  - Including early discussions of any potential surrogate or intermediate endpoints to support accelerated approval

Benefits of RMAT Designation (cont'd.)

- May be eligible for priority review
- May be eligible for accelerated approval, as agreed upon during product development, based on:
  - Surrogate or intermediate clinical endpoints reasonably likely to predict long-term clinical benefit, or
  - Reliance upon data obtained from a meaningful number of sites, including through expansion to additional sites, as appropriate

RMAT Designation Requests Status

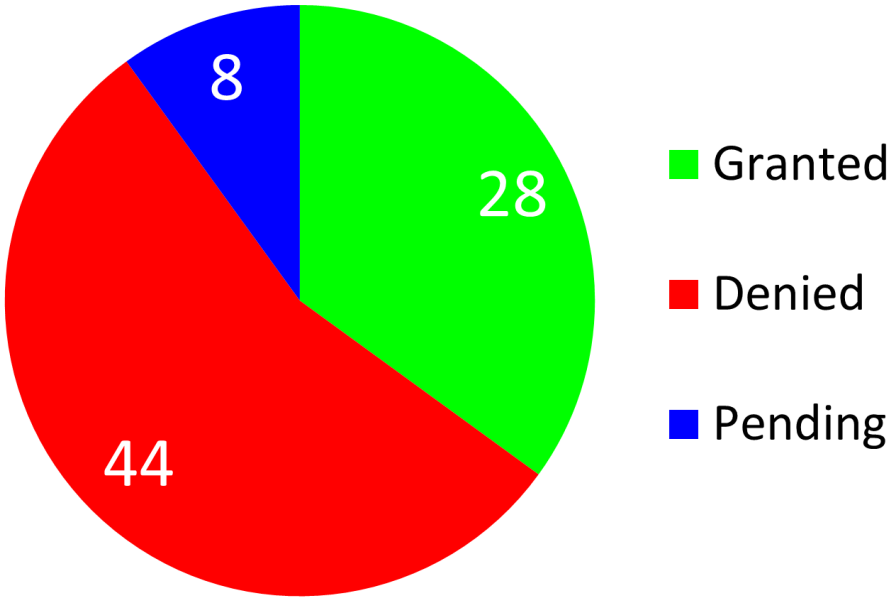
- as of November 06, 2018



12/13/2016 – 11/06/2018

RMAT Designation Requests

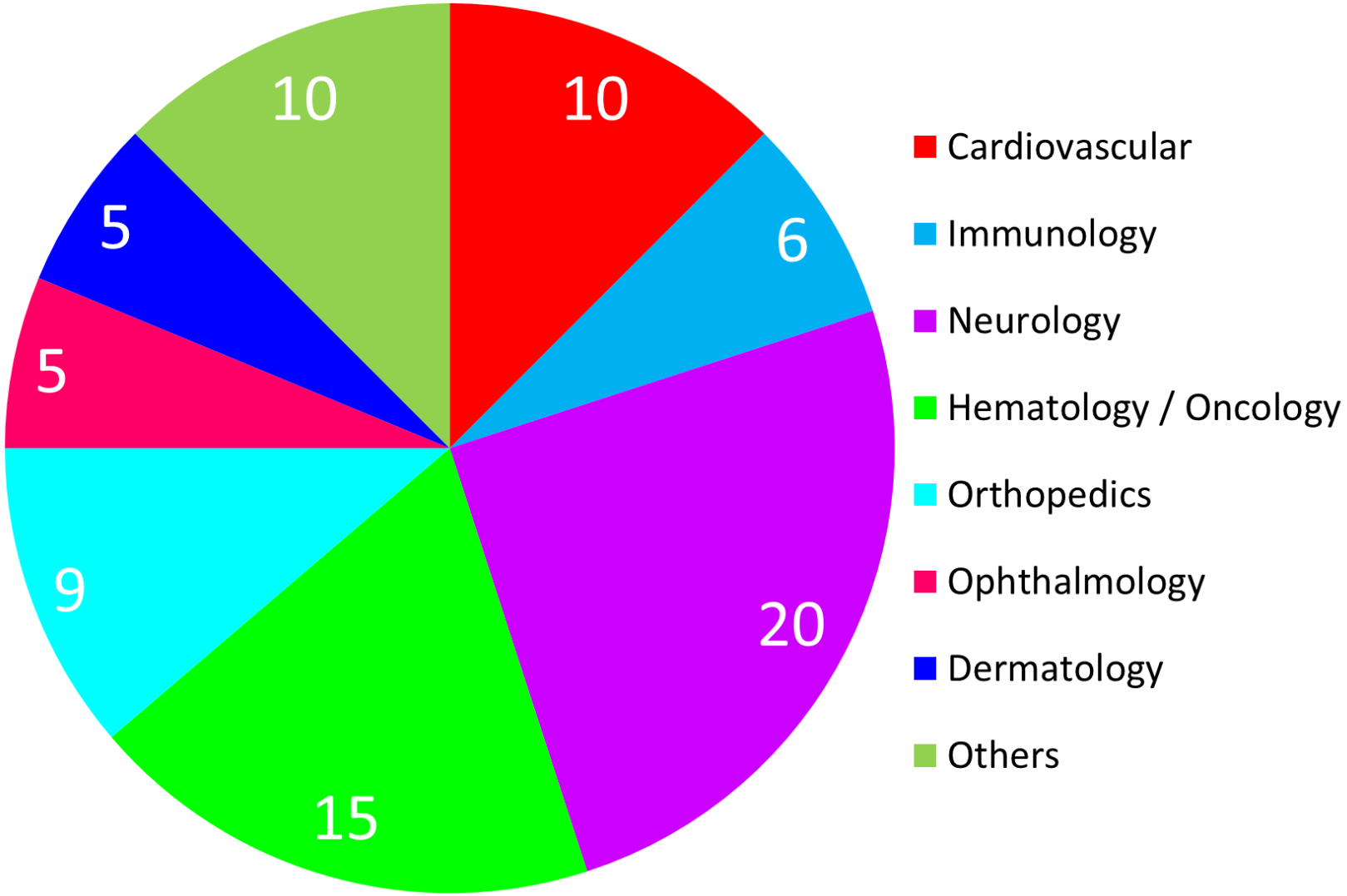
Status as of November 06, 2018



Analysis of Denied RMAT Requests

- Administrative Reasons
  - Inactive IND
  - No preliminary clinical evidence submitted
- CMC Reasons
  - Different product
- Insufficient Preliminary Clinical Evidence
  - Study design issues
  - Inconsistent results with regard to product activity

RMAT Designation Requests
- Distribution by Specialty



INTERACT: Early Communication with OTAT

- **INitial Targeted Engagement for Regulatory Advice on CBER producTs** *(previously known as **pre-pre-IND** interactions)*
  https://www.fda.gov/BiologicsBloodVaccines/ResourcesforYou/Industry/ucm611501.htm
- **Goal:** *To obtain early feedback on a product development program for a novel/innovative investigational agent*
- **Purpose**
  - A mechanism for early communication with OTAT
  - Non-binding, informal scientific discussions between CBER/OTAT review disciplines
  - Initial targeted discussion of specific issues
  - Meet specific requirements for requests to be granted

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

Useful FDA Information

- References for the Regulatory Process for the Office of Cellular, Tissue, and Gene Therapies (OCTGT) http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/ucm094338.htm

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

Contact Information

- **Raj K. Puri, M.D., PhD**
  Email: raj.puri@fda.hhs.gov
- **Regulatory Questions:**

  OTAT Main Line – 240 402 8190

  Email: OTATRPMS@fda.hhs.gov and

  Lori.Tull@fda.hhs.gov

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
- **Consumer Affairs Branch**: ocod@fda.hhs.gov
- **Manufacturers Assistance and Technical Training Branch**: industry.biologics@fda.hhs.gov
- **Follow us on Twitter:** https://www.twitter.com/fdacber

Acknowledgements

- Wilson Bryan, M.D.
- Rachael Anatol, Ph.D.
- Steven Oh, Ph.D.
- Xiaofei Wang, Ph.D.
- Lei Xu, M.D.


FDA
U.S. FOOD & DRUG
ADMINISTRATION