

Regulatory Pathways for Rare Diseases

Celia M. Witten, Ph.D., M.D.

Deputy Director, FDA

Center for Biologics Evaluation and Research

**Emerging Technologies for Rare Diseases: Clinical and
Regulatory Case Studies and Approval Pathways**

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Outline

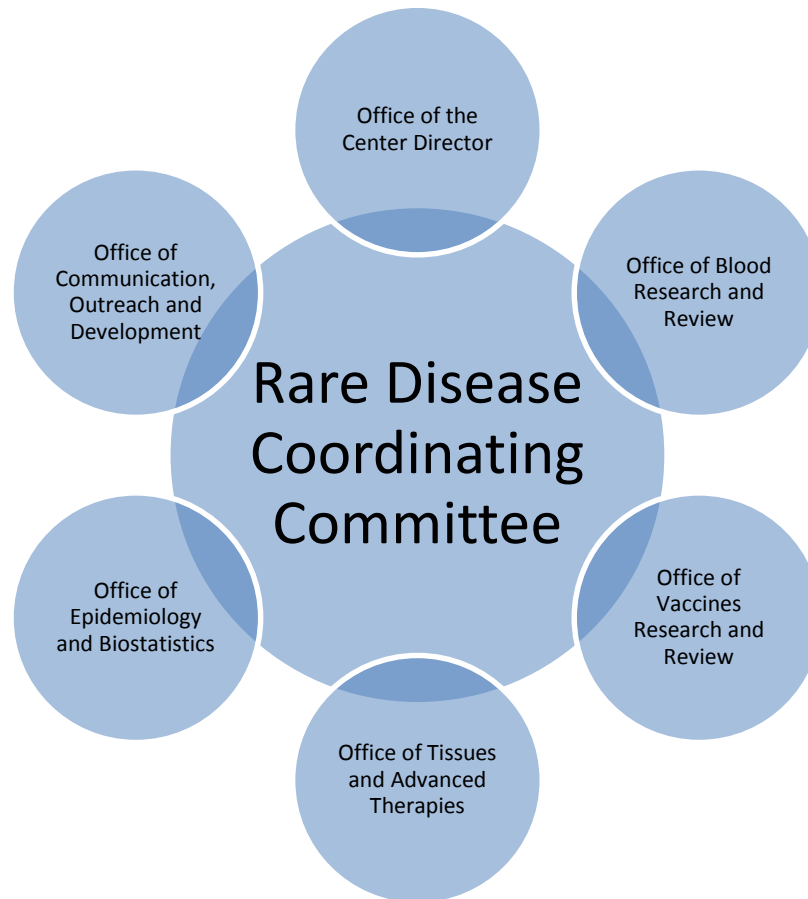
- CBER Overview
- Advancing Product Development
 - Breakthrough
 - RMAT
- Gene Therapy Products

What Products Does CBER Regulate?



- Allergenicics
- Blood Products
- Devices (subset including some IVDs)
- Gene Therapy Products
- Human Tissues and Cellular Products
- Vaccines (preventative and therapeutic)
- Xenotransplantation products

Rare Disease Activities in CBER



CDER-licensed Products

Used in Rare Diseases and Conditions



- Human immune globulins
- Hyperimmune globulins (human or animal)
- Blood Factors (human or recombinant)
- C-1 esterase inhibitor (human or recombinant)
- Preventive vaccines for certain indications
- Cord blood
- Other miscellaneous products





Advancing Product Development and Approval

- Priority Review Designation 1992
- Accelerated Approval 1992
- Fast Track Designation 1997
- **Breakthrough Designation 2012 (FDASIA)**
- Regenerative Medicine Advanced Therapy Designation (RMAT) 2016 (21st Century Cures Act)

Breakthrough Therapy Designation Criteria

- A drug that is intended to treat a serious condition, AND
- Preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies.

See 506(a) of FD&C Act, as added by section 902 of FDASIA

Breakthrough Therapy Designation

Features

- Intensive FDA guidance on efficient drug development
- Organizational commitment
 - e.g., intensive involvement of senior managers & experienced review staff
- Rolling review
- Other actions to expedite review
 - e.g., more frequent meetings with FDA

Breakthrough Therapy Designations in CBER (7/9/2012-6/30/2017)

- 30 of the 102 requests received were granted
- 19 of the 30 designations granted are for rare disease indications
- 16 of the 30 designations were for gene therapy products

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Regenerative Medicine Advanced Therapy (RMAT) Provisions

- Section 3033
 - Accelerated Approval for Regenerative Advanced Therapies
- Section 3034
 - Guidance Regarding Devices Used in the Recovery, Isolation, or Delivery of Regenerative Advanced Therapies
- Section 3035
 - Report on Regenerative Advanced Therapies
- Section 3036
 - Standards for Regenerative Medicine and Regenerative Advanced Therapies



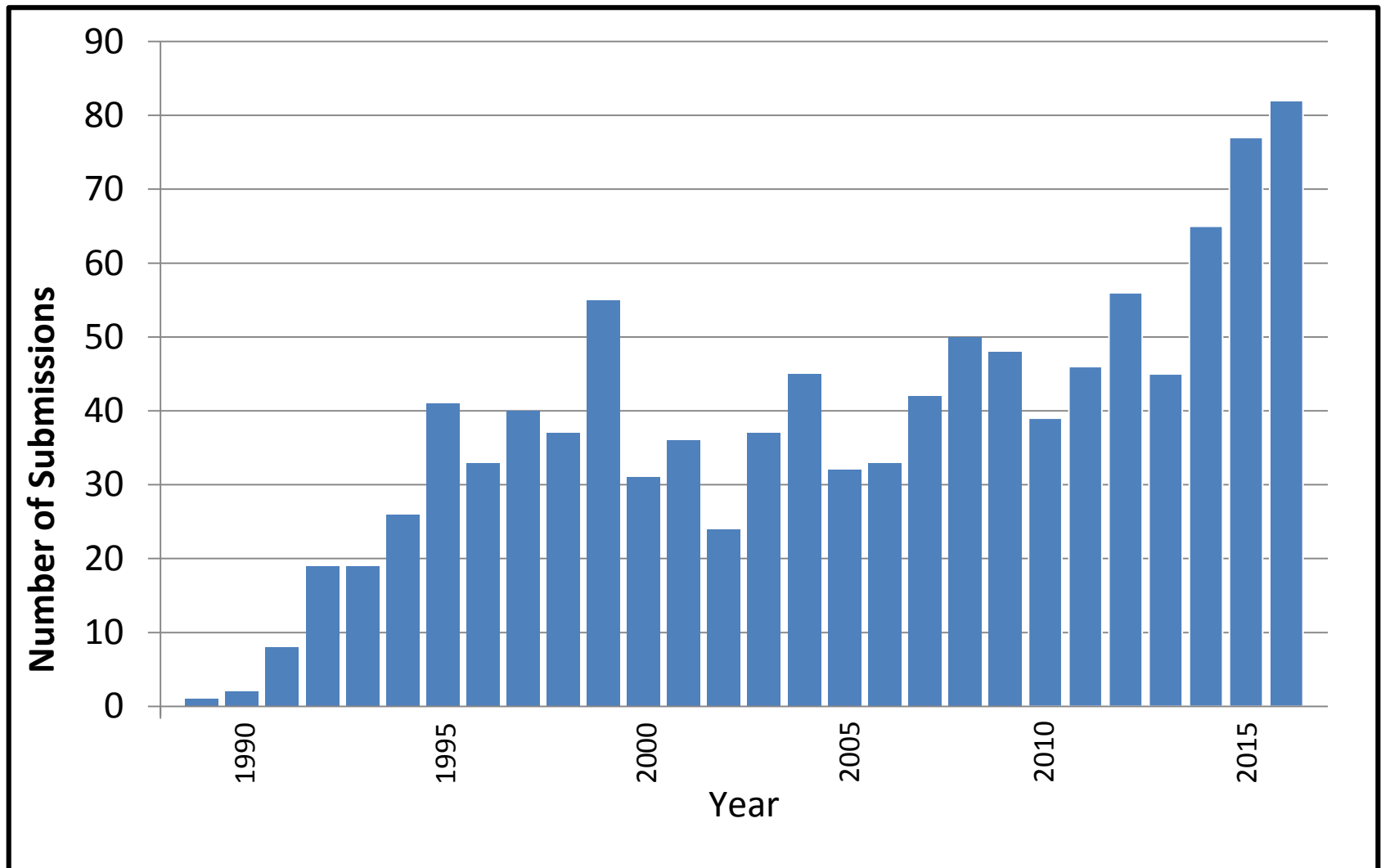
RMAT Experience*

Since December 2016, CBER has received 25 requests for RMAT designation*:

- 4 of the 5 products granted RMAT designation have orphan product designation
- 14 requests were denied.
- 6 requests are pending.

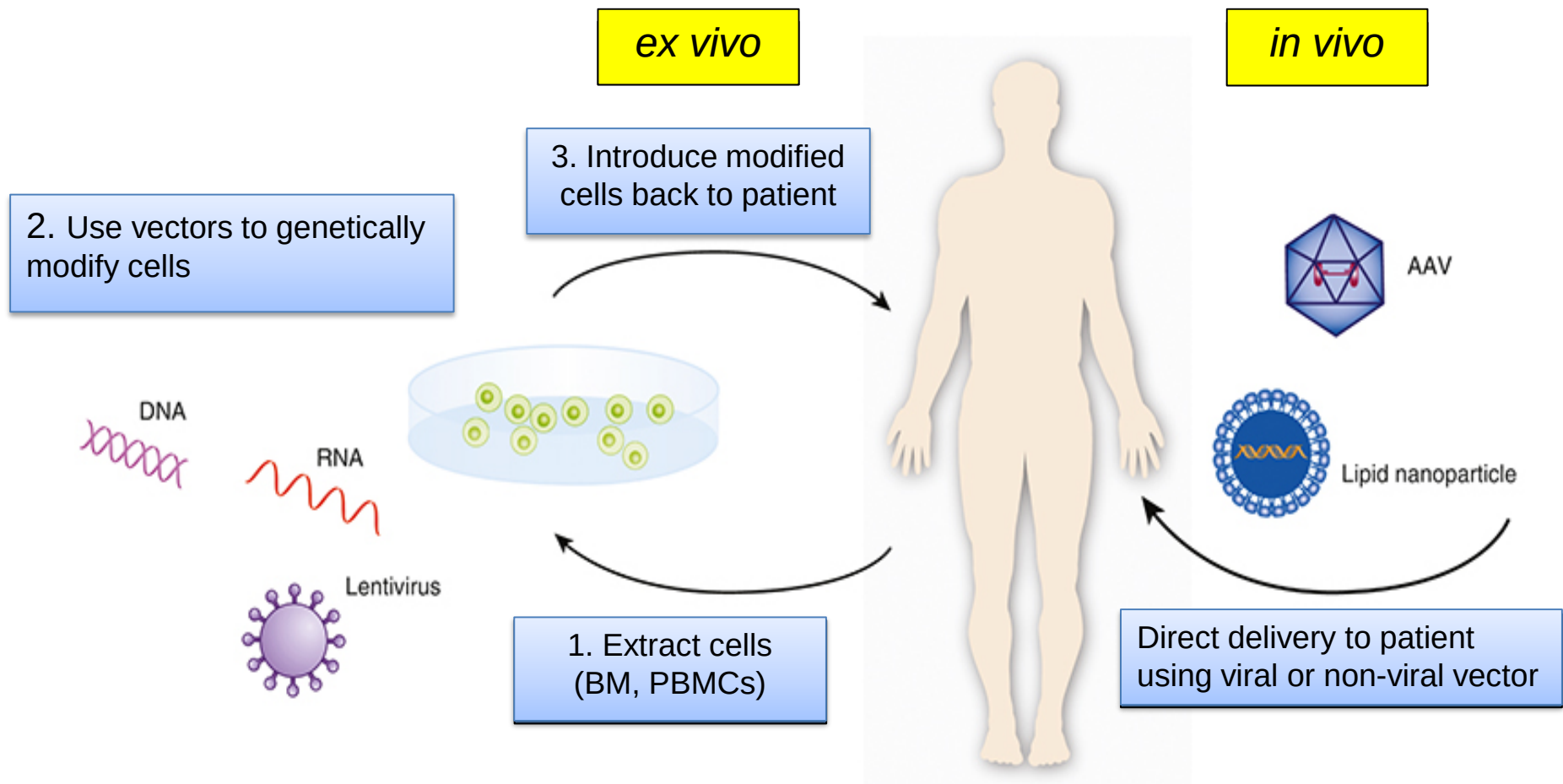
* As of 7/28/17

Number of Gene Therapy INDs Submitted to CBER by Year



Human Gene Therapy:

Ex vivo and in vivo Administration



Gene Therapy

Requirements and Risks

- Requirements:
 - Long lasting expression
 - Depends on indication
 - Targeted expression
 - Efficient delivery
- On target gene modification
- Risks:
 - Germ line transmission
 - Immune response to vector or transgene
 - Insertional mutagenesis
 - Off target expression
 - Off target editing

~Risk Benefit Analysis is Critical~

Gene Therapy History

- 1989: Gene Marking study: retrovirus expressing neomycin into TILs (melanoma, S. Rosenberg)
- 1990: First FDA-approved gene therapy trial (*ex vivo* gene transfer for treatment of ADA-SCID)

Gene Therapy History (continued)

- 1999: Death in a gene therapy study for treatment of Ornithine Transcarbamylase Deficiency (OTC)
- 2002: Patient developed leukemia in French X-SCID trial

Gene Therapy Advances

- Human genome sequenced; rapid sequencing tools developed
- New vectors for gene therapy
- CAR-T cells
- Gene editing

Chimeric Antigen Receptor T Cells

- Conventional *ex vivo* expanded T cells targeting tumor antigens show some efficacy but poor persistence
- Genetically modified T cells harness immunity (cytotoxic functions, cytokine secretion, etc.) to attach tumor or other immune effector cells
- Gene transfer improves functional properties of transduced T cells (e.g. antigen recognition, effector function)

Tisagenlecleucel

- BLA 125646 discussed at Oncologic Drugs Advisory Committee July 12, 2017
- Proposed indication is for the treatment of pediatric and young adult patients 3 to 25 years of age with relapsed/refractory B-cell acute lymphoblastic leukemia (ALL)
- Advisory Committee recommended approval 10-0

Summary

FDA is committed to bringing the promise of innovative, safe and effective new therapies to those in need of them, as quickly as possible.



Contact Information

Celia Witten, Ph.D., M.D.
Deputy Director, FDA
Center For Biologics Evaluation And Research
10903 New Hampshire Ave
Silver Spring, MD 20993
240-402-8351
celia.witten@fda.hhs.gov

Public Access to CBER

- **CBER website:**
<http://www.fda.gov/BiologicsBloodVaccines/default.htm>
- **Phone: 1-800-835-4709**
- **Consumer Affairs Branch (CAB)**
Email: ocod@fda.hhs.gov
- **Manufacturers Assistance and Technical Training Branch (MATTB)**
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