U.S. FOOD & DRUG ADMINISTRATION

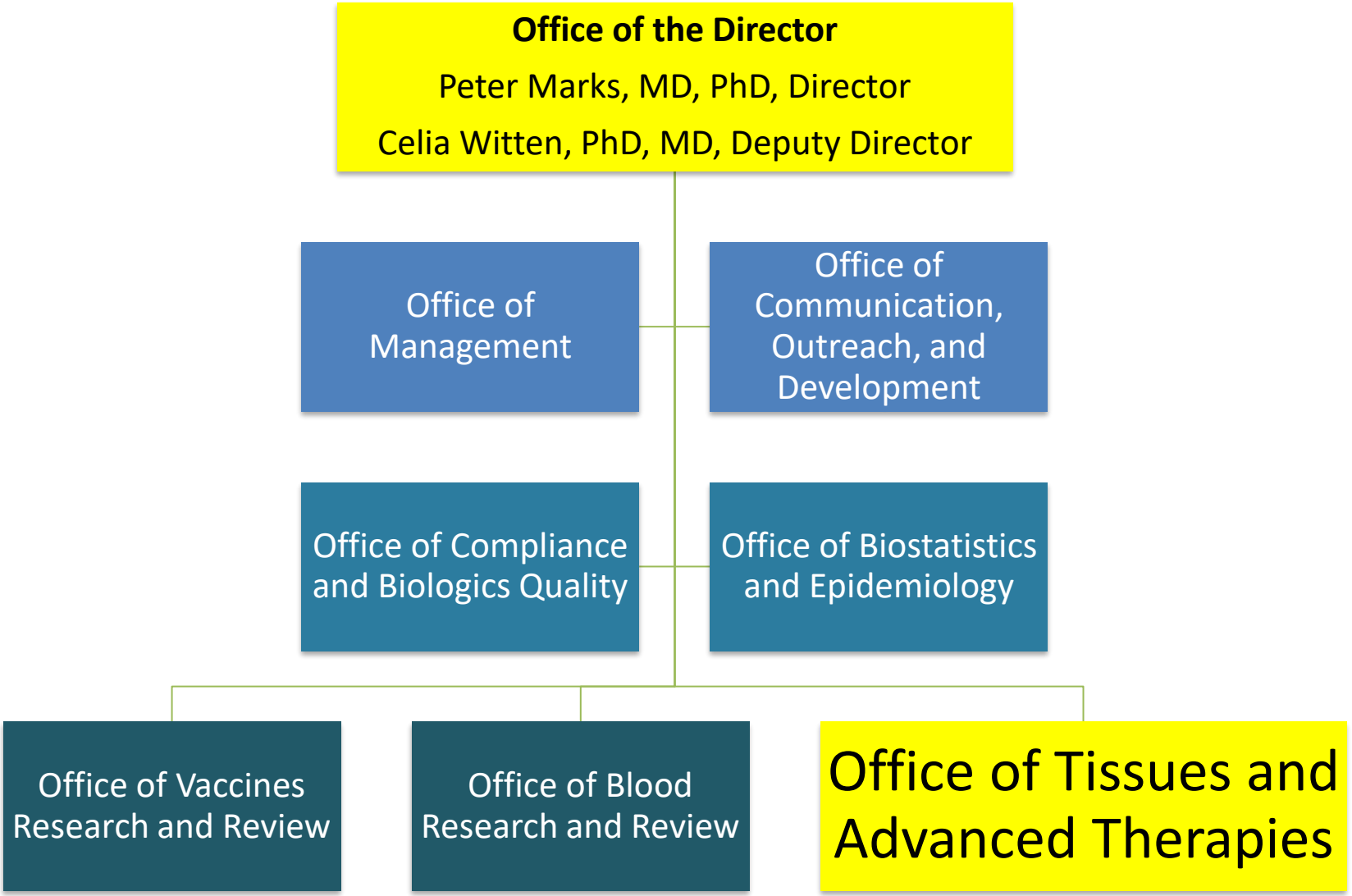
FDA / CBER
Office of Tissues and Advanced Therapies (OTAT)
Update

American Society of Gene & Cell Therapy (ASGCT)
Liaison Meeting

November 8, 2021

Wilson W. Bryan, MD

Center for Biologics Evaluation and Research (CBER)



Diversity of OTAT-Regulated Products

- **Gene therapies (GT)**
  - Ex vivo genetically modified cells
  - Non-viral vectors (e.g., plasmids)
  - Replication-deficient viral vectors (e.g., adenovirus, adeno-associated virus, lentivirus)
  - Replication-competent viral vectors (e.g., measles, adenovirus, vaccinia)
  - Microbial vectors (e.g., Listeria, Salmonella)
- **Stem cells/stem cell-derived**
  - Adult (e.g., hematopoietic, neural, cardiac, adipose, mesenchymal)
  - Perinatal (e.g., placental, umbilical cord blood)
  - Fetal (e.g., neural)
  - Embryonic
  - Induced pluripotent stem cells (iPSCs)
- **Products for xenotransplantation**

- **Functionally mature/differentiated cells** (e.g., retinal pigment epithelial cells, pancreatic islets, chondrocytes, keratinocytes)
- **Therapeutic vaccines and cellular immunotherapies** including antigen-specific active immunotherapies
- **Blood- and Plasma-derived products**
  - Coagulation factors
  - Fibrin sealants
  - Fibrinogen
  - Thrombin
  - Plasminogen
  - Immune globulins
  - Anti-toxins
  - Venom antisera for snakes, scorpions, and spiders
- **Combination products**
  - Engineered tissues/organs
- **Devices**
- **Tissues**

Approved Gene Therapies

- KYMRIAH (tisagenlecleucel)
- YESCARTA (axicabtagene ciloleucel)
- TECARTUS (brexucabtagene autoleucel)
- **BREYANZI** (lisocabtagene maraleucel)
- **ABECMA** (idecabtagene vicleucel)
- LUXTURNA (voretigene neparvovec-rzyl)
- ZOLGENSMA (onasemnogene abeparvovec-xioi)

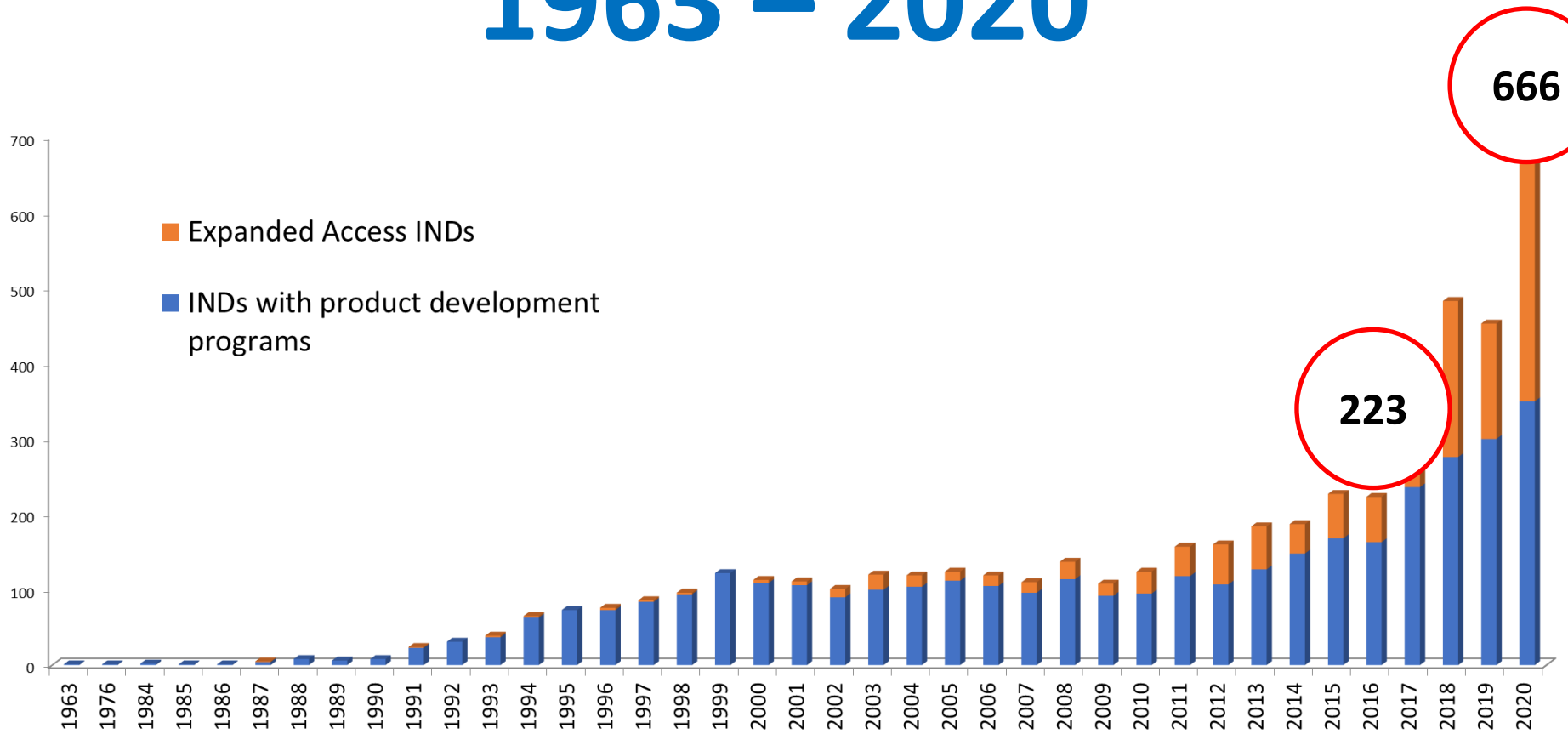
Approved Cellular Therapy Products

- PROVENGE (sipuleucel-T)
- Hematopoietic Progenitor Cells, Cord Blood
- LAVIV (azficel-T)
- GINTUIT (allogeneic Cultured Keratinocytes and Fibroblasts in bovine collagen)
- MACI (autologous Cultured Chondrocytes on porcine collagen membrane)
- **STRATAGRAFT** (allogeneic cultured keratinocytes and dermal fibroblasts in murine collagen-dsat)
- **RETHYMIC** (allogeneic processed thymus tissue–agdc)

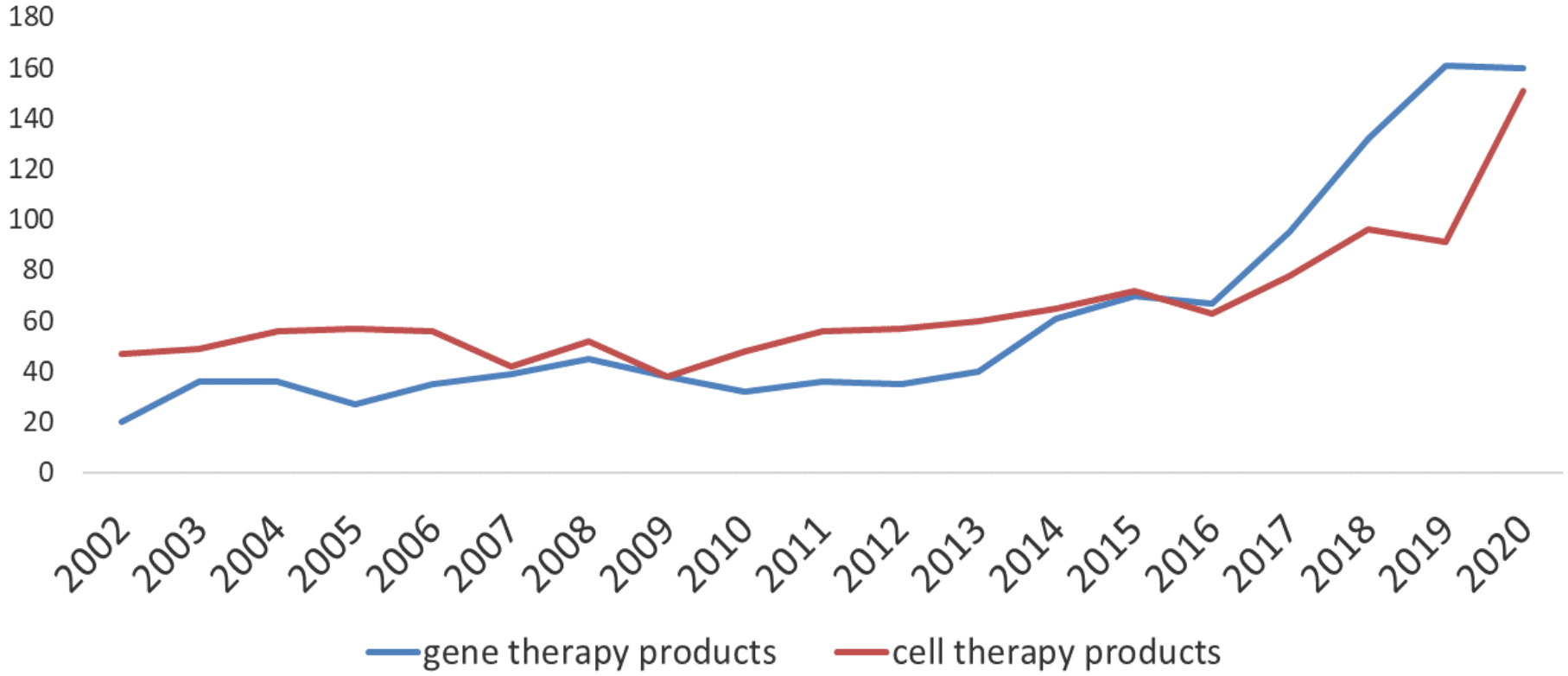
All OTAT INDS

(i.e., Research and Expanded Access (EA))

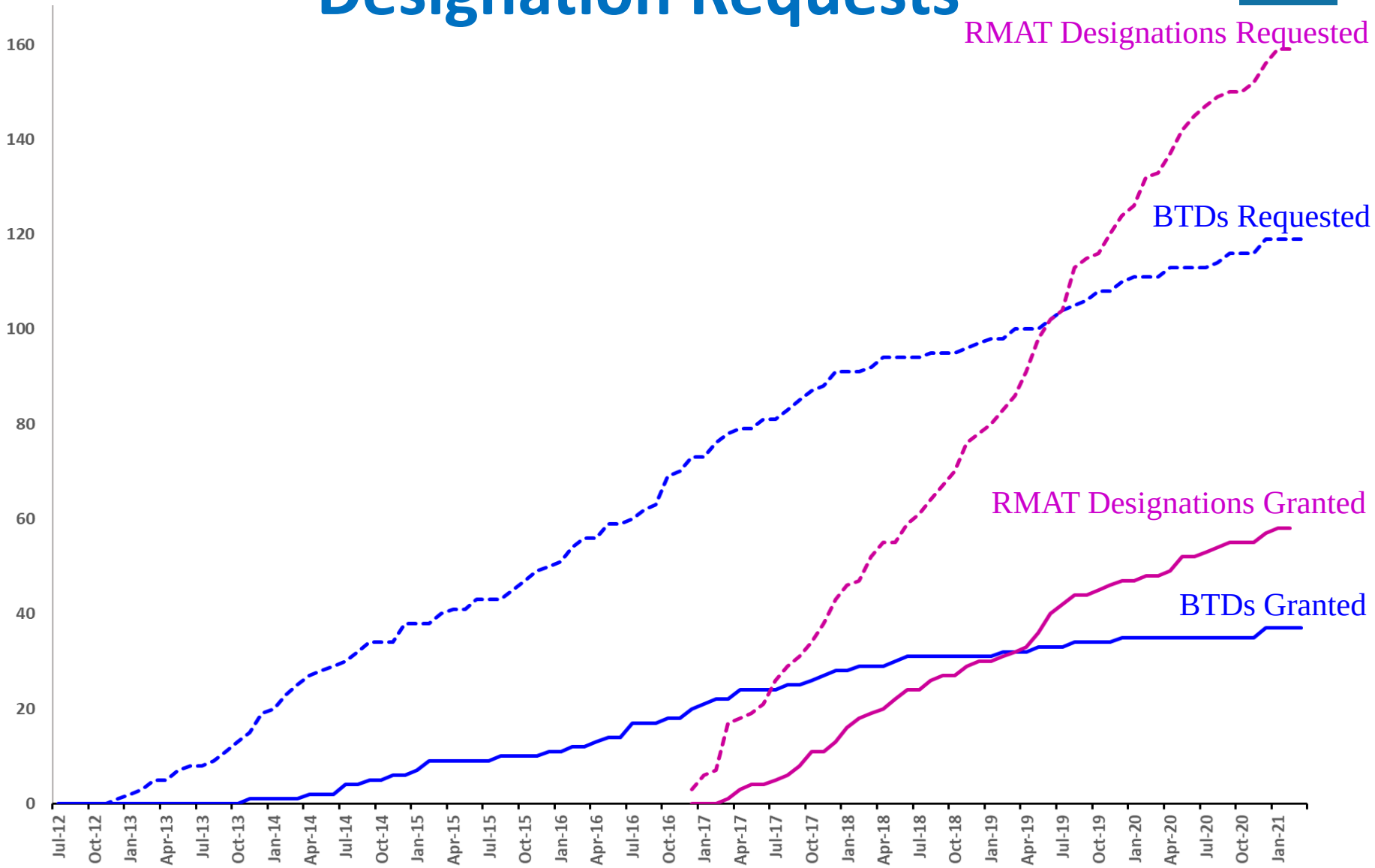
1963 – 2020



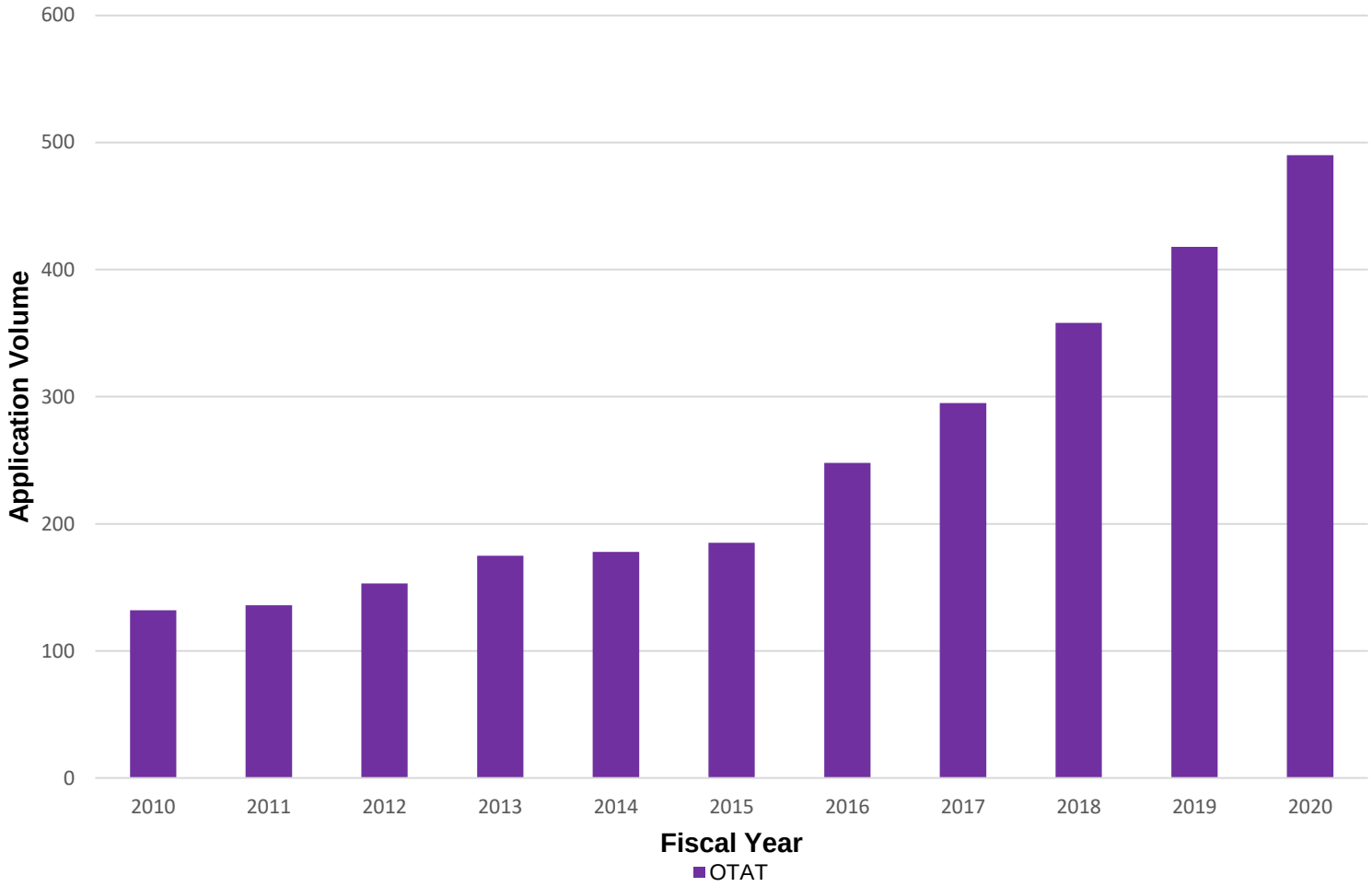
Cell and Gene Therapies: Research INDs 2002 – 2020



Breakthrough (BT) and RMAT Designation Requests

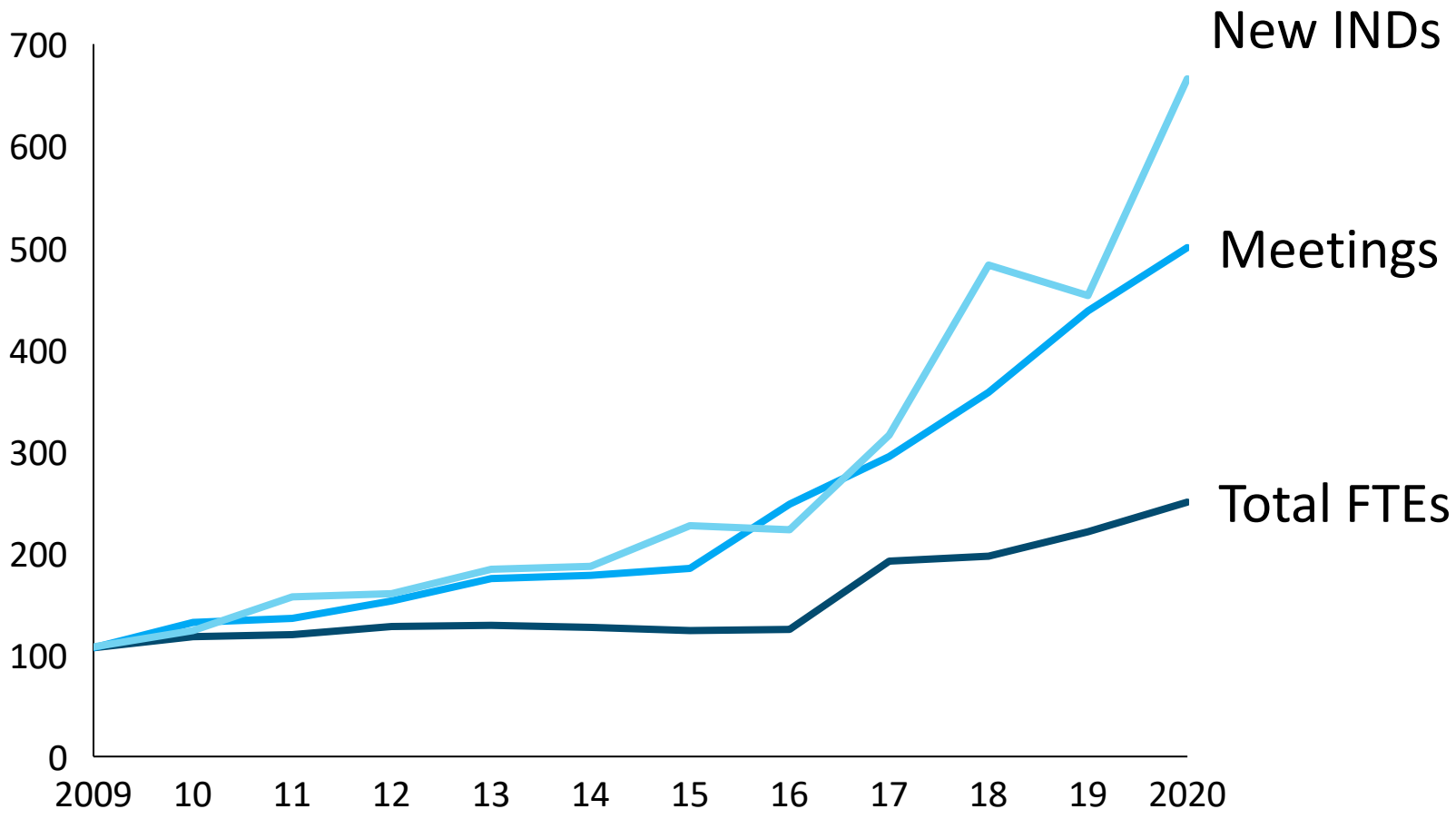


All Meeting Types (A, B, C, and Other)



OTAT workload outpaces FTE increases

FTE, Total Meetings, and INDs (across OTAT)



FDA/CBER/OTAT

GROWTH PROGRAM

OTAT Growth Program

Primary Goals

- Expedite advances in cell and gene therapy
- Improve staff satisfaction and sustainability

Program Phases

- Generate ideas
- Prioritize objectives and pilot solutions
- Refine and implement solutions

OTAT Growth Program: Generate Ideas

- Interviews and focus groups with CBER and OTAT staff
  - Analysis of workload data
- Interviews and listening sessions with sponsors and industry trade groups
  - 25 sponsor interviews
  - Listening sessions with four trade organizations, including ASGCT
- Data analysis to characterize and quantify opportunities
- Prioritize ideas

What we heard from OTAT Staff

Challenges in interactions with sponsors

1) More staff is needed to meet increasing workload
2) Difficult to meet expectations for the degree of engagement
3) Submissions may arrive missing key documents or information
4) Sponsors do not necessarily communicate changes in a way that facilitates efficient review
5) Limited precedents for some products, questions have become more complex and time-intensive to address

What we heard from sponsors

Strengths in interactions with OTAT

1) High quality scientific advice
2) Strong working relationships with OTAT staff (e.g., responsive/engaged interactions with project managers)
3) Digital innovations implemented as a result of the COVID-19 pandemic (e.g., digital submissions)
4) PDUFA timelines are being met
5) OTAT staff clear commitment to the patient mission

What we heard from sponsors

Challenges in interactions with OTAT

1) Response quality and consistency varies, especially for more nascent technologies
2) Clarity and specificity of OTAT responses is mixed (e.g., in written responses)
3) Limited opportunities for informal interactions and follow-ups to answer clarifying questions (e.g., after meetings)
4) Unclear expectations on several topics

OTAT Growth Program: Idea Summary

- Rapid growth in the development of cell and gene therapies has created new challenges for OTAT.

- OTAT is undertaking a variety of initiatives to meet these challenges, including:
  - improving communications with stakeholders and
  - increasing capacity and efficiency in OTAT operations

OTAT Growth Program: Prioritize Objectives

Four priority objectives to support initiatives and achieve primary goals:

1) Clarify expectations and create tools to help sponsors engage OTAT productively
2) Re-design core operational practices to drive efficiency, transparency, and collaboration
3) Increase frequency of scientific exchange externally and internally
4) Create more staff and management capacity and sustainability

Objective 1 - Pilot Solutions

1) Clarify expectations and create tools to help sponsors engage OTAT productively

- Revise website, with initial focus on meetings with OTAT

- Consolidate resources related to cell and gene therapies on CBER's website (e.g., OTAT Learn recordings, guidance documents)

Objective 2 - Pilot Solutions

2) Re-design core operational practices to drive efficiency, transparency, and collaboration

- Standardize practices for clarifications after meetings, particularly after “Written Responses Only”
- Investigate opportunities for increased communication regarding status of submissions, including both original INDs and IND amendments

Objective 3 - Pilot Solutions

3) Increase frequency of scientific exchange externally and internally

- Collaborate with trade and scientific organizations (e.g., ASGCT) to facilitate mutual learning
  - Identify priority topics
  - Webinars
  - Workshops
  - White Papers

Pending 2021 OTAT Guidances

FINAL GUIDANCES

- Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps): Small Entity Compliance Guide
- Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations

DRAFT GUIDANCE

- Considerations for the Development of Human Gene Therapy Products Incorporating Human Genome Editing
- Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products
- Studying Multiple Versions of a Cellular or Gene Therapy Product in an Early-Phase Clinical Trial

Objective 4 - Pilot Solutions

4) Create more staff and management capacity and sustainability

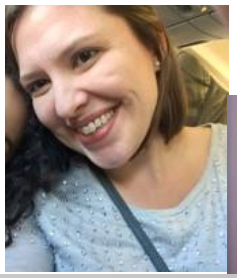
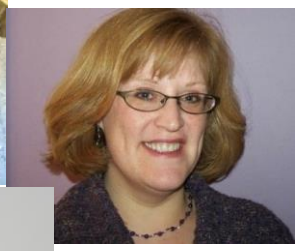
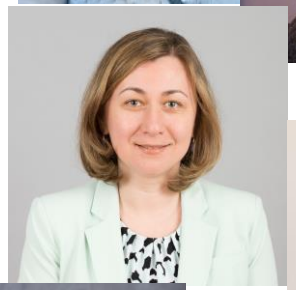
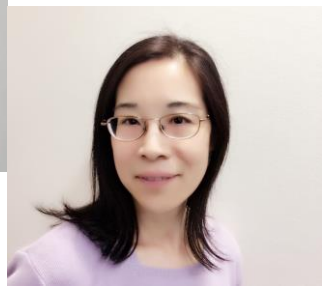
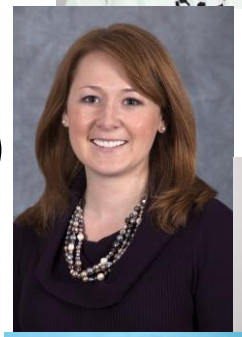
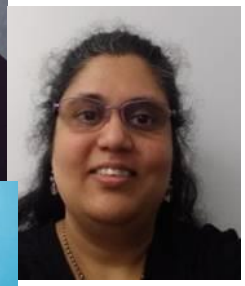
- PDUFA VII
- Reconsider OTAT structure

Summary

- There is a commitment to patients and high-quality scientific exchange in the development of cell and gene therapies.
- Rapid growth in the development of cell and gene therapies has created new challenges for OTAT
- Ideas from OTAT staff and sponsors spurred initiatives to sustain strengths and meet challenges
- OTAT is piloting solutions to
  - improve communications with stakeholders and
  - increase capacity and efficiency in OTAT operations

Acknowledgements

- Rachael Anatol, PhD
- Kim Benton, PhD
- Larissa Lapteva, MD
- Wei Liang, PhD
- Anne Rowzee, PhD
- Ramani Sista, PhD
- Xiaofei Wang, PhD


Contact Information

Wilson W. Bryan, M.D.

wilson.bryan@fda.hhs.gov

Contact Information

- **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

U.S. FOOD & DRUG ADMINISTRATION

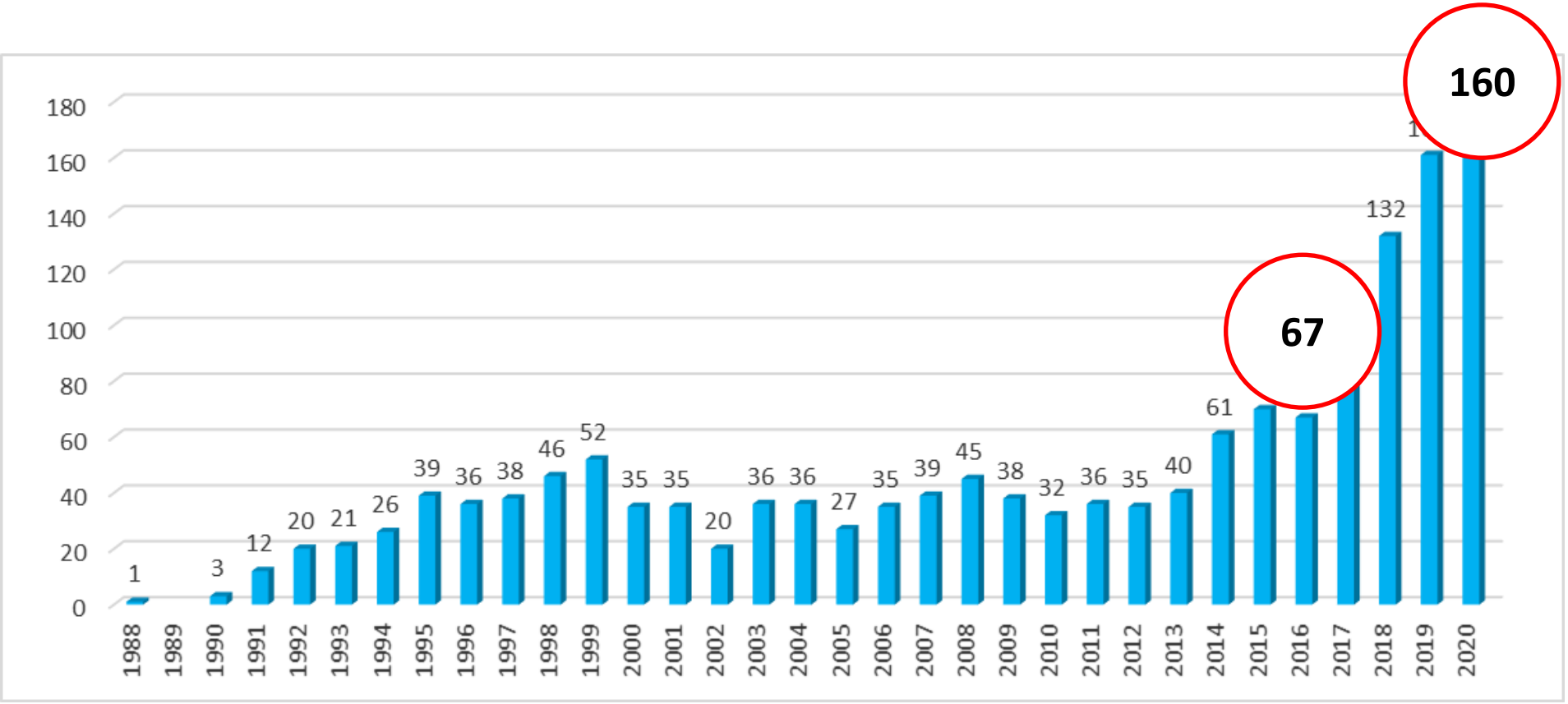
FDA / CBER
Office of Tissues and Advanced Therapies (OTAT)
Update

American Society of Gene & Cell Therapy (ASGCT)
Liaison Meeting

November 8, 2021

Wilson W. Bryan, MD

Research INDs: Gene Therapy



Research INDs: Cell Therapy