U.S. FOOD & DRUG ADMINISTRATION

Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

FDLI

Regenerative Medicine

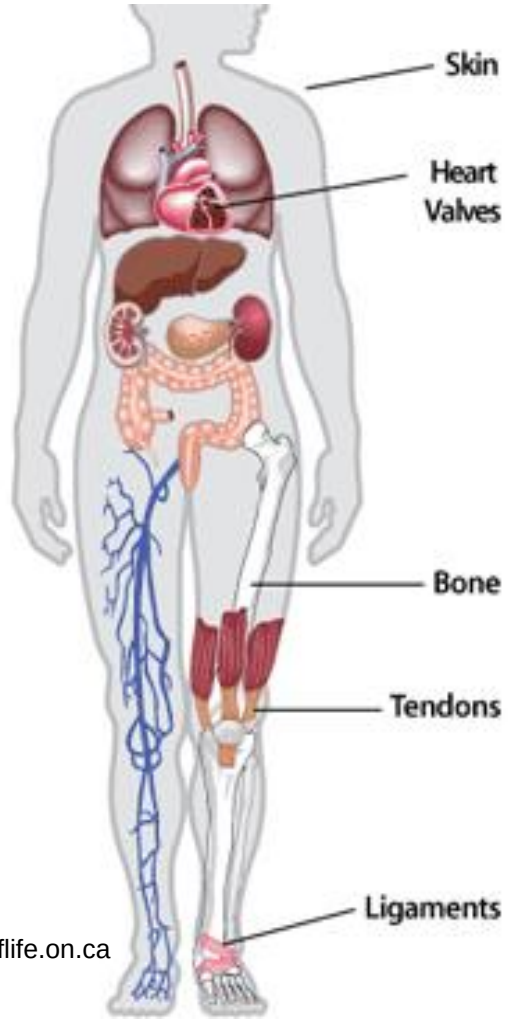
June 8, 2021

Wilson W. Bryan, MD

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

What are HCT/Ps?

- Human cells or tissues that are intended for implantation, transplantation, infusion, or transfer to a human recipient
- Includes bone, ligament, skin, adipose tissue, amnion/placenta, umbilical cord, hematopoietic stem/progenitor cells, stem cells, reproductive cells, etc.
- Not HCT/Ps: blood or blood-derived products (e.g., platelet-rich plasma, serum), minimally manipulated bone marrow for homologous use and not combined with another article, secreted or extracted products, among others
- Rules became fully effective May 25, 2005



giftoflife.on.ca

§ 1271.3(d)

Two Regulatory Tiers for HCT/Ps

1. Drugs, devices, biological products (351 HCT/Ps)
   - Regulated under authority of sections 361 and 351 of Public Health Service (PHS) Act and/or the Federal Food, Drug, & Cosmetic Act, and the implementing regulations
   - FDA premarket review and approval **required**
2. 361 HCT/P
   - Regulated solely under authority of section 361 of PHS Act and 21 CFR Part 1271
   - Premarket review and approval **not required**

21 CFR 1271.10(a) criteria

To be regulated solely under section 361 of the PHS Act, HCT/Ps must meet **ALL** of the following criteria:

1. Minimally manipulated (MM);
2. Intended for homologous use (HU) only, as indicated by the manufacturer's objective intent;
3. Not combined with another article (with some exceptions); AND
4. Either:
   i. Does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or
   ii. Has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and is for autologous, 1st or 2nd degree blood relative, or reproductive use

HCT/P Guidances

- Share FDA's current thinking on the existing regulations to help sponsors determine if they need to obtain premarket authorization for their products
- Issued November 2017
  - Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception – Final
  - Regulatory Considerations for Human Cell, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use – Final

Compliance and Enforcement Policy

To give manufacturers **time to determine if they need to submit an IND [Investigational New Drug Application] or marketing application … and, if such an application is needed, to prepare the IND or marketing application,** the guidance describes a period of enforcement discretion for products based on a determination of the risk to public health.

Period of Enforcement Discretion

A product that requires but lacks premarket approval may not be lawfully marketed, including when a sponsor has an IND or is pursuing a BLA.

Period of Enforcement Discretion

- 14 Warning Letters
- 24 Untitled Letters
- 400 Letters to manufacturers and health care providers who may be offering violative stem cell or related products
- Two enforcement actions for injunction against manufacturers of violative HCT/Ps
  - *United States vs. US Stem Cell Inc. et al*
  - *United States vs. Cell Surgical Network et al*

Period of Enforcement Discretion

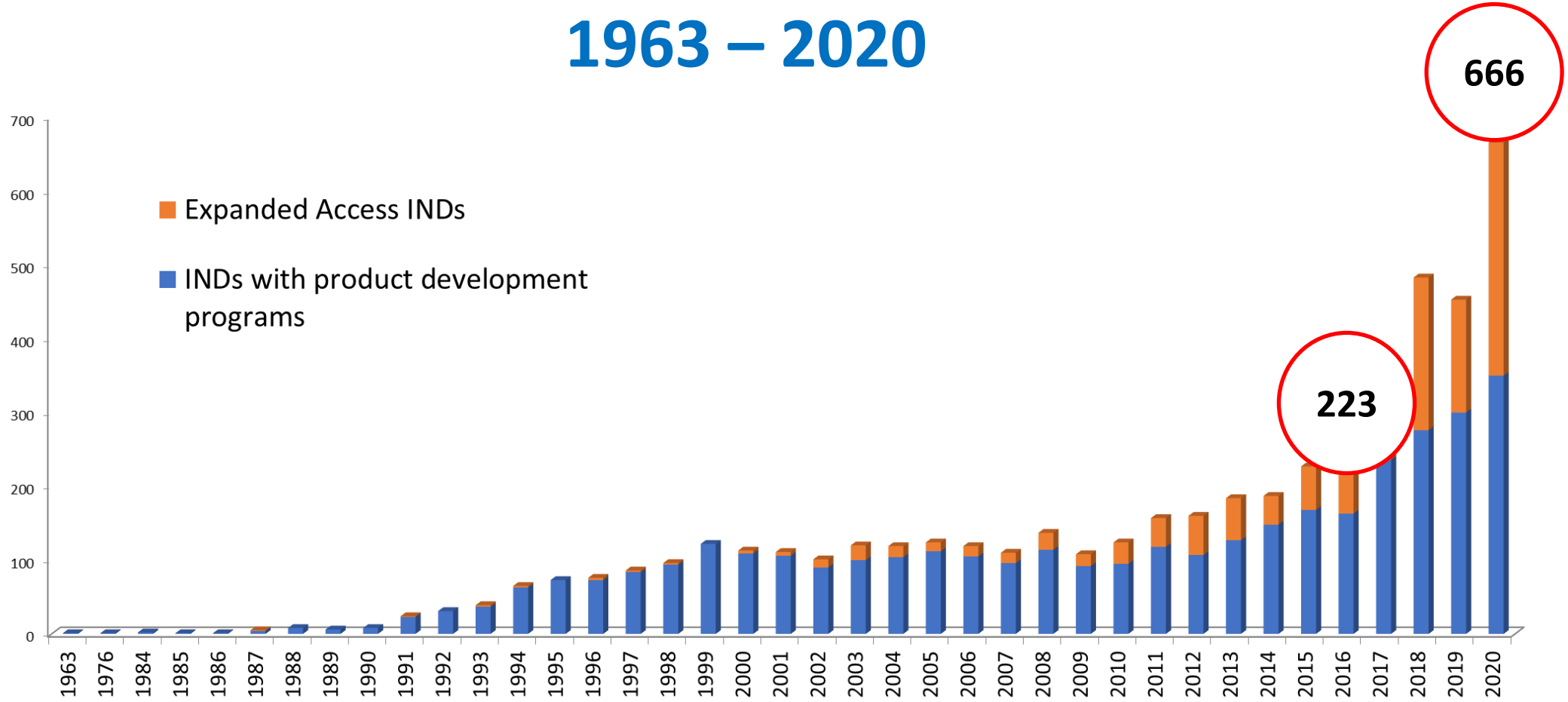
- May 31, 2021: Last day of “Period of Enforcement Discretion”

- Does any specific product require an IND?
  - Tissue Reference Group (TRG)
  - Request for Designation (RFD) process
  - Pre-RFD process

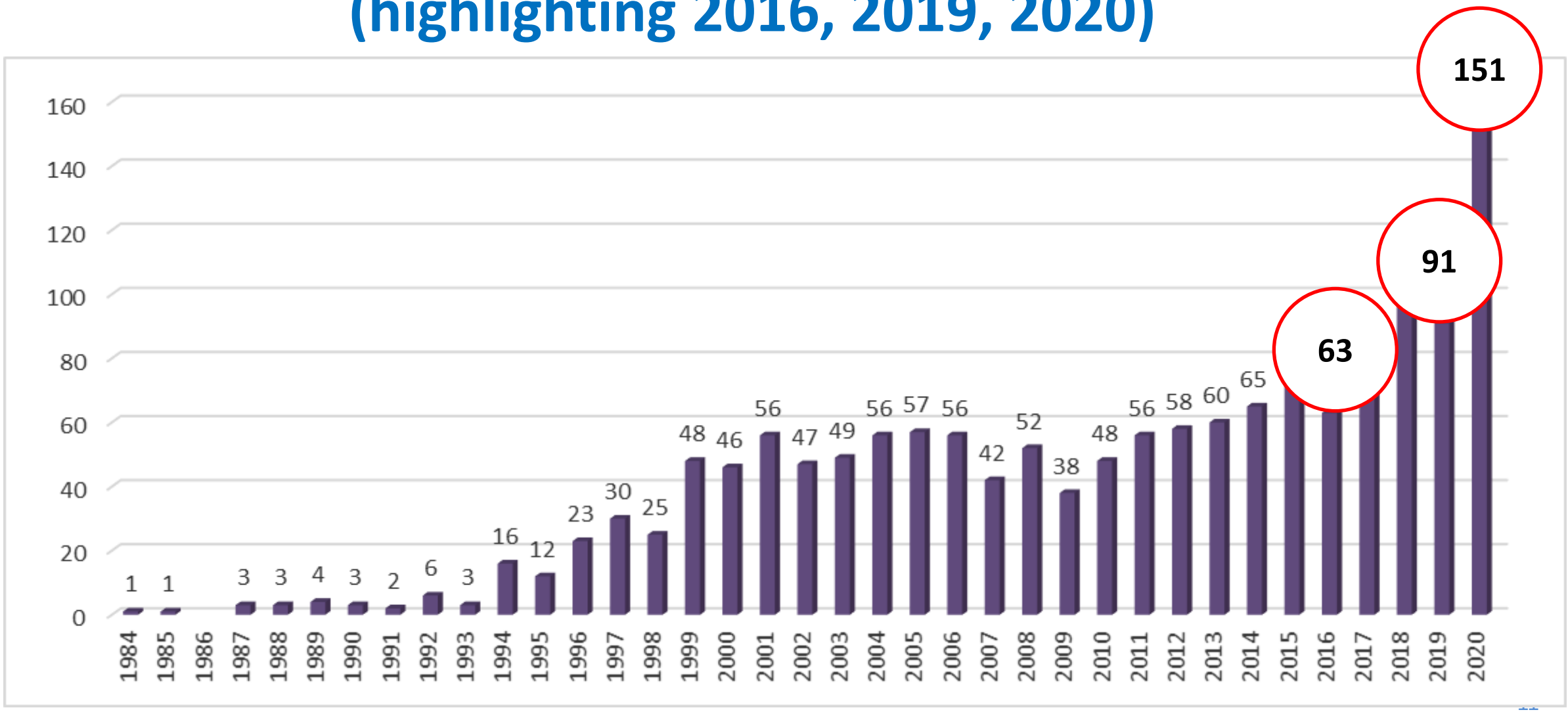
OTAT Investigational New Drug Applications (INDS)

(includes Research and Expanded Access (EA) INDs)

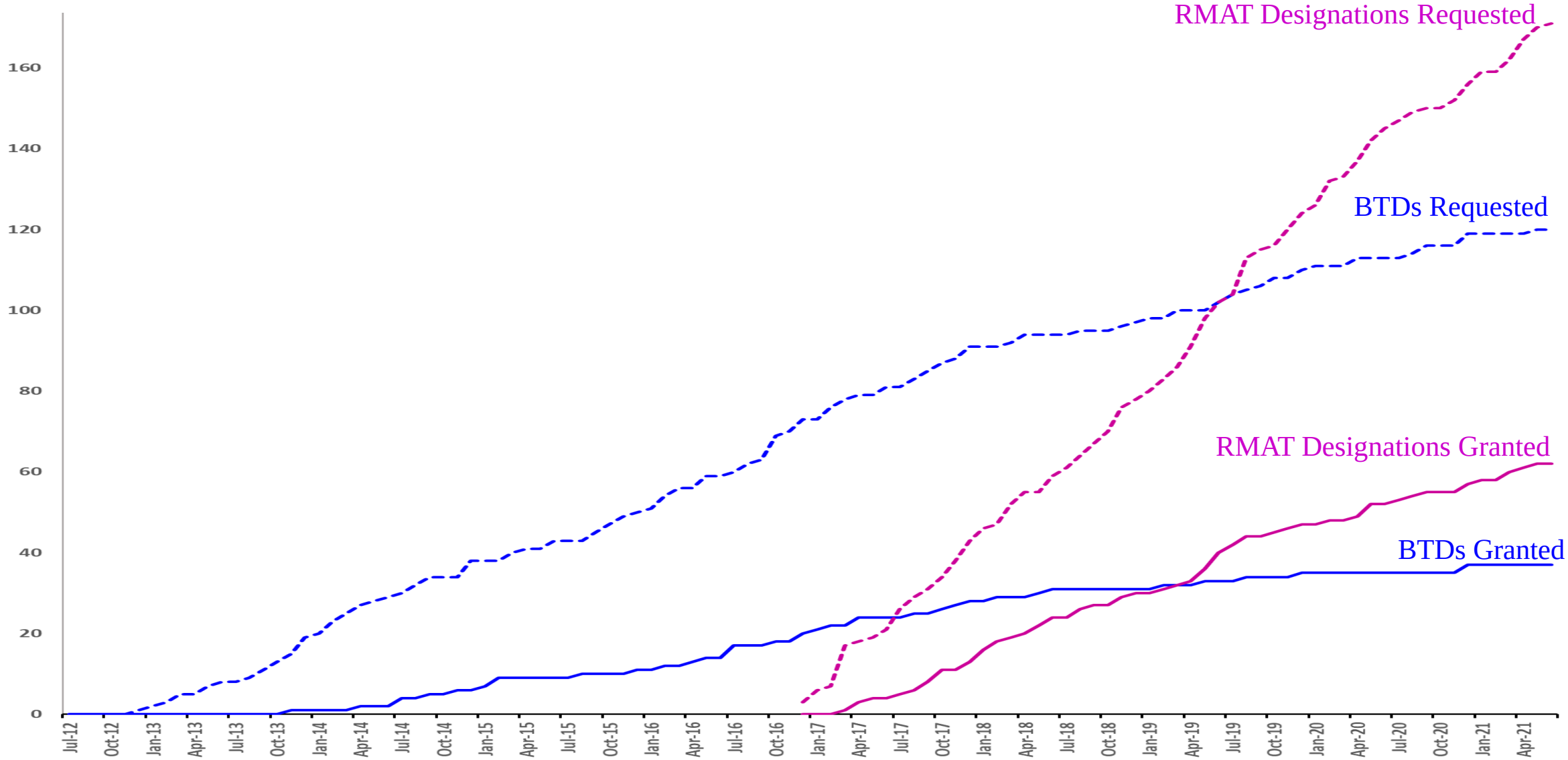
1963 – 2020



Research INDs: Cell Therapy
(highlighting 2016, 2019, 2020)



Cumulative Overview of Breakthrough and RMAT Designation Requests



Acknowledgements

- Rachael Anatol, PhD
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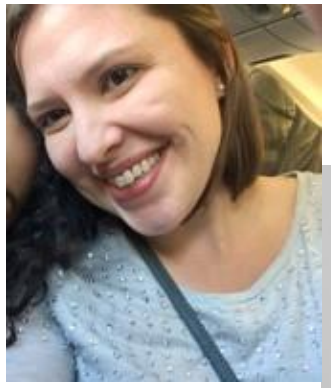

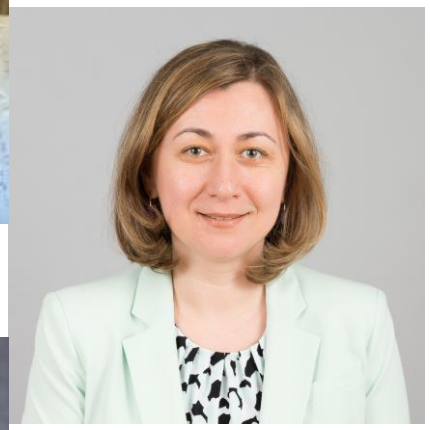

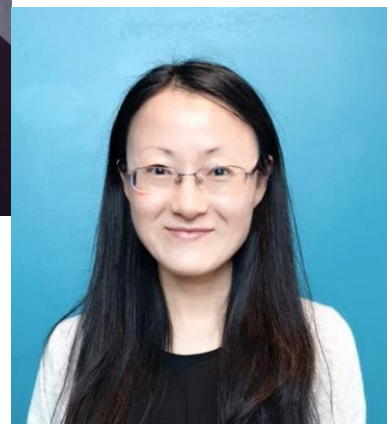

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FDA Headquarters

- **OTAT Learn Webinar Series:**

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

- **CBER website:** www.fda.gov/BiologicsBloodVaccines/default.htm
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Updates on FDA's Comprehensive Regenerative Medicine Policy Framework

June 8, 2021 (virtual session)

Regenerative Medicine: Regulatory, Legal, and Compliance Challenges for Cell and Gene Therapies

FDLI

Session Speakers

- Dr. Wilson Bryan, Director, CBER Office of Tissues and Advanced Therapies
- Lauren Miller, Senior Counsel, AbbVie

Moderated by Joanne Hawana, Member of the Health Law/FDA Practice Group, Mintz

Session Agenda

- Introduction and Poll Questions
- Dr. Bryan – Cell and Tissue Therapy Activity Update
- Panel Discussion and Audience Q&A

FDA Authority under Section 361 of the PHS Act

- Historically, tissue products were not subject to active federal regulation. Instead, human tissues were primarily regulated by voluntary quality assurance programs, such as standards established and maintained by the American Association of Tissue Banks. A small minority of states also regulated tissue bank operations.
- Case-by-case exercise of jurisdiction by FDA.
- **Issues with disease transmission eventually led FDA to promulgate regulations in 2001.**
- Human cells, tissues, and cellular and tissue-based products now fall within the HCT/P regulations codified at 21 C.F.R. Part 1270 and Part 1271.

FDA Oversight of HCT/Ps Lagged Industry

- Between 2001 and 2017, enforcement under these regulations was limited, and stem cell therapy purveyors and clinics mushroomed.
- But the science of “regenerative medicine” writ large (to include gene therapy) progressed rapidly in the first two decades of the 21st Century, which led to huge increases in investment and legitimate therapeutic product development in these exciting areas.
- FDA finally saw the need to invest too, especially after the RMAT mandates in the 21st Century Cures Act (enacted in December 2016), and the agency responded forcefully to both challenges.

FDA's 21st Century Cures Mentality

"We're bearing witness to the beginning of a **paradigm shift in the practice of medicine**.

These concepts are no longer the stuff of science fiction, but rather **real-life science** where cells and tissues can be engineered to grow healthy, functional organs to replace diseased ones; where new genes can be introduced into the body to combat disease; and where adult stem cells can generate replacements for cells that are lost to injury or illness. **The promise of this technology is why the FDA is so committed to encouraging and supporting innovation in this field**."

- *Former FDA Commissioner Scott Gottlieb, Nov. 15, 2017 press statement*

Comprehensive Regenerative Medicine Policy Framework

- Initiative announced by Dr. Gottlieb in August 2017, with the first slew of guidance documents and new enforcement policy released in November 2017.
- Two-pronged approach:
  - *“Efficient Regulation”*
  - *“Stepped Up Enforcement”*

“Stepped Up Enforcement”

- Following the 2017 announcement, FDA increased it enforcement activity for HCT/Ps and particularly against unapproved stem cell products it deemed to pose the greatest risks.
- Also provided a 3-year enforcement discretion period (which was originally set to end November 2020, and subsequently extended to May 31, 2021).
- Non-exempt HCT/Ps should be in commerce either under an IND or as an FDA-approved product, otherwise they are subject to enforcement.

“Efficient Regulation”

- We heard this afternoon from Dr. Marks about gene therapy regulatory developments at FDA/CBER and the gene therapy-related guidance documents that have been recently issued and are in development.
- We’ll hear next about cell therapy-related developments at the Agency from Dr. Bryan, including on the enforcement side of its two-pronged approach to comprehensive regulation.

Poll Questions

How would you rate FDA's regulatory support and guidance to the regenerative medicine industry (writ large) over the past 3 years?

- Poor
- Fair
- Good
- Excellent

Poll Questions

I think that the FDA's enforcement discretion period to come into compliance with HCT/P regulations was:

- too long.
- too short.
- about right.
- about right, although another Covid-related extension would have been nice.

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Panel Discussion and Q&A

- Please submit your questions in the Zoom panel below!