U.S. FOOD & DRUG ADMINISTRATION

FDA Regulation of Advanced Therapies

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Center for Biologics Evaluation and Research (CBER)

SITC Cancer Immunotherapy Winter School,
Mesa, AZ Feb 18-22, 2019
Presentation: on Feb 22, 2019

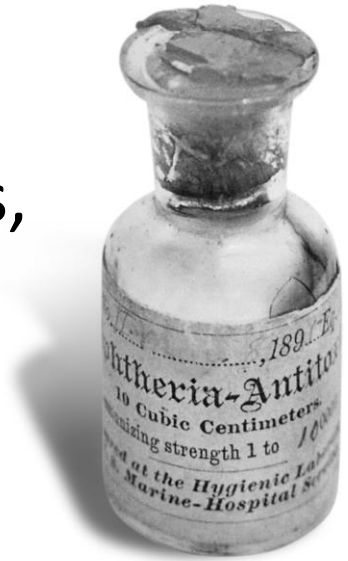
Outline

- FDA Facts and Organization
- CBER Mission and Activities
- FDA regulation of biologics
- OTAT Products
- Interaction with FDA
- FDA Expedited Programs
- Regenerative Medicine Advanced Therapies (RMAT)
- Guidances

U.S. Food and Drug Administration (FDA)

FDA protects the public health by assuring the safety, efficacy and security of:

- Human and veterinary drugs,
- Biological products,
- Medical and radiation-emitting devices,
- Foods and cosmetics



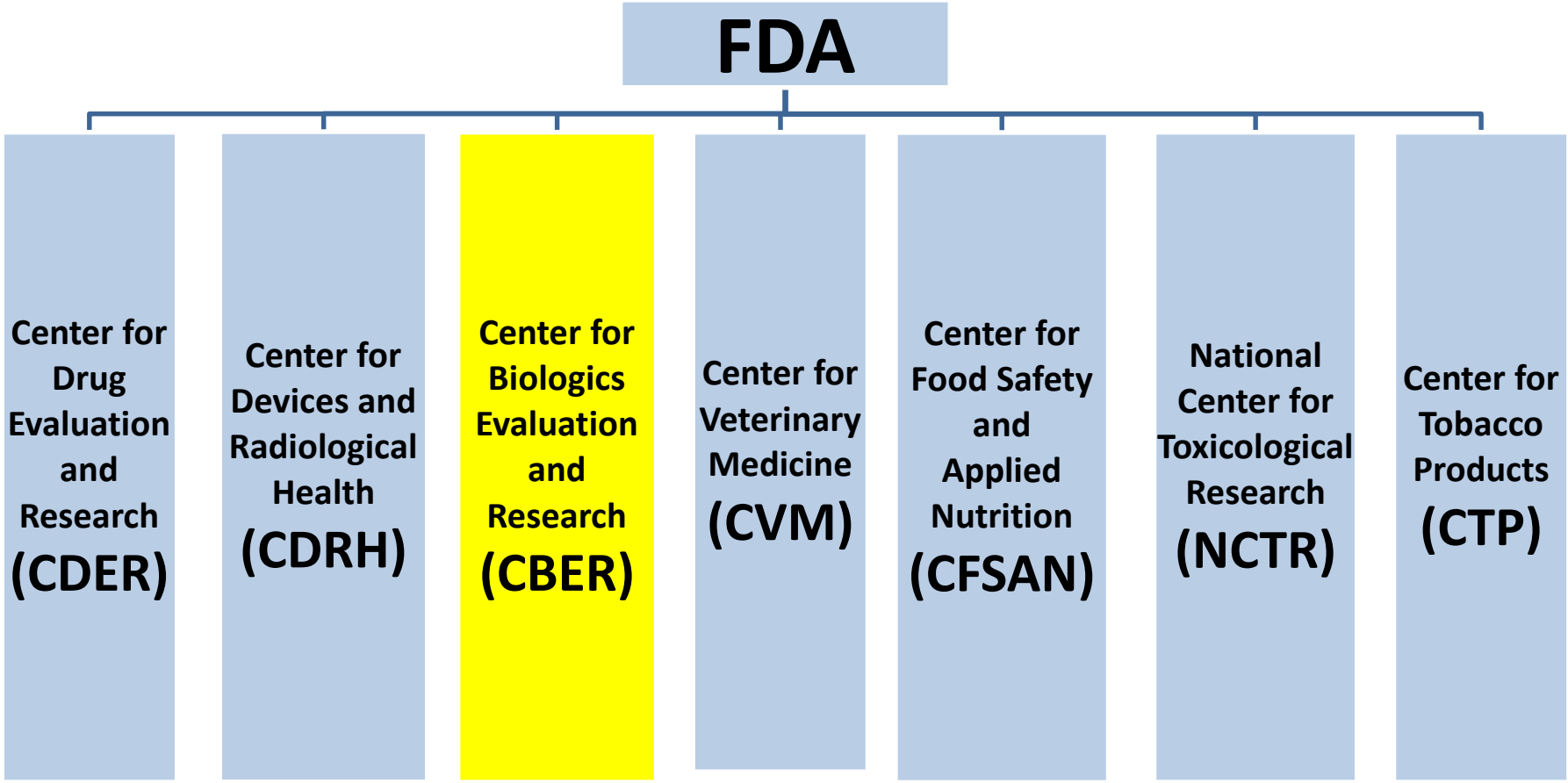
FDA Facts

- ~>14,000 scientists, inspectors, reviewers, statisticians, physicians, veterinarians, administrators, legal and support staff.

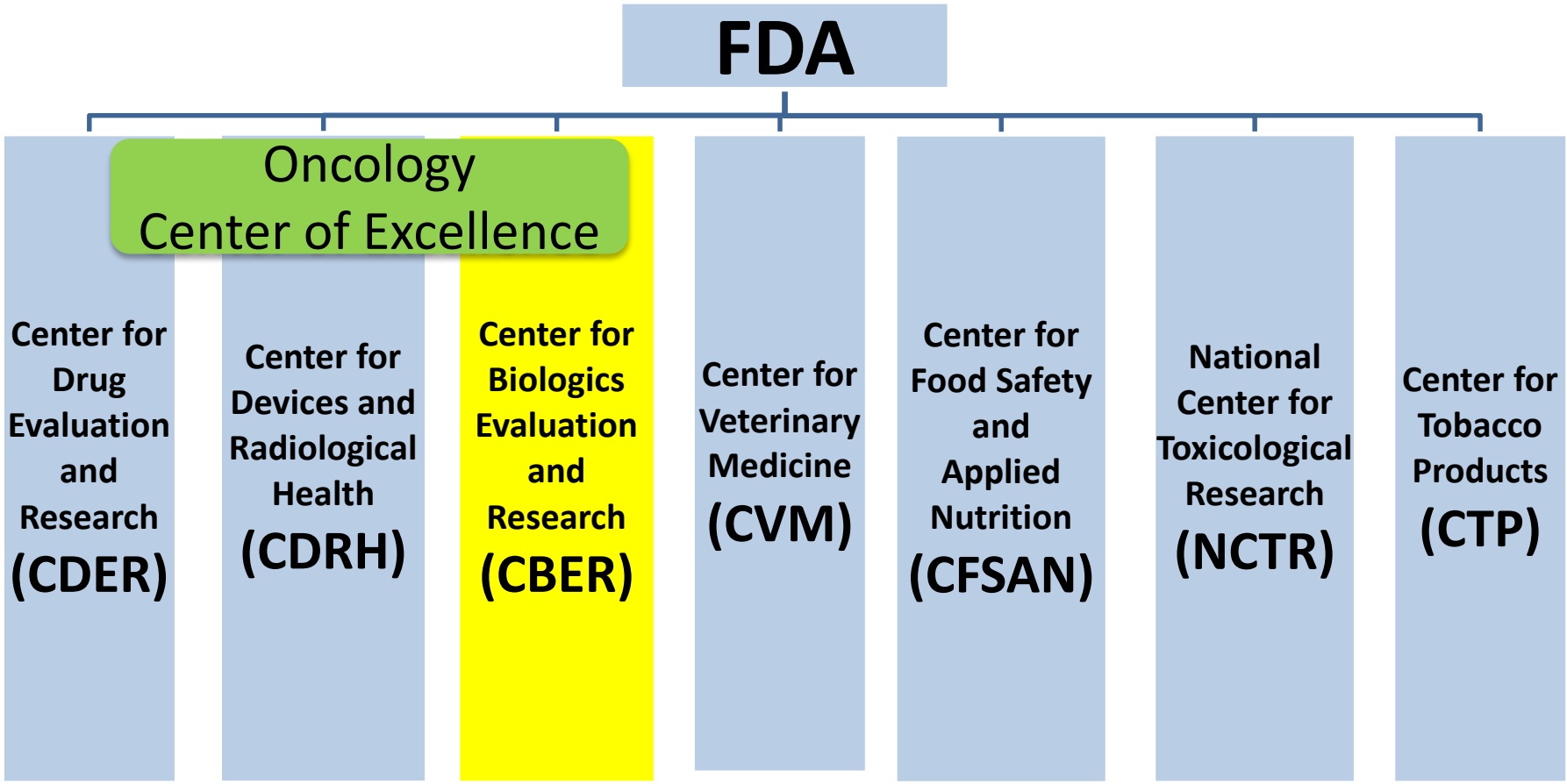
- Regulates ~25 cents of every U.S. consumer dollar spent or about $1 Trillion of the U.S. consumer market.

- Regulated firms employ ~1.5 million U.S. workers and products equal ~13% of U.S. manufacturing.

FDA Organization

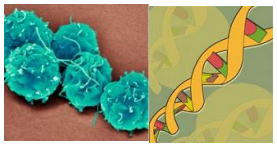


FDA Organization



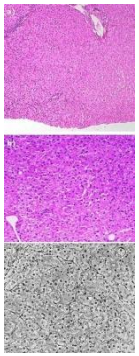
CBER Regulates Complex Products

Cell & Gene Therapies



Blood, Blood Components and Derivatives

Xenotransplantation

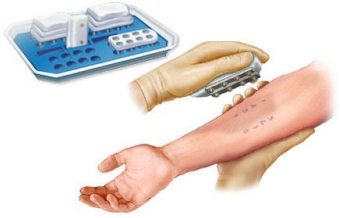


Tissues

Vaccines: Preventive & Therapeutic

Live Biotherapeutics

Related Devices



Allergenic Products

CBER's Mission

To ensure the safety, purity, potency, and effectiveness of biological products, including vaccines, blood and blood products, and cells, tissues and gene therapies for the prevention, diagnosis, and treatment of human diseases, conditions or injury.

CBER Activities

CBER has the scientific expertise needed to:

- Ensure that products are safe, effective and pure
- Inspect manufacturing facilities (plants, blood banks)
- Conduct surveillance of adverse events
- Conduct Regulatory Science related research for safer and more effective products

CBER Products

- ~40 Billion USD in investment per year

Public Health Impact:

- 235 Million vaccinations
- 14 Million units of blood and blood components transfused
- 1.6 Million tissue transplants
- Post-licensure surveillance of adverse events or complications
- Cell and Gene therapy products

Biologicals: Unique Issues

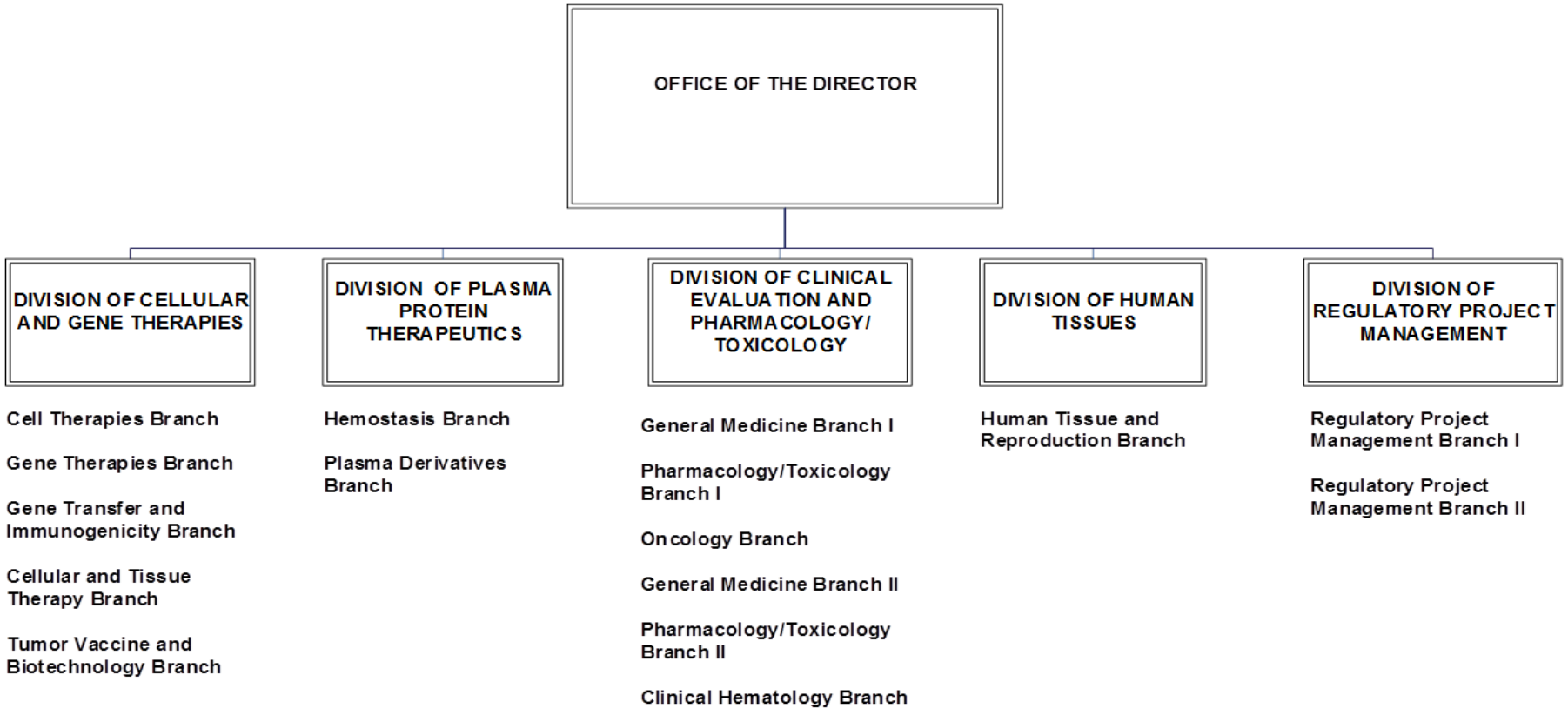
- Some complex biologic products such as cell and gene therapy products are defined by the process
- Complex aseptic manufacturing processes & facilities
- Extensive process controls, standards and assays
- Highest safety standards - given to healthy individuals
  - Vaccines (235 million), Blood (30 M), Tissues (>1 M)
- Market incentives may be weak
  - Income from the sale of all vaccines does not equal income from a single widely prescribed drug
  - Gene therapy for rare genetic diseases

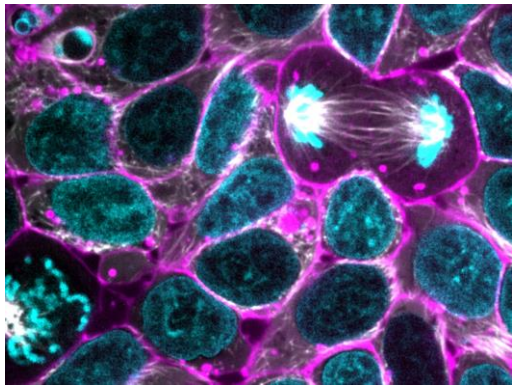
CBER Components

- Office of the Director
- Office of Biostatistics and Epidemiology
- Office of Blood Research and Review
- **Office of Tissues and Advanced Therapies**
- Office of Vaccines Research and Review
- Office of Compliance and Biologics Quality
- Office of Communication, Outreach and Development
- Office of Management

Office of Tissues and Advanced Therapies (OTAT)

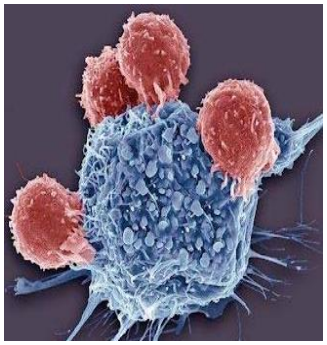
Previously Office of Cellular, Tissue and Gene Therapies (OCTGT)



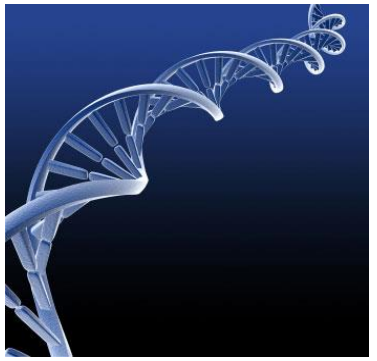


OTAT Products

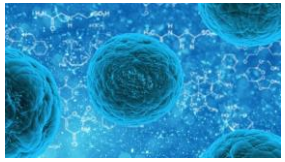
- Stem cell and stem cell-derived products
  - Hematopoietic, mesenchymal, cord blood, embryonic, iPSCs
- Somatic cell therapies
  - Pancreatic islets, chondrocytes, myoblasts, keratinocytes, hepatocytes
- Therapeutic vaccines and other antigen-specific active immunotherapies
  - Cancer vaccines and immunotherapies, such as dendritic cells, lymphocyte-based therapies, cancer cell-based therapies
  - Therapeutic vaccines, such as peptides, proteins, small molecules



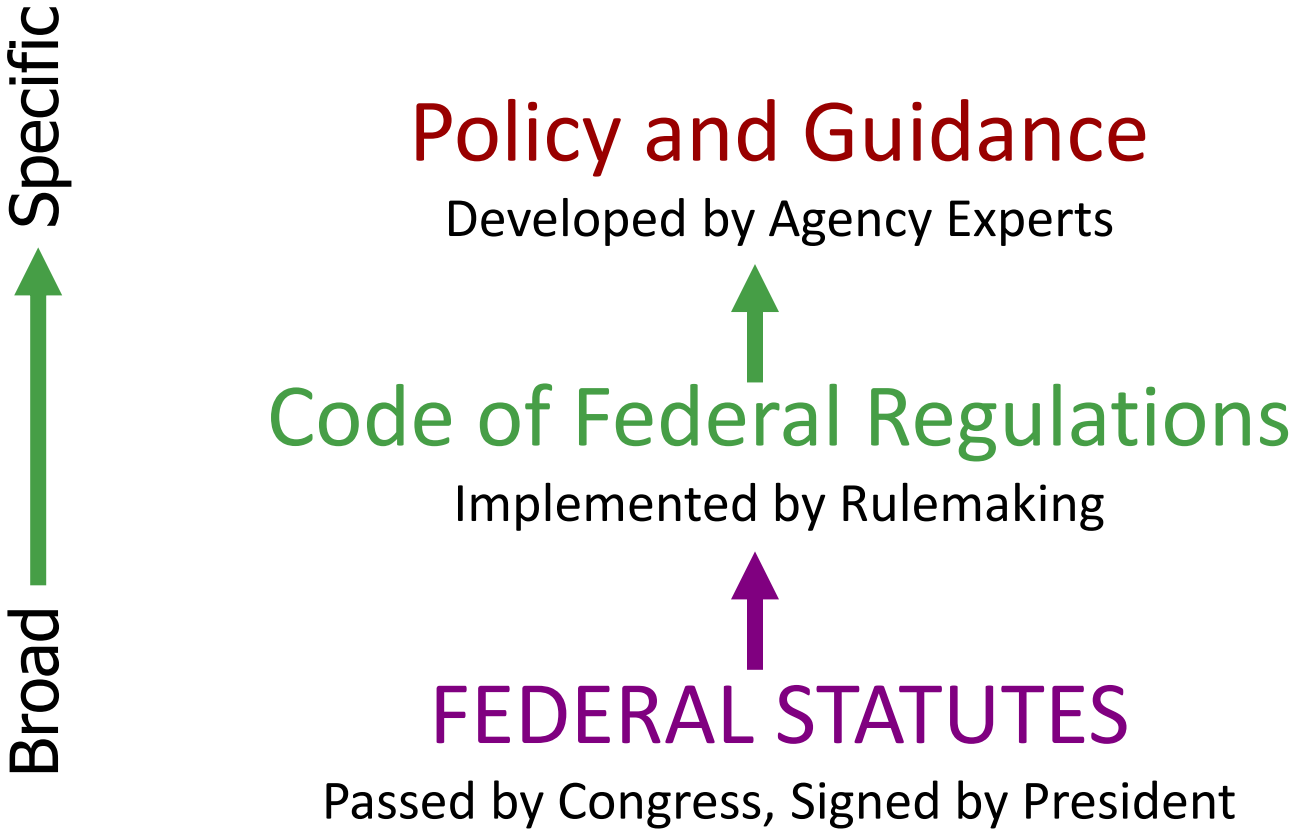
OTAT Products, Continued



- Gene therapies
  - Genetically modified cells e.g., CAR-T cells
  - Plasmids, viral vectors, bacterial vectors
- Xenotransplantation products
- Purified and recombinant proteins for hematology (e.g., coagulation factors, thrombin, botulism antitoxin, diphtheria anti-toxin, fibrin sealants)
- Antivenins
- Devices and combination products
  - Devices with a cellular component
  - Devices for the manufacture or delivery of cells



FDA Laws, Regulations, Policy



U.S. Paradigm for Medical Product Regulation

- **Centralized authority for oversight**
  - FDA oversees the **entire lifecycle** of a medical product from investigational product development to post-marketing surveillance/study
- **Applicable laws with enforcement provisions**
  - Medical products subject to laws and regulations regarding **clinical investigations** and **marketing authorization**
- **Documented policies and guidelines available to public**
  - Federal Register (FR)
  - FDA Guidance Documents
- **Transparency / forum for public discussion**
  - FDA advisory committees; FDA-sponsored public workshops
  - Formal interactions with NIH, NIST, USP, ICH, EMA and other governmental bodies

Biologics Approval

How is a Biologic Approved?

Biologics Approval

Be able to show:

- How you derived your Biologic Material
- How you make the Biologic Product
- How it works
- That it works
- That it is safe

Biologics Approval

Know the Regulations

National Archives and Records Administration

code of federal regulations

Biologic Regulations

Major biologic regulations (21 CFR §)

- General Provisions: 600
- Licensing: 601
- Current GMPs for Blood: 606
- General biologic standards: 610
- General requirements for blood: 630
- Additional standards: 640, 660, 680

Drug Regulations

Major Drug Regulations (21 CFR §)

- Labeling: 201
- Advertising: 202
- Registration and Listing: 207
- Current Good Manufacturing Practices: 211
- Investigational New Drug Application: 312
- New Drug Applications: 314
- Bioavailability/Equivalence 320

Biologics Approval

Guidance Resources:

CBER

http://www.fda.gov/cber/guidelines.htm

ICH Guidance

http://www.ich.org/cache/compo/276-254-1.html

Product Approval Steps

IND	Goal	Subjects
Phase I	Safety	10-20
Phase II	Dosing/Safety	~20 to 3-400
Phase III	Efficacy/Safety	Large Clinical Trial

BLA – Approval To Market

Post Market Post- Approval Commitments,
Product surveillance
Periodic inspections

Investigational New Drug (IND)

- An IND is required to conduct a clinical trial of an unapproved drug or an approved product for a new indication or in a new patient population
- IND regulations are in 21 CFR 312:
  - IND content and format, sponsor responsibilities, other
- Sponsor:
  - Responsible for the IND (initiates and conducts the clinical trial)
  - Sponsor can be a company, institution, or an individual investigator

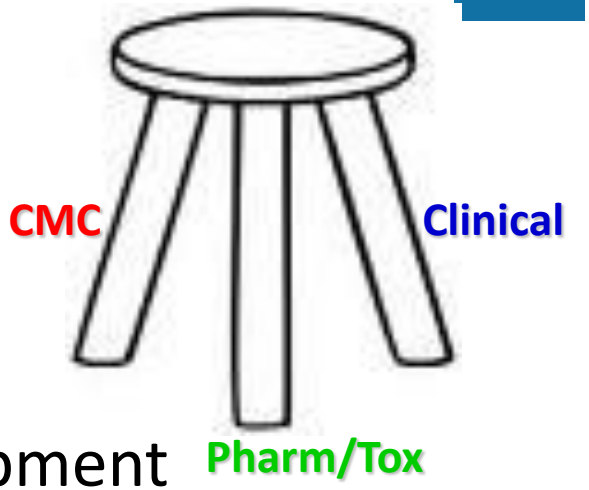
Objective of FDA Review

FDA's *primary* objectives in reviewing an IND are, in all phases of the investigation, *to assure the safety and rights of subjects*,

and, in Phase 2 and 3, to help assure that the quality of the *scientific evaluation* of drugs is *adequate to permit an evaluation of the drug's effectiveness and safety*.

[21 CFR 312.22(a)]

FDA Review of Safety and Effectiveness



- FDA review is product-based
  - Parallels prudent product development
  - Early interactions with sponsors facilitate effective product development
  - Detailed manufacturing information is needed during product development
  - Preclinical studies designed to support the use of specific products
  - Clinical trial design supported by manufacturing, preclinical data

Review Steps for a Product

- Pre-filing meeting with review team and sponsor
- Conduct preclinical studies
- File Investigational New Drug (IND) application
- Conduct clinical studies
- File marketing submission (BLA / 510(k) / PMA)
  - Conduct Facility Inspection
  - Conduct lot release activity
- Approve product
- Post Market Surveillance

Investigational New Drug (IND)

- Investigational plan
- Investigator's instructions
- Study protocols
- Manufacturing information
- Pharmacology / Toxicology
- Environmental information
- Previous human experience

http://www.fda.gov/cber/ind/ind.htm

http://www.fda.gov/cber/ind/indpubs.htm

Biologics License Application (BLA)

A request for permission to introduce, or deliver for introduction, a biologic product into interstate commerce

- Labeling
- Manufacturing information
- Clinical trial results
- Pharmacology / Toxicology
- Statistics
- Facility information

Product Approval and Beyond

- Pre-Approval Facility Inspection
- Lot Release (BLA)
- Postmarketing commitments
  - surveillance/adverse event reporting
- Manufacturing changes require prior approval
- Annual reporting; facility inspections

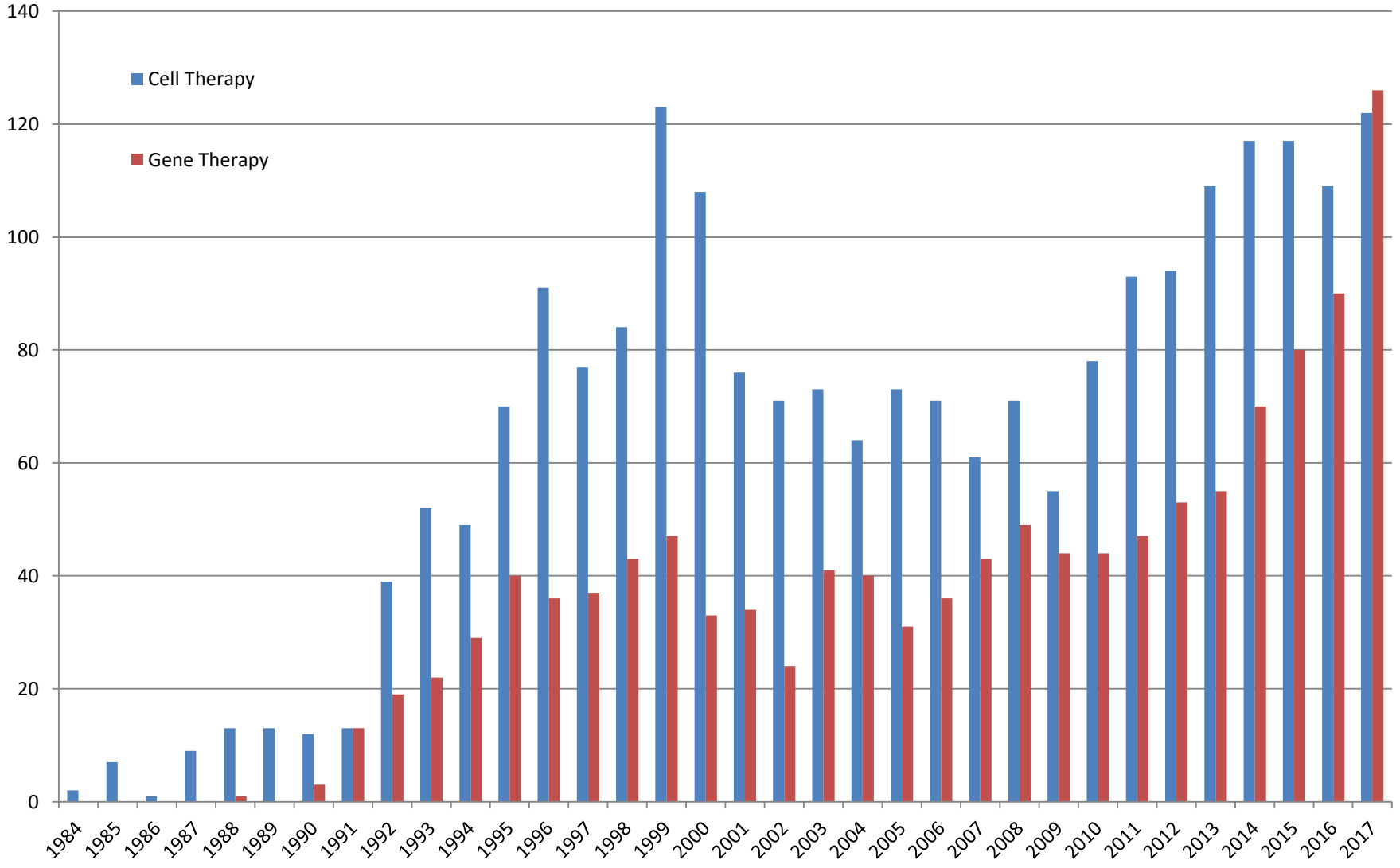
CBER's Unique Research

- Problem solving vs. discovery
- Performed by Researcher-Reviewers
  - Hundreds of applications (IND and BLA) have been *directly* supported by CBER research and expertise
- Driven by FDA's "big picture" perspective
- Not NIH research – may be done with NIH
- Regulatory science tackles public health issues

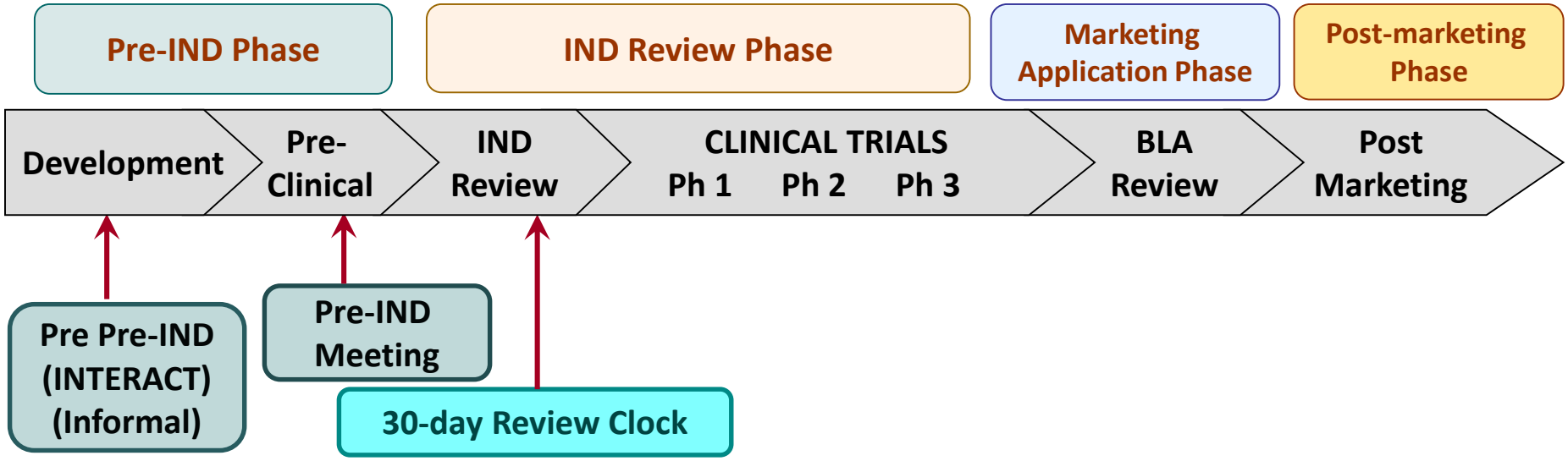
  - product class challenges
- Collaborates to access needed expertise

Regulatory Science is defined as: Development and use of the scientific knowledge, tools, standards, and approaches necessary for the assessment of medical product safety, efficacy, quality, potency, and performance.

INDs/IDEs Received per Calendar Year in OTAT



Opportunities for Pre-Submission Interaction with FDA



Product development is an iterative process involving FDA – sponsor interactions may occur over the entire life-cycle of product development, clinical testing, and license application including prior to the original IND submission.

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

Types of Pre-Submission Interactions

- **Pre-pre IND (INTERACT):** Informal, non-binding discussion, no meeting minutes generated
  - Requests for a pre-pre IND interaction are granted as FDA resources permit.

- Pre-IND / Type B –Formal Meeting, Minutes Generated, Non-Binding Recommendations: (http://www.fda.gov/downloads/Drugs/Guidances/ucm153222.pdf)
  - Sponsors and CBER/FDA staff discuss product development activities prior to submission of an Investigational New Drug application (IND): may touch on CMC, Preclinical and Clinical topics
  - Represents a key juncture in the regulatory process
  - ***Rule of Thumb:*** Grant one Type B / pre-IND meeting prior to the submission of an IND: Exceptions do occur when circumstances dictate. Follow-up communication/interaction is not uncommon.

Food and Drug Administration Safety and Innovation Act (FDASIA)

- Signed into law July 9, 2012
- Fifth reauthorization of PDUFA
- Section 901: Enhancement of Accelerated Patient Access To New Medical Treatments
  - Clarifies provisions and encourages expanded use and scope, listing types of evidence FDA can rely upon
- Section 902: Breakthrough Therapies
  - New designation with goal of expediting development of drugs that offer substantial improvement over existing therapies

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)

Comparison of Expedited Programs for Serious Conditions

	Fast Track (FT)	Breakthrough Therapy (BT)	Accelerated Approval (AA)	Priority Review (PR)
Criteria	**Serious Condition** -Nonclinical or clinical data demonstrate the potential to address unmet medical need Note: Information to demonstrate potential depends upon stage of development at which FT is requested	**Serious Condition** Preliminary clinical evidence indicates that the drug may demonstrate **substantial improvement over available therapy on one or more clinically significant endpoints**	**Serious Condition** Meaningful advantage over available therapies Demonstrates an **effect on** either a **surrogate endpoint** or **an intermediate clinical endpoint**	**Serious Condition** Demonstrates **potential to be a significant improvement in safety or effectiveness**

Comparison of Expedited Programs

	Fast Track (FT)	Breakthrough Therapy (BT)	Accelerated Approval (AA)	Priority Review (PR)
Features	**Frequent Meetings** Frequent written communication Eligible for *: • **Accelerated Approval** • **Priority Review** **Rolling Review** *if relevant criteria are met	**All of FT Features +** • **Intense guidance** on an efficient drug development program, beginning as early as Phase 1 • Organizational commitment **involving senior managers**	Approval based on surrogate or intermediate clinical endpoints* • **Save valuable time** in the drugs approval process • **Reduce waiting period to obtain clinically meaningful benefit** * AA will include PMR for a confirmatory study	• **Shorter Review Clock** • **FDA will take action on an application with 6 months** (compared to 10 months under standard review)

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

Breakthrough Therapy

Benefits:

Intent is to expedite the development and review of a drug.

- Intensive guidance on efficient drug development
- Organizational commitment
- Other actions to expedite review (e.g., rolling review)

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

- Signed into law December 13, 2016
- Section 3033: Accelerated Approval for Regenerative Advanced Therapies
- Creates program for designation as a regenerative medicine advanced therapy

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

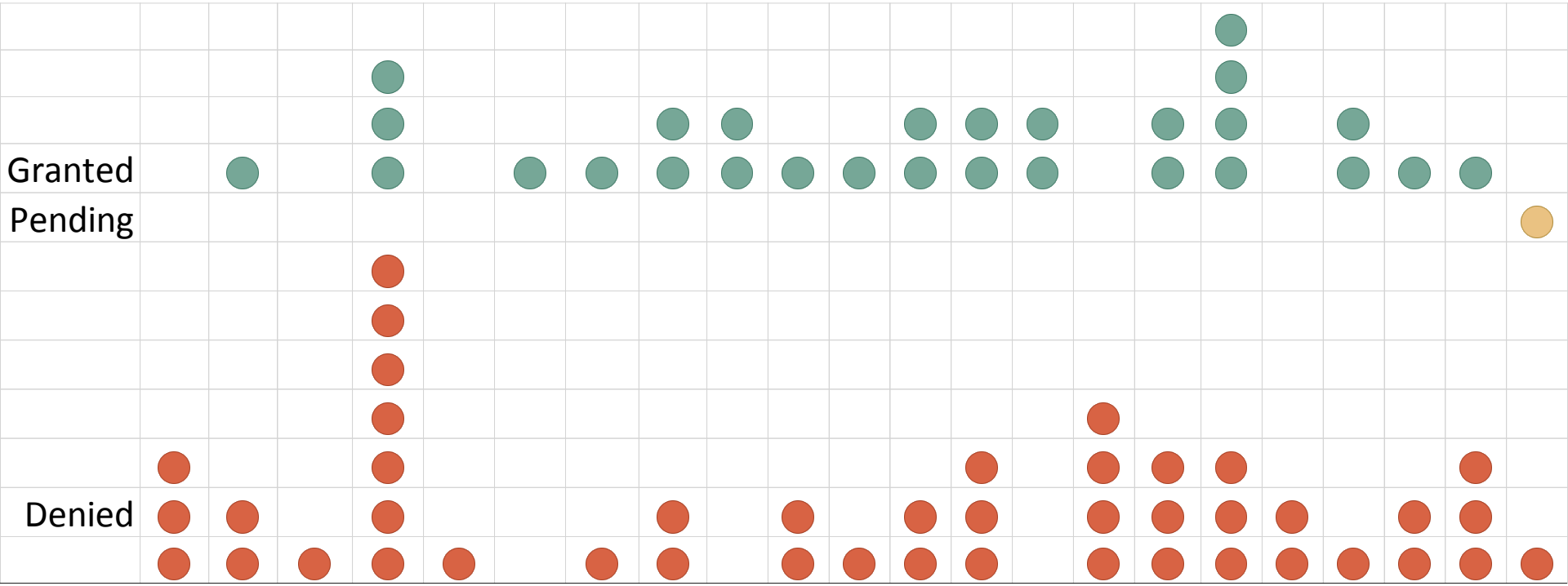
- Interactions with FDA to expedite development and review of regenerative medicine advanced therapies
  - Benefits available to breakthrough therapies
  - Including early discussions of any potential surrogate or intermediate endpoints to support accelerated approval

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

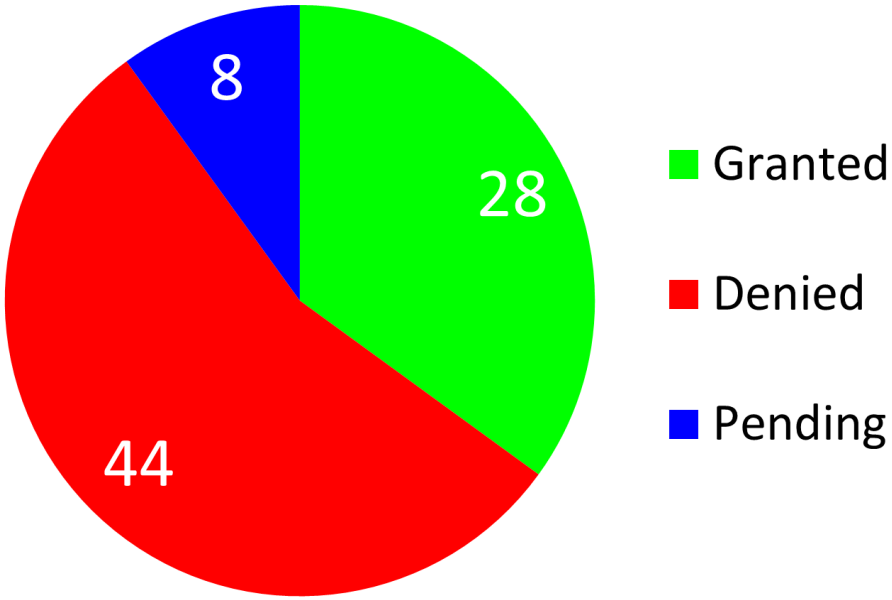
- as of November 06, 2018



12/13/2016 – 11/06/2018

RMAT Designation Requests

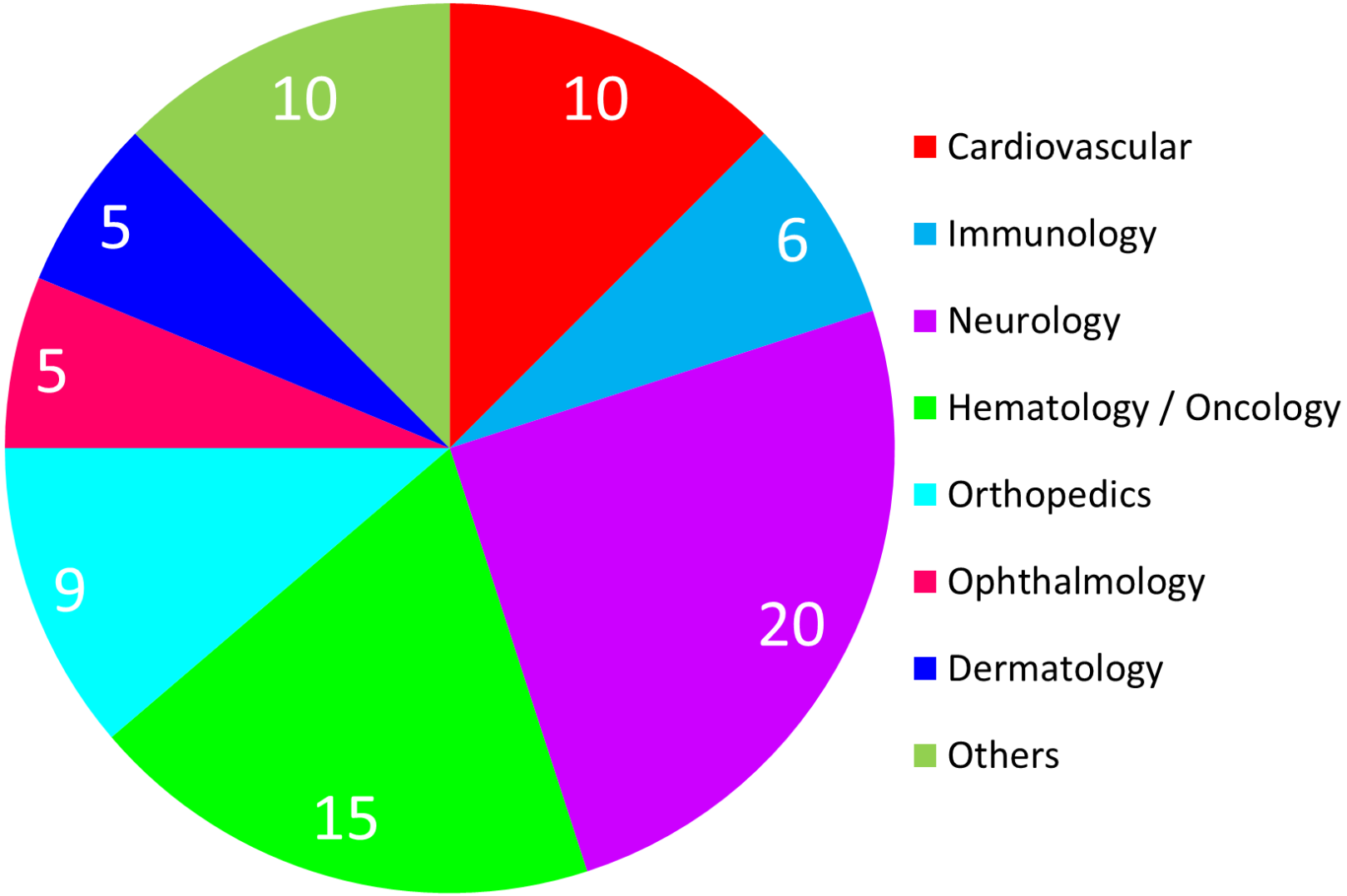
Status as of November 06, 2018



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



Proposal to Amend NIH Guidelines Related to Human Gene Transfer

- August 17, 2018/83 FR 41082
- Streamline oversight for human GT clinical research protocols
  - Eliminate RAC protocol review
  - Eliminate reporting requirements to NIH, including adverse events
  - Modify roles and responsibilities of investigators, institutions, IBCs, the RAC, and NIH
- Submit comments by October 16, 2018

41082 Federal Register / Vol. 83, No. 160 / Friday, August 17, 2018 / Notices

humans or animal models that could be addressed with new technologies.
• Considerations for data sharing infrastructure and policies.
• Areas and topics for research on the ethical implications of BRAIN Initiative-supported emerging neurotechnologies and advancements and their applications.
• Approaches for disseminating new tools and technologies as well as training the broader neuroscience research community.
• Any other topic relevant to the strategic plan of the BRAIN Initiative.
Responses to this RFI are voluntary. Any personal identifiers will be removed when responses are compiled. Individual feedback will not be provided to any responder. Proprietary, classified, confidential, or sensitive information should not be included in your response. This Request for Information (RFI) is for planning purposes only and is not a solicitation for applications or an obligation on the part of the United States (U.S.) Government to provide support for any ideas identified in response to it. Please note that the U.S. Government will not pay for the preparation of any comment submitted or for its use of that comment.

Dated: August 10, 2018.

Lawrence A. Tabak,

Deputy Director, National Institutes of Health.

[FR Doc. 2018–17759 Filed 8–16–18; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Institutes of Health (NIH) Office of Science Policy (OSP) Recombinant or Synthetic Nucleic Acid Research: Proposed Changes to the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)

AGENCY: National Institutes of Health, HHS.

ACTION: Notice.

SUMMARY: The National Institutes of Health (NIH) seeks public comment on its proposal to amend the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)* to streamline oversight for human gene transfer clinical research protocols and reduce duplicative reporting requirements already captured within the existing regulatory framework. Specifically, NIH proposes amendments to: Delete the NIH protocol registration submission and reporting requirements under Appendix M of the *NIH Guidelines*, and modify the roles and responsibilities of entities that involve human gene transfer or the Recombinant DNA Advisory Committee (RAC).

DATES: To ensure consideration, comments must be submitted in writing by October 16, 2018.

ADDRESSES: Comments may be submitted electronically by visiting: *https://osp.od.nih.gov/comment-form-nih-guidelines/*. Comments may also be sent via fax to 301–496–9839, or by mail to the Office of Science Policy, National Institutes of Health, 6705 Rockledge Drive, Suite 750, Bethesda, Maryland 20892–7985. All written comments received in response to this notice will be available for public inspection at NIH Office of Science Policy (OSP), 6705 Rockledge Drive, Suite 750, Bethesda, MD 20892–7985, weekdays between the hours of 8:30 a.m. and 5 p.m. and may be posted without change, including any personal information, to the NIH OSP website.

FOR FURTHER INFORMATION CONTACT: If you have questions, or require additional background information about these proposed changes, please contact the NIH by email at *SciencePolicy@od.nih.gov*, or telephone at 301–496–9838. You may also contact Jessica Tucker, Ph.D., Director of the Division of Biosafety, Biosecurity, and Emerging Biotechnology Policy, Office of Science Policy, NIH, at 301–451–4431 or *Jessica.Tucker@nih.gov*.

SUPPLEMENTARY INFORMATION: NIH is proposing a series of actions to the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)* to streamline oversight of human gene transfer research (HGT), and to focus the *NIH Guidelines* more specifically on biosafety issues associated with research involving recombinant or synthetic nucleic acid molecules. The field of HGT has recently experienced a series of advances that have resulted in the translation of research into clinical practice, including U.S. Food and Drug Administration (FDA) approvals for licensed products. Additionally, oversight mechanisms for ensuring HGT proceeds safely have sufficiently evolved to keep pace with new discoveries in this field.

At this time, there is duplication in submitting protocols, annual reports, amendments, and serious adverse events for HGT clinical protocols to both NIH and FDA that does not exist for other areas of clinical research. Historically, this duplication was conceived as harmonized reporting, enabling FDA to provide regulatory oversight while NIH provided a forum for open dialogue and transparency. However, since these complementary functions were first envisioned, we have now seen several converging systems emerge that provide some of these functions. For instance, *ClinicalTrials.gov* has been instituted, which provides a transparent and searchable database for clinical trials. In addition, the protection of human research subjects was improved through changes that updated provisions of the Common Rule. In 2018, FDA released a suite of draft guidance documents pertaining to gene therapy that includes new guidance on manufacturing issues, long-term follow-up, and pathways for clinical development in certain areas, including hemophilia, ophthalmologic indications, and rare diseases.

While the science and oversight system have evolved, HGT protocols continue to receive special oversight that is not afforded to other areas of clinical research. This observation was also noted in a 2014 Institute of Medicine of the National Academies report, *Oversight and Review of Clinical Gene Transfer Protocols: Assessing the Role of the Recombinant DNA Advisory Committee*, in which it was recommended that NIH begin to limit RAC review to only exceptional HGT protocols that meet certain criteria and that would significantly benefit from RAC review. As very few protocols have been assessed by NIH to merit review under this new system, NIH asserts it is an opportune time to make changes to the *NIH Guidelines* to make oversight of HGT commensurate with oversight afforded to other areas of clinical research given the robust infrastructure in place to oversee this type of research.

Briefly to summarize, NIH proposes amending the *NIH Guidelines* to:

1. Eliminate RAC review and reporting requirements to NIH for HGT protocols.
2. Modify roles and responsibilities of investigators, institutions, IBCs, the RAC, and NIH to be consistent with these goals including:
   a. Modifying roles of IBCs in reviewing HGT to be consistent with review of other covered research, and
   b. Eliminating references to the RAC, including its roles in HGT and biosafety.

NIH suggests that the series of changes proposed in this Notice is a rational next step in the process of considering appropriate oversight of HGT. Consistent with these proposed changes to the *NIH Guidelines*, Section I–A, the Purpose of the *NIH Guidelines*, is proposed to be amended to clarify that the focus of the policy is biosafety

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

Summary

- CBER products are diverse and rapidly evolving. They require new regulatory paradigms which are developing rather than established
- Sponsors are encouraged to refer to:
  - Guidance documents and educate themselves
  - Communicate with CBER staff
  - Start solving the problems early: plan ahead
  - Keep good records
- Our scientists facilitate development of, approval of, and access to safe and effective medical products
- Scientists also performs Regulatory Science related research: fill gaps, deal with scientific challenges, figure out what is important

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

OTAT Learn Webinar Series

- Introduction and Scope of OTAT
- IND Basics in OTAT
- Sponsor Meetings with OTAT
- “361” Human Cells, Tissues, & Cellular and Tissue-Based Products
- The Chemistry, Manufacturing and Controls (CMC) Section of a Gene Therapy IND
- Advanced Topics: Successful Development of Quality Cell and Gene Therapy Products
- Cellular Therapy Products
- Advanced topics: Design and Analysis of Shedding Studies
- Advanced Topics: Determining the Need for and Content of Environmental Assessments for Gene Therapies, Vectored Vaccines and Related Recombinant Viral Vectors or Microbial Products
- Preclinical Considerations for Products Regulated in OTAT
- Regulatory Obligations for Investigator-Sponsored Research
- Fast Track (FT) for Products Regulated in OTAT
- Endpoint Assessment and Adjunction Committees (EAACs)

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FDA Headquarters

- **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

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Common Reasons for BTDR Denial

- Evidence is too preliminary (quantity and/or quality) to be considered reliable
  - Small sample size
  - Lack of appropriate control
  - Post-hoc analyses of failed studies that identify a subset that may benefit
- Improvement over available therapy does not appear to be "substantial"
- Modification of product

Cumulative Overview of BTD and RMAT Designation Requests (excluding withdrawn and pending request)