



# Regenerative Medicine, Gene Therapies, and FDA Regulation

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and Popeo, PC



# Regenerative Medicine, Gene Therapies, and FDA Regulation

May 3, 2019

# Session Outline

- Overview of FDA's Comprehensive Regenerative Medicine Regulatory Framework
- Update from CBER Deputy Director Dr. Celia Witten
- Industry Perspectives
  - Clinical Research and Patient Registries (Marc Scheineson)
  - Expedited Approval and Commercialization Challenges (Michael Werner)
- Discussion among panelists and with audience members

# FDA's Comprehensive Framework

- First announced in August 2017 and fleshed out in November
- Two parallel initiatives – (1) increasing regulatory certainty and clarifying approval pathways for legitimate product development; and (2) enforcing HCT/P legal requirements against “unscrupulous actors”
- Following years of Agency inertia, there has been a rapid advancement of new policies and other actions on the heels of Dec. 2016 Cures Act, which created the RMAT Designation (“Regenerative Medicine Advanced Therapy”) and signaled Congress’s directive to focus agency resources on the field.

# FDA's Comprehensive Framework

1. **Increasing regulatory certainty and clarifying approval pathways for legitimate product development**
  - INTERACT Program (“Initial Targeted Engagement for Regulatory Advice on CBER Products”)
  - Guidance on and implementation of the RMAT Designation
  - Multiple draft guidance documents on FDA’s expectations for Gene Therapy products, expected to be finalized this year
  - Announcement of cellular therapy and clinical guidance documents that are in development, as well as plans for a future public meeting on manufacturing changes
  - “Clinical Trial Endpoints for Approval of Cancer Drugs and Biologics”

# FDA's Comprehensive Framework

## 2. Enforcing HCT/P legal requirements against “unscrupulous actors”

- Multiple (5) warning letters and 2 federal complaints seeking permanent injunctions – issued based on a risk continuum
- Larger number (~45) of “It Has Come to Our Attention” letters seeking to educate product developers about their obligations
- Three-year enforcement discretion period (through November 2020) for non-compliant entities to obtain INDs or BLAs or to otherwise engage with CBER on development plan

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# Regenerative Medicine, Gene Therapies, and FDA Regulation

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FDLI

May 3, 2019

Washington, D.C.

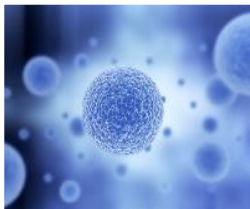
# Outline

- CBER Overview
- Regenerative Medicine
- Gene Therapy Update
- Other Initiatives

# Promoting Product Development

- An increasingly important part of FDA's mission is to facilitate the development and approval of innovative products that address unmet medical needs

# What Products Does CBER Regulate?



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

# 21<sup>st</sup> Century Cures Act: 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

# Regenerative Medicine Advanced Therapy Designation

- 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 the drug has the potential to address unmet medical needs for such disease or condition

# Regenerative Medicine Therapies

- 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 sustained effect on cells or tissues

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



# Regenerative Medicine Standards

- Contract with Nexight Group and the Standards Coordinating Body (SCB) to coordinate community efforts towards the development of standards for regenerative medicine advanced therapies
  - Develop processes to identify, prioritize, and assess the feasibility for the development and implementation of specific standards
  - Regenerative Medicine Standards Landscape, published February 2018
    - <http://nexightgroup.com/projects/identifying-regenerative-medicine-standards-and-standard-development-processes/>
- CBER Standards Guidance: *Standards Development and the Use of Standards in Regulatory Submissions Reviewed in the Center for Biologics Evaluation and Research*, March 2019

# Suite of Regenerative Medicine Guidance Documents

1. Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception – Final
2. **Regulatory Considerations for Human Cell, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use – Final**
3. Evaluation of Devices Used with Regenerative Medicine Advanced Therapies – Final
4. Expedited Programs for Regenerative Medicine Therapies for Serious Conditions – Final

<https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/default.htm>

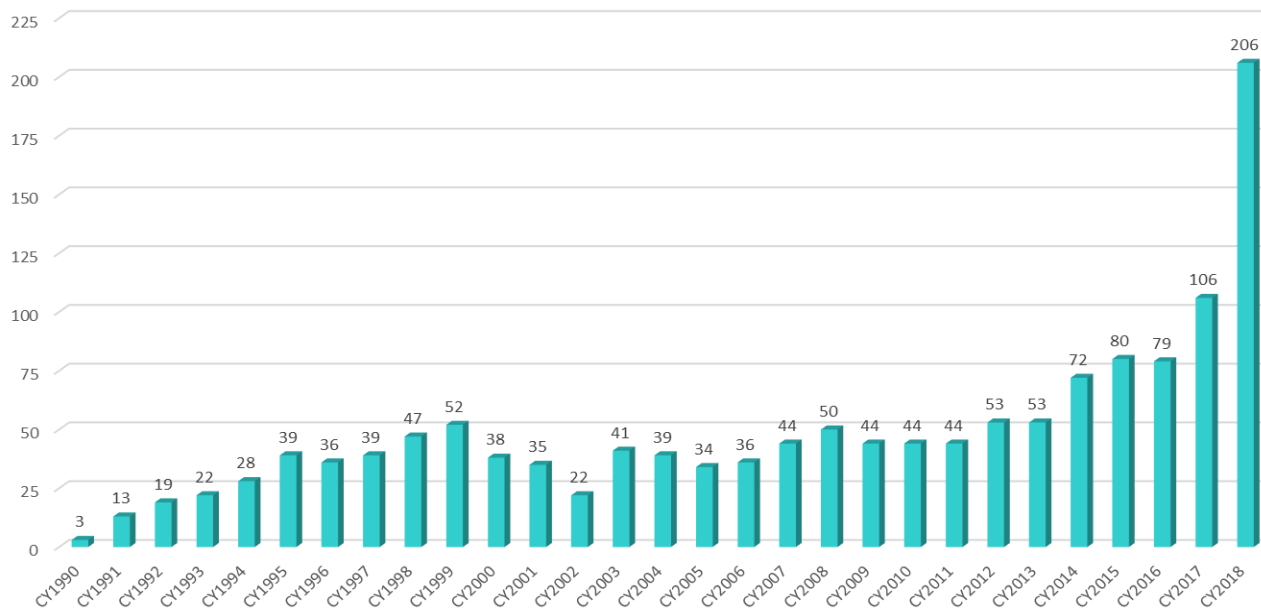
# Regulatory Considerations for Human Cell, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use

- Compliance and enforcement policy provides manufacturers time to determine if they need to submit an IND or marketing application and submit such application when use of the HCT/P does not raise reported safety concerns or potential significant safety concerns
- FDA to focus enforcement actions on products with higher risk, including based on the route and site of administration
  - Routes of administration associated with higher risk prioritized over those associated with lower risk
    - Higher risk: IV injection or infusion, aerosol inhalation, intraocular injection, or injection or infusion into the central nervous system
    - Lower risk: intradermal, subcutaneous, or intra-articular injection
  - HCT/Ps intended for non-homologous use, particularly those intended to be used for the prevention or treatment of serious and/or life-threatening diseases and conditions

# How Can Sponsors Determine How Their Product is Regulated

- FDA's HCT/Ps regulations, which have been fully effective since May 2005, outline the criteria to determine how HCT/Ps are appropriately regulated
- The 2017 FDA guidance documents were intended to facilitate stakeholder's understanding of how the criteria apply but do not change the regulatory status of any products
- FDA will not notify stakeholders about how products are appropriately regulated. Instead, stakeholders are expected to continue to self-determine the appropriate regulatory status
- FDA provides manufacturers several ways to obtain information about the regulatory status of a product:
  - Tissue Reference Group (TRG) provides product sponsors with an informal process through which they may obtain an Agency recommendation regarding the application of the criteria in 21 CFR 1271.10(a) to their HCT/P for a given indication <http://www.fda.gov/biologicsbloodvaccines/tissuetissueproducts/regulationoftissues/ucm152857.htm>
  - Request for Designation (RFD) process may be used to obtain a formal Agency decision regarding the regulatory identity or classification of an HCT/P <https://www.fda.gov/CombinationProducts/RFDProcess/default.htm> and <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126053.htm>
  - Pre-RFD to obtain preliminary feedback on the classification of an HCT/P as well as assistance on how to prepare an RFD <https://www.fda.gov/Regulatoryinformation/Guidances/ucm126053.htm>

# New Gene Therapy Product IND Submissions (1990-2018)



# 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

<https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/default.htm>

## New Initiatives

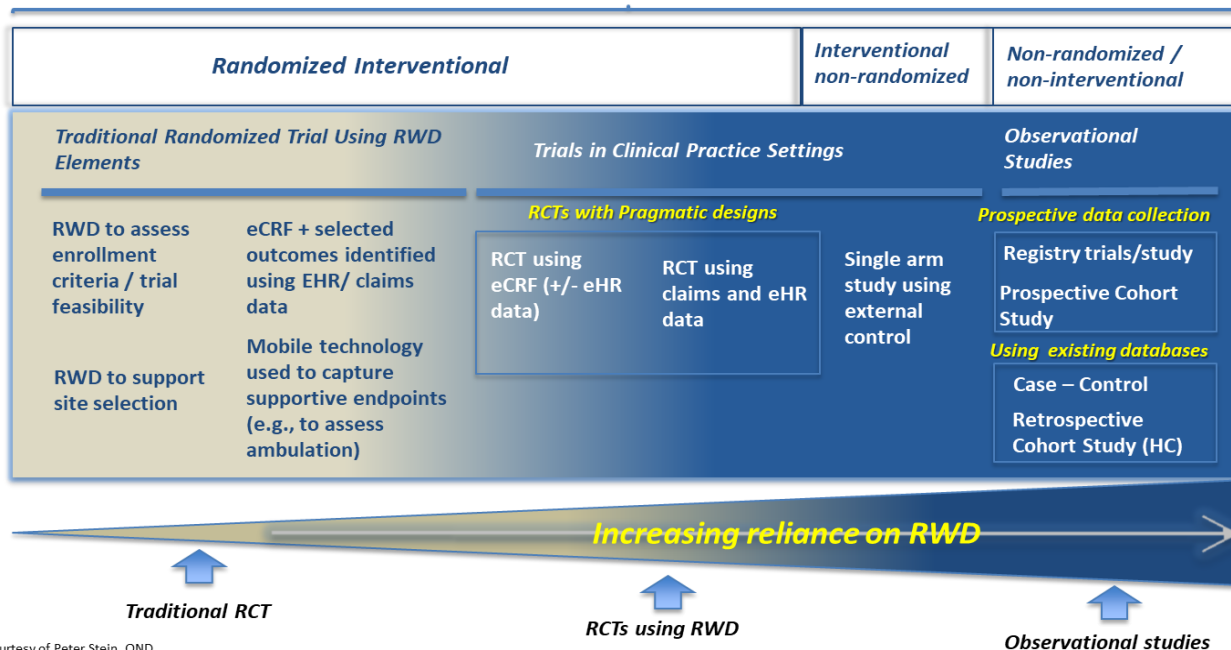
- INTERACT meetings
- Advanced Manufacturing
- Real World Evidence
- Medical Product Development Tools
- Patient Engagement

# Advancing New Drug Therapies: Advanced Manufacturing

- Why advanced manufacturing? Products may require complex manufacturing processes, advanced manufacturing may bring new tools to address:
  - Flexibility
  - Availability
  - Scalability
  - Cost
- What do we mean by advanced manufacturing? Innovative technologies that could include:
  - Cell culture systems supporting large scale or rapid production
  - Enabling tools such as measurement technology



# Wide Spectrum of Potential Uses of RWD / RWE in Clinical Studies



Courtesy of Peter Stein, OND

# Advancing New Drug Therapies: Medical Product Development Tools

- Methods, materials, and measures that can potentially facilitate drug (biological product) development
- May be developed, qualified, and/or used within individual product programs OR outside any specific product development in the pre-competitive space through the existing regulatory qualification programs
  - Animal Model Qualification Program
  - Biomarker Qualification Program
  - Clinical Outcomes Assessment Qualification Program
  - <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm335850.htm>

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## Patient Engagement @ CBER

Activities involving patient stakeholders sharing their experiences, perspectives, needs, and priorities to help inform FDA's public health mission.

## Products CBER regulates

- Allergens
- Blood and blood products
- Gene therapy products
- Human tissue and cellular products
- Vaccines
- Xenotransplantation
- Certain medical devices

## CBER engagement with individuals with rare diseases and caregivers\*

### Patient-Focused Drug Development meetings:

- Alpha-1 antitrypsin deficiency
- Alport syndrome
- Amyotrophic lateral sclerosis
- Barth syndrome
- Charcot-Marie-Tooth
- Cystic fibrosis
- Duchenne muscular dystrophy
- Epidermolysis bullosa
- Friedrich ataxia
- Hemophilia A and B, von Willebrand & other heritable bleeding disorders
- Hereditary angioedema
- Juvenile idiopathic arthritis
- Pachyonychia congenita

### Patient group meetings:

- Angelman syndrome
- Biliary atresia
- Microtia and atresia
- Myotonic dystrophy
- Pemphigoid and pemphigus
- Progressive familial intrahepatic cholestasis
- Sanfilippo syndrome
- Sickle cell anemia
- Wilson disease

### NORD/FDA Listening Sessions:

- Congenital hyperinsulinism
- Fabry disease
- Hemophilia and gene therapy

\* Examples of CBER patient engagement activities between 2013 and 2019

## Share your knowledge and health experiences with CBER

Patients provide an important and unique perspective that is critical for consideration as part of the regulatory process. We highly value patient engagement and its contribution to the development of biological products.



### Impact of the disease and its treatment

- chief complaints (most bothersome signs/symptoms)
- burden of living with and managing a disease or condition
- impacts from disease or condition on activities of daily living and functioning



### Perspectives about current and potential treatment approaches

- expectations of benefits
- tolerance for harms or risks
- patient preference
- unmet medical needs



### Clinical trial considerations

- e.g., views on gene therapy
- burden of participating in clinical studies
- risk tolerance

## How to provide your unique perspective to CBER

- Participate in FDA Advisory Committee meetings
- Submit comments on guidance documents and proposed rules to [regulations.gov](https://www.fda.gov/regulations)
- Attend product meetings upon invitation of the product developer
- Attend FDA public meetings in person or via remote access
- Participate in a NORD/FDA listening session
- Interact with FDA via social media
- Become an FDA patient representative
- Coordinate an externally-led Patient-Focused Drug Development meeting: <https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm453856.htm>
- Patient groups can request a meeting with CBER by emailing: [CBERPatientEngagement@fda.hhs.gov](mailto:CBERPatientEngagement@fda.hhs.gov)

## CBER's Patient Engagement groups

### CBER Patient Engagement Workgroup

- Staff share knowledge and input on CBER's patient engagement activities

### CBER Rare Disease Coordinating Committee

- Facilitates and advances the development and timely approval of safe and effective biologics to improve the lives of children and adults with rare diseases

### Science of Patient Input (SPI) Initiative

- supports incorporation of patient perspectives into CBER's regulatory framework

## Agency-wide coordination

CBER works closely with patient engagement staff across the FDA to maximize opportunities for CBER staff to hear the patient's voice. This includes participation in:

- Regular cross-center coordination meetings
- Public workshops
- Patient-Focused Drug Development meetings
- FDA's Patient Representatives program
- FDA's Patient Engagement Collaborative
- NORD/FDA Listening Sessions
- Guidance development

## Resources

- CBER Website  
<https://www.fda.gov/biologicsBloodVaccines/default.htm>
- Learn About FDA Patient Engagement  
<https://www.fda.gov/forpatients/patientengagement/default.htm>
- Patient-Focused Drug Development  
<https://www.fda.gov/drugs/developmentapprovalprocess/ucm579400.htm>

## 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

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# 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](mailto:ocod@fda.hhs.gov)
- **Manufacturers Assistance and Technical Training Branch (MATTB)**  
Email: [industry.biologics@fda.gov](mailto:industry.biologics@fda.gov)
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# Regenerative Medicine, Gene Therapies and FDA Regulation Enforcement, INDs and Registries

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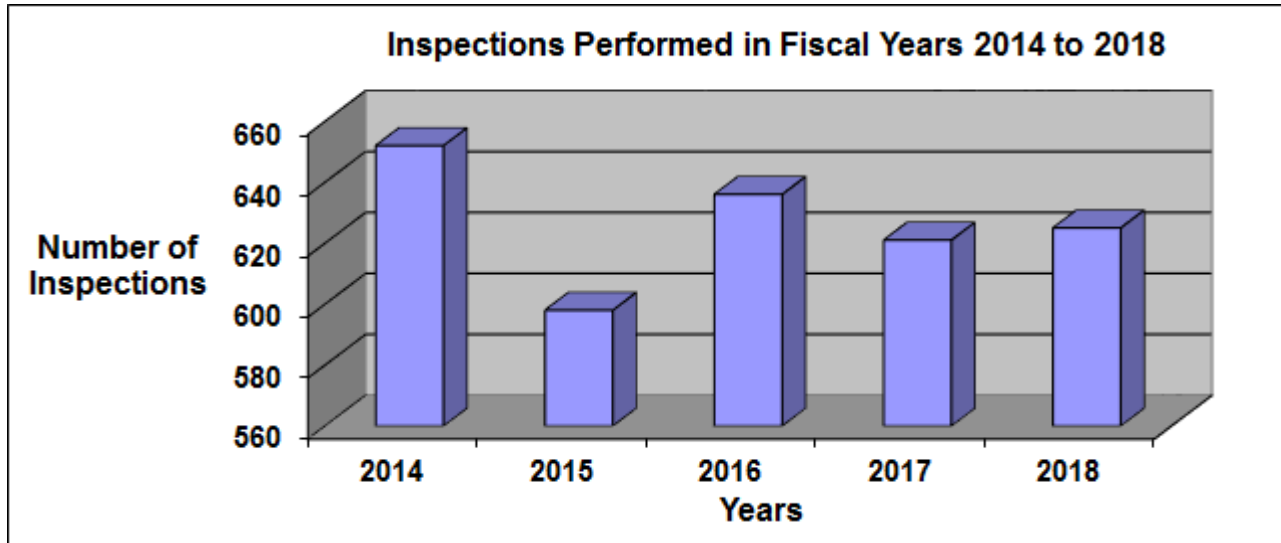
# Current Dilemma Facing FDA-CBER

- Approximately 6,770 clinical studies currently listed on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) investigating use of stem cells
- Over 400 stem cell clinics operating in the U.S.; most without FDA registration or Part 1271 compliance
- Another 1,000+ stem cell clinics operating OUS recruiting U.S. patients for “medical tourism”
- Interpretation of “homologous use” and “more than minimally manipulated” remains ambiguous
- Clinics and researchers generating vast amounts of clinical data concerning tens of thousands of procedures; data not being adequately documented, reported, correlated, submitted or reviewed by FDA

## Current Dilemma Facing FDA-CBER (cont.)

- Guidance issued to expedite INDs and treatment for “minimally manipulated, unrelated allogeneic placental, umbilical cord intended for hematopoietic and immunologic reconstruction in patients with disorders affecting hematopoietic system” (3/14)
- Final FDA stem cell guidance issued for:
  - Minimal Manipulation and Homologous Use
  - Same Surgical Procedure
- FDA shut down use of stem **cells** derived from adipose tissue (stromal stem cells, mesenchymal stem cells (MSCs), etc.) unless use reflected function of underlying **tissue** (structural support of cushioning)
- Use of cord blood stem cells (hematopoietic) permitted with less Agency oversight, at least for blood diseases

# HCT/P Inspections Performed for FY 2014-2018



## Current Dilemma Facing FDA-CBER (cont.)

- Part 1271 defines “minimal manipulation” as:
  - For **structural tissue**-processing that does not alter original relevant characteristics of tissue...
  - For **cells** or non structural tissues, processing that does not alter the relevant biological characteristics of the cells or tissues
- FDA could have viewed extraction and separation of MSC cells independently from underlying function of structural tissue, where **cells** are intended product and not **tissue** from which harvested

## Current Dilemma Facing FDA-CBER (cont.)

- Same Surgical Procedure Final Guidance
  - Processing must be limited to “rinsing, cleansing, sizing or shaping” to qualify for exemption to §1271
  - Any use of enzymes or other medium to isolate adipose (or other tissue)-derived MSCs from tissue, or to effectuate proliferation or differentiation, disqualifies procedure from exemption

## Current Dilemma Facing FDA-CBER (cont.)

- Guidance “closed a door” but “opened a window”
- Unclear if “window opened wide enough”
- FDA provided that over next 36-mos. (until Nov. 17, 2020) will exercise enforcement discretion under limited conditions for IND applications and BLA requirements for certain HCT/Ps
- Contemporaneous lawsuits seeking injunctions against *U.S. Stem Cell Clinic* (Sunrise, FL) and *CA Stem Cell Treatment Center* (Rancho Mirage and Beverly Hills, CA)
- Recent Warning Letters to Genetech, Inc. (CGTP concerns) and Cord-for-Life, Inc. (bacterial contamination )

# Challenges with Current Recommendations

- Requirement for each establishment to apply for BLA misguided
  - Risk and complexity based assessments of products should be undertaken
  - For low risk products, registration and reporting to registry enough
  - For high risk, high complexity products, BLA should be required
- Using 'identical' manufacturing at multiple sites unlikely

# How Does FDA Benefit from Registry?

- Allows responsible and accountable third-party to set standards, compile information, data, AERs and “separate wheat from chaff”
  - Researchers and clinics encouraged to register with third-party
  - Registry information available to FDA
  - Information shared to support INDs; protocol design and post-market surveillance
  - Unapproved treatment converted into monitored research
  - Provides accurate “snap shot” of 1271 and unapproved use
  - Reduces consumption of limited Agency resources for enforcement and investigational review
  - Compliant clinics most likely to register; unregistered clinics focus of enforcement



# What Does FDA Give in Exchange?

- Sponsors won't register unless see some benefit
- Paradigm similar to FDA regulation/oversight of bone marrow, cord blood and organ banks
- FDA recognition of stem cell registry as accepted voluntary third-party regulatory standard
- Registered research programs not Agency enforcement priority “within enforcement discretion” as long as IND filed by 11/17/20
- Agency statement or guidance that registered programs using same treatment protocol for same intended use may participate in blanket IND/IDE
- Understanding that human registry data, if compiled consistently with FDA IND/IDE rules, could eliminate need for pre-clinical animal toxicology data to support IND/IDE approval



# Expedited Approval for Regenerative Medicine Therapies: RMAT Status and Commercialization Issues

Michael J. Werner  
Partner, Holland & Knight

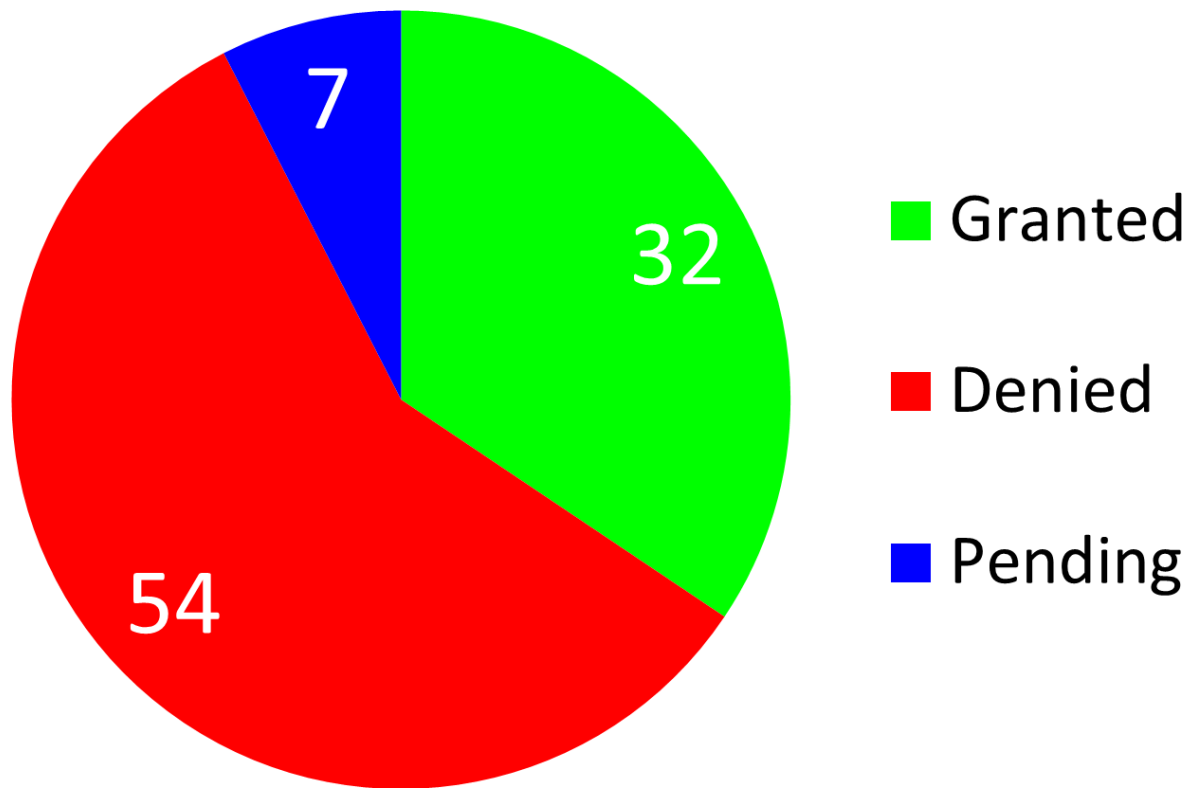
# Section 3033 of 21<sup>st</sup> Century Cures Act

- Created a new designation for a regenerative medicine advanced therapy
- Defined a “regenerative medicine therapy” and establishes an accelerated approval pathway for a drug that qualifies.
- **Regenerative medicine therapy** - “**cell therapy**, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products”
- Drug is eligible if:
  - Regenerative medicine therapy, *and*
  - Intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; *and*
  - Preliminary clinical evidence indicates the potential to address unmet medical needs

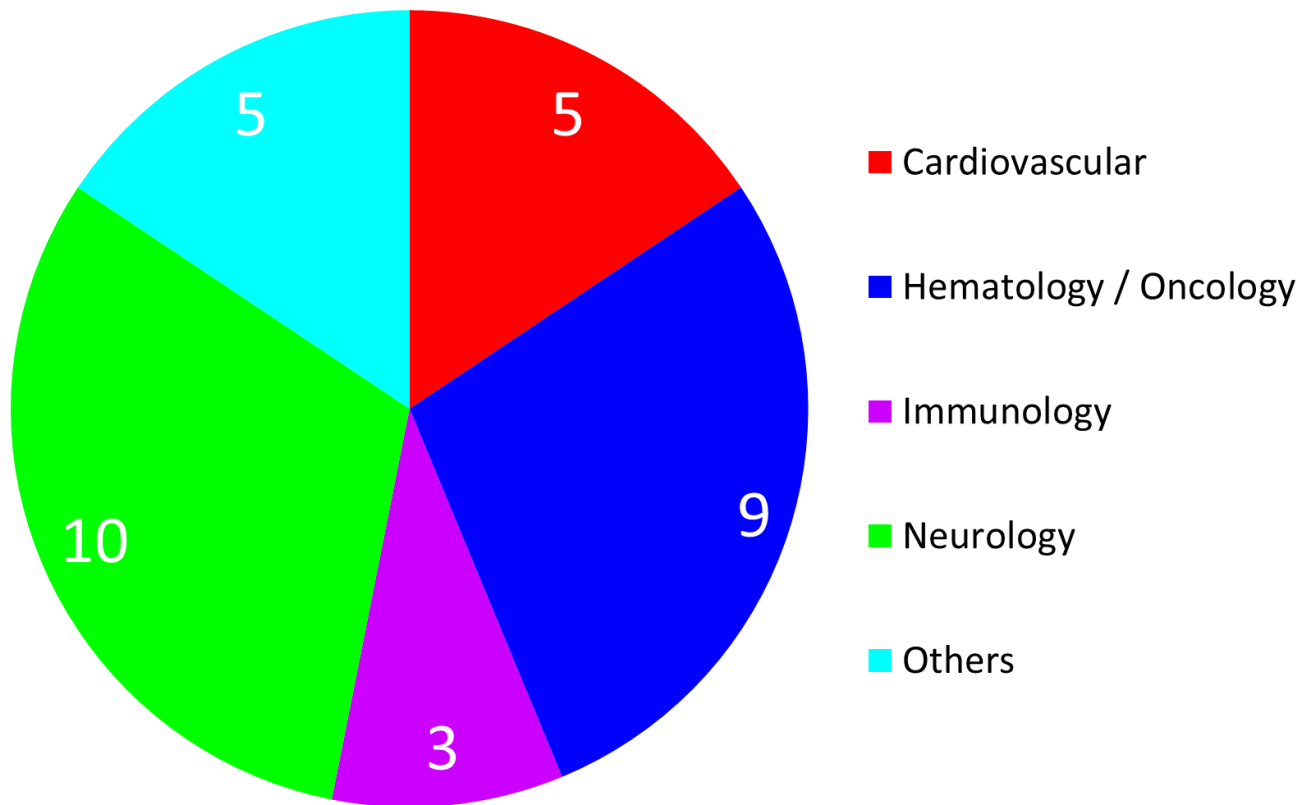
# RMAT Designation

- Effect of designation:
  - FDA must take actions to **expedite development** and review of the drug
  - **Early dialogue** with FDA regarding clinical trials, drug development, and any potential surrogate or intermediate endpoints to support accelerated approval
  - Eligible for **priority review**
  - Eligible for **accelerated approval** (AA) based on 1) surrogate or intermediate endpoints or 2) reliance on data obtained from a meaningful number of sites, including through expansion to additional sites, as appropriate
    - AA **Postapproval confirmatory studies** may be met through (1) submitting clinical evidence, clinical studies, **patient registries**, or other sources of **real world evidence, such as electronic health records**; (2) **collecting larger confirmatory data sets**; or (3) **postapproval monitoring** of all patients treated with the therapy prior to its approval
- FDA Guidance for Industry (Feb. 2019): Expedited Programs for Regenerative Medicine Therapies for Serious Conditions
- Interprets RMT definition to also include:
  - Gene therapies that lead to a sustained effect on cells or tissues

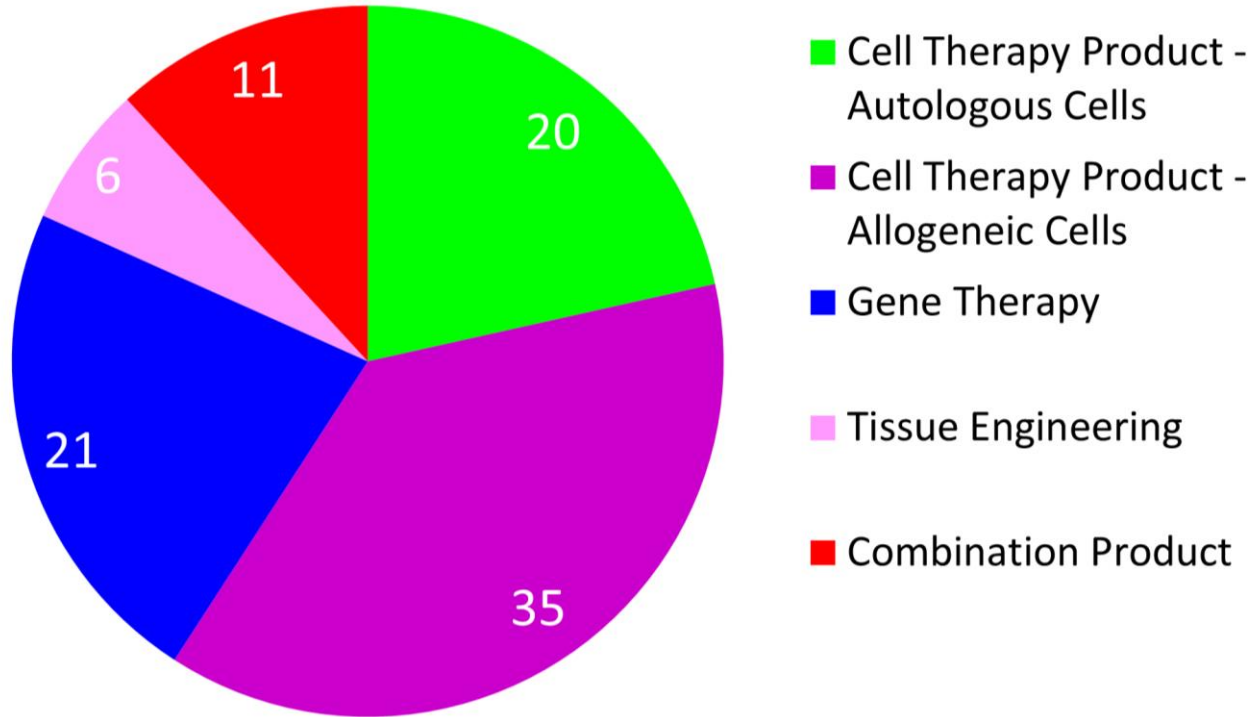
## RMAT Designation Requests Status – as of March 24, 2019



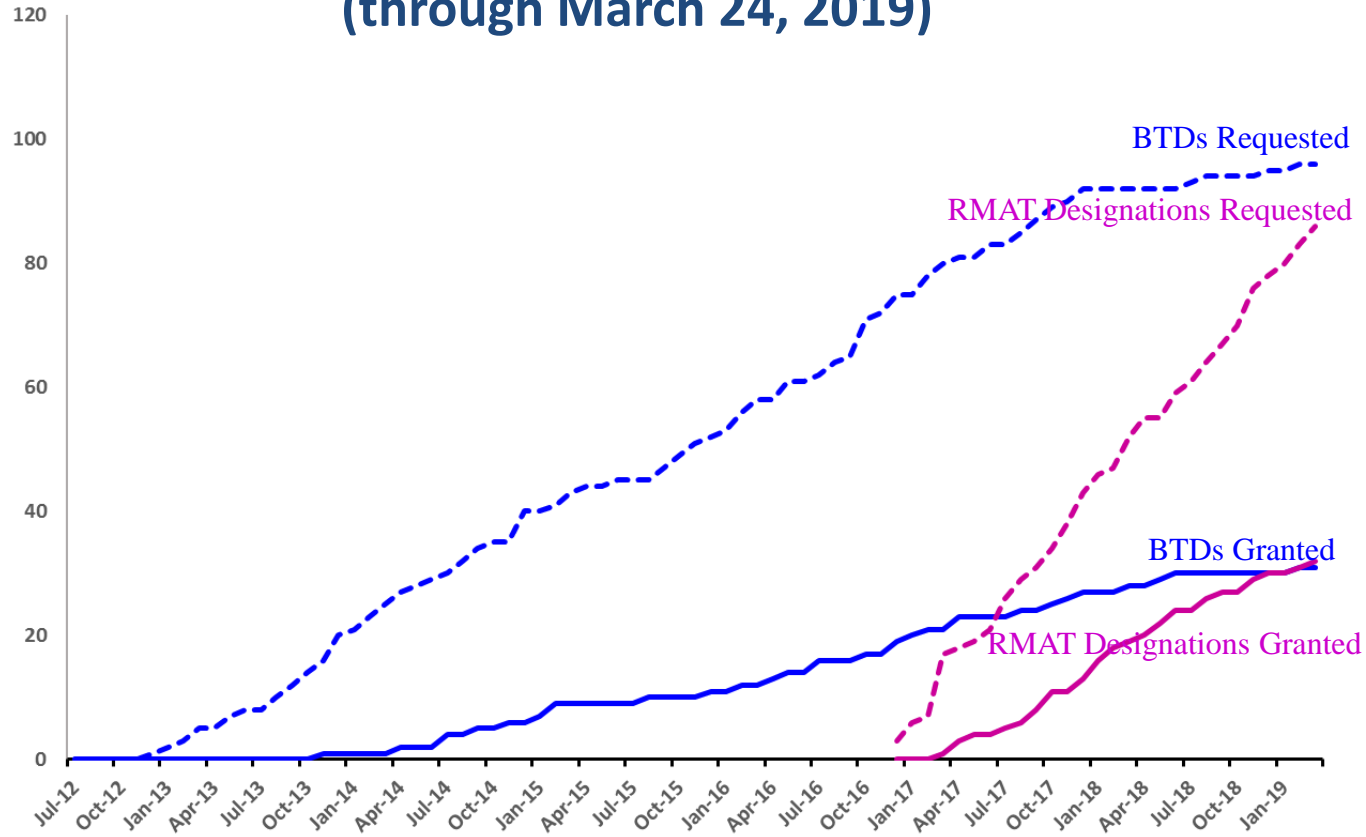
## Granted RMAT Designation Requests, Specialties as of March 24, 2019



## RMAT Designation Requests – Distribution by Product Type



# Cumulative Sum of BTD and RMAT Designation Requests and Granted BTDs and RMAT Designations (through March 24, 2019)





# Impact on Commercialization

- FDA approval necessary for reimbursement
- Health plan medical directors/CMS coverage officials care about extent and benefit of clinical benefit
  - Worried about “certainty”
- How does your product compare to existing therapies and how much will it cost?
- How will CMS/payers account for RMAT or other expedited approval designations when making its own decisions?

# CAR-Ts Provide a Glimpse into CMS' Thinking

- CMS policies re: CAR-T therapies illustrate Medicare's acknowledgement of the dramatic clinical benefit of new therapies but indicate the agency wants to go slow to see how cost and clinical data evolves
- Proposed National Coverage Decision
  - CMS imposing additional criteria re: treatment center, registry, small clinical trials
- IPPS Proposed Rule re: New Technology Add-On Payments
  - New technology
  - Inadequate payment for therapy as compared with established payment rate (MS-DRG)
  - "Substantial clinical improvement" = FDA standard for RMAT or BT?
- CMS and congressional attention to a "value-based" payment paradigm in Medicare could have a significant impact
  - Details still developing but generally if product developers can demonstrate value – such as cost effectiveness versus other existing treatments – new payment arrangements can be developed

# Implications for Strategy

- Reinforces need to integrate clinical and reimbursement strategy
- Meet with payers to understand their views and needs
  - FDA strategy is a good template – meet early with payers; design trials accordingly
  - Collect appropriate data for FDA and payers
- Focus on CMS/congressional activity in the area

