FDA's Approach to the Development of Cell and Gene Therapy Products

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

Deputy Director, FDA

CASS

June 10, 2019

Bethesda, Maryland

Outline

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

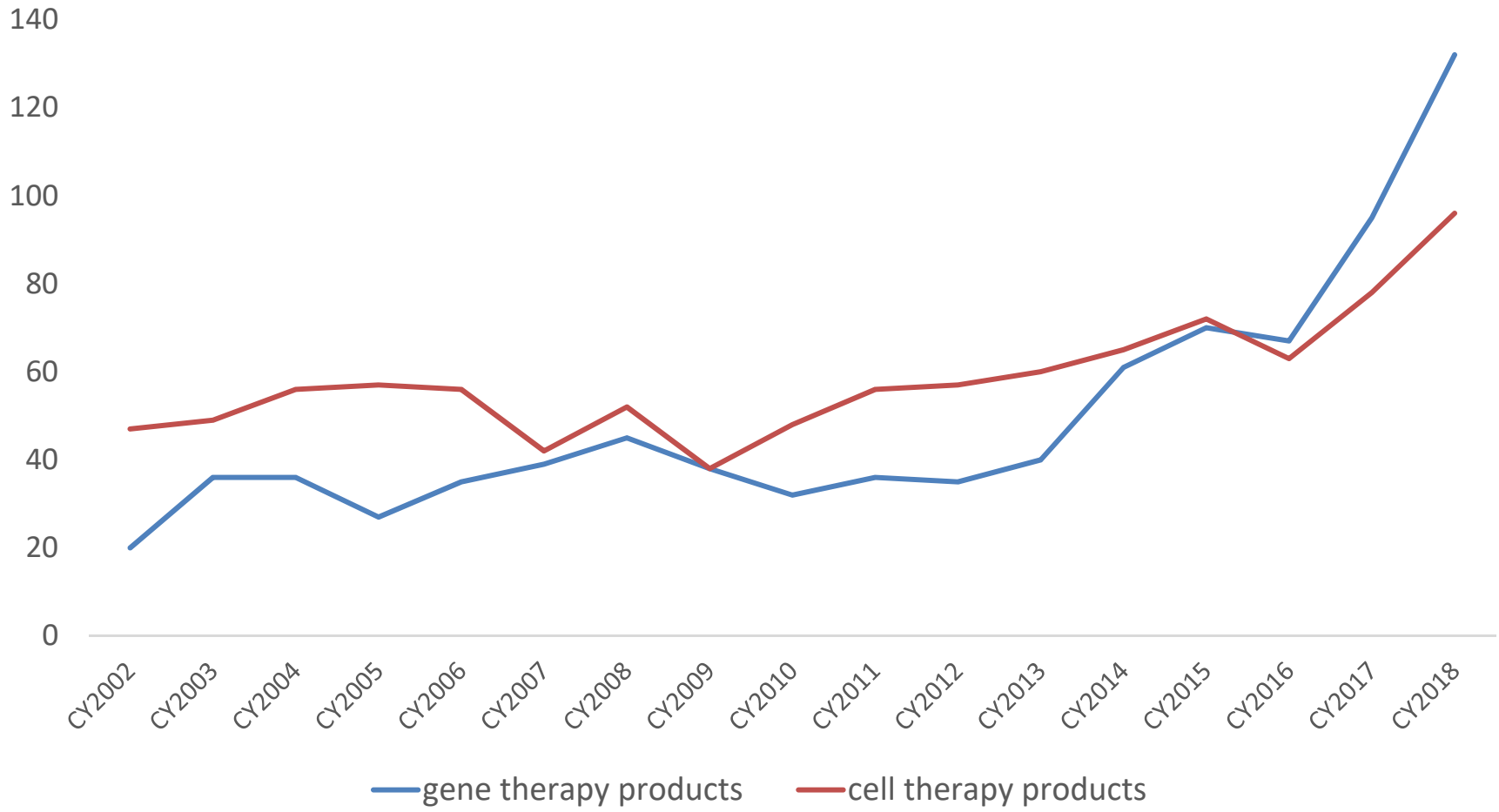
Promoting Product Development

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

Products Regulated by CBER

- Allergenics
- Blood and Blood Components
- Blood Derivatives
- Devices Related to Biologics
- Gene Therapies
- Human Tissues and Cellular Products
- Vaccines (preventative and therapeutic)
- Live Biotherapeutic Products
- Xenotransplantation Products
- Certain Combination Products

Development Programs for Cell and Gene Therapies: INDs submitted in 2002-2018



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
    - https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM585417.pdf
- Section 3035
  - Report on Regenerative Advanced Therapies
- Section 3036
  - Standards for Regenerative Medicine and Regenerative Advanced Therapies

Regenerative Medicine Advanced Therapy Designation

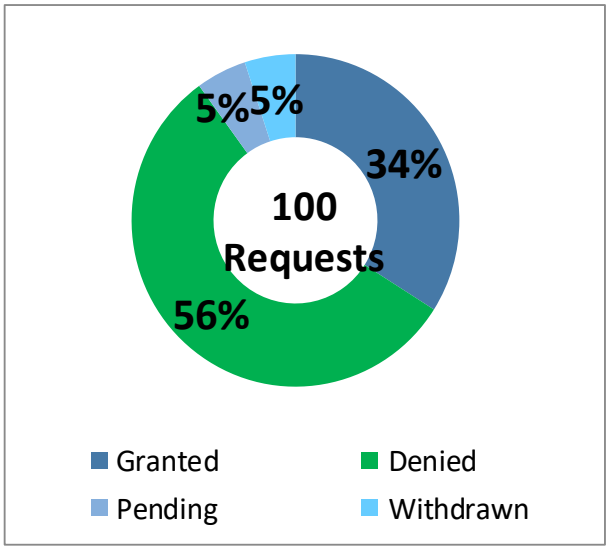
- A drug is eligible for designation if:
  - It is a regenerative medicine therapy
  - The drug is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; and
  - Preliminary clinical evidence indicates the drug has the potential to address unmet medical needs for such disease or condition

RMAT Accelerated Approval Provisions

- Post-approval requirements can be fulfilled as appropriate through submission of
  - Clinical evidence, clinical studies, patient registries or other sources of real world evidence such as electronic health records
  - Collection of larger confirmatory datasets as agreed upon
  - Post-approval monitoring of all patients treated with such therapy prior to approval of the therapy

Regenerative Medicine Advanced Therapy (RMAT) Designations Granted

34 Designations Granted



Data through May 1, 2019

- 68 of the 100 are Cell Therapy products
- 20 of the 34 RMAT Granted products have Orphan Product designation
- 11 of the 34 RMAT Granted products have Fast Track designation

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

Regenerative Medicine Standards

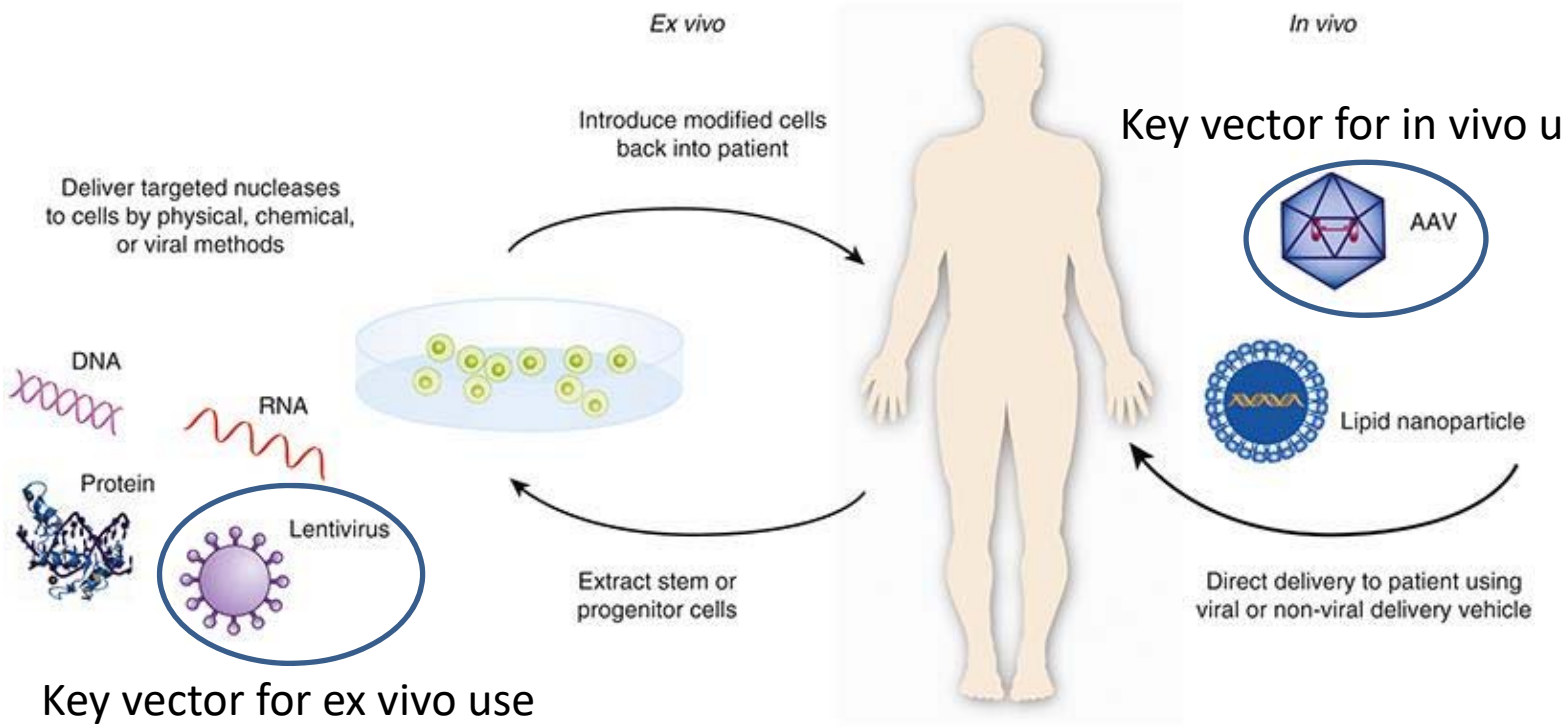
- Contract with Nexight Group and the Standards Coordinating Body (SCB) to coordinate community efforts towards the development of standards for regenerative medicine advanced therapies
  - Develop processes to identify, prioritize, and assess the feasibility for the development and implementation of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

Standards Collaborations with NIST

- Co-sponsored workshops that support standards development
  - "Sharing practices in Cell Counting" and "Building Measurement Assurance in Flow Cytometry" (2017)
  - Realizing the Benefit of 21st Century Cures through Standards Development (with Nexight) March 18-19, 2019
- Joint work on ASTM and ISO standards
- Laboratory collaborations on flow cytometry, cell counting, and cell viability

Somatic Cell Gene Therapy

- Non-heritable correction of defects by replacing, repairing, or inactivating a gene
- Vector used to introduce the gene modification; different vectors exist for use
- Cell-based gene therapy: cells taken from the body, modified in culture, returned
- Directly administered gene therapy: gene therapy given directly to patient



Key vector for in vivo use

Key vector for ex vivo use

Prior Gene Therapy Approvals

- **Tisagenlecleucel (KYMRIAH)** [*ex vivo*]
  - Treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) refractory or in second or later relapse; Relapsed or refractory large B-lymphoma indication subsequently added
- **Axicabtagene ciloleucel (YESCARTA)** [*ex vivo*]
  - Treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy
- **Voretigene neparvovec-rzyl (LUXTURNA)** [*in vivo*]
  - Treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy in patients with viable retinal cells as determined by the attending physician(s)

Spinal Muscular Atrophy (SMA)

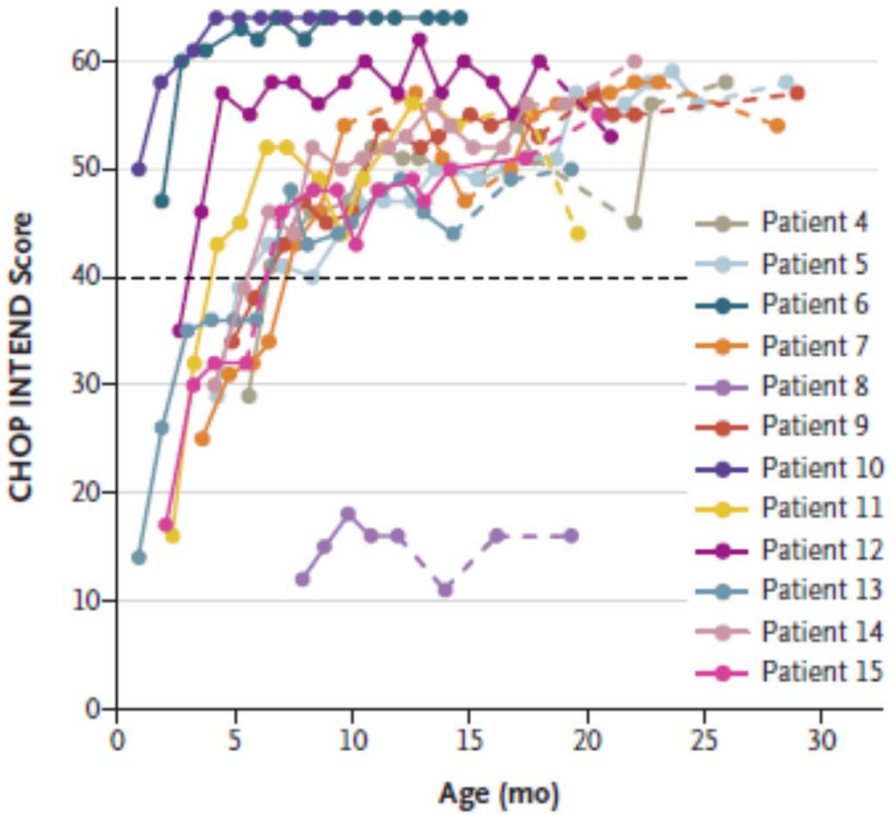
- Genetic disorder affecting about 1:10,000 characterized by a loss of specialized nerve cells, called motor neurons that control muscle movement
- The most severe forms of SMA commonly present with muscle weakness that is evident at birth or within the first few months of life – children cannot sit unassisted or breathe normally
- Caused by deficiency in the SMA1 protein that is needed for the survival of motor neurons
  - SMA2 is a very similar protein; how much SMA2 protein is expressed determines severity of disease and timing of its onset
- One existing therapy, an antisense oligonucleotide approved in 2016, nusinersen (Spinraza) that increases production of SMA2
  - Must be given by spinal tap every 4 months after 4 loading doses

Onasemnogene abeparvovec-xioi (Zolgensma)

- First gene therapy approved to treat children less than two years of age with infantile-onset SMA
- AAV9 vector containing a full length copy of the SMA1 gene that is given once by intravenous injection
- The safety and effectiveness of onasemnogene was determined based on an ongoing clinical trial and a completed clinical trial involving a total of 36 pediatric patients with infantile-onset SMA between the ages of approximately 2 weeks and 8 months at study entry
  - Most common side effects were liver function abnormalities and vomiting

Onasemnogene Clinical Results

Clinical trial results: patients with infantile-onset SMA that are untreated never develop a CHOP INTEND score (a test for neuromuscular disorders) greater than 40



Agency Actions to Advance the Development of Gene Therapy

- Recent suite of six guidance documents
- Reduction of administrative burden w/NIH
- Development of manufacturing standards
- Clinical development initiatives
- Research on improved vector production

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

Ongoing International Engagements

- International Pharmaceutical Regulators Programme (IPRP)
- International Council for Harmonisation (ICH)
- Asia-Pacific Economic Cooperation (APEC) Regulatory Harmonization Steering Committee (RHSC)

  and

- Information exchanges with foreign counterparts, including confidential discussions

International Pharmaceutical Regulators Program (IPRP) http://www.iprp.global/home

- Regulators only forum, no industry involvement
  - Share information, best practices, promote regulatory convergence
  - No formal guidance is developed but reflection papers are written and published
- Cell Therapy Working Group (CTWG)

  Scope: Cell and tissue based products (without gene modification), tissue engineered products, xenotransplantation products
  - In 2018, finalized Reflection Paper: "General Principles to Address the Nature and Duration of Clinical Trials Using Cell Therapy Products" (2018)
- Gene Therapy Working Group (GTWG)

  Scope: Viral vectors, oncolytic vectors, genetically modified bacterial vector-based products, genome editing technologies
  - In 2018, finalized Reflection Paper: "Expectations for Biodistribution Assessments for Gene Therapy Products"
- Currently updating previous regulatory landscaping document to reflect current state-of-play in regulatory frameworks of members

International Council for Harmonisation (ICH)

- IPRP Management Committee meets at time of the biannual ICH meetings, facilitates the participation of international regulators who also participate in ICH, and supports synergy between the two initiatives
- ICH is currently prioritizing new topics for initiating in 2019 which includes a gene therapy topic proposal using IPRP reflection paper on BD as foundation (assessment of biodistribution of gene therapy vectors)
- Decision expected in June 2019 –Would be first ICH gene therapy guideline

APEC Regulatory Harmonization Steering Committee (RHSC)

- Mandate: To promote a more ***strategic***, ***effective*** and ***sustainable*** approach to harmonization by:
  - Proactively identify and prioritize projects seen to be of greatest value
  - Strengthen linkages with harmonization initiatives, training organizations and other key players to promote complementary actions and most effective use of resources
  - Leverage work with other harmonization initiatives – avoid duplication of work
  - Ensure sustained efforts
- Members are Regulators from Asia-Pacific economies; industry coalitions for research-based pharmaceuticals, medical devices, generic pharmaceutical, biotech products, advanced therapies; and Center of Excellence Coalition of Training Partners
- Does not produce harmonized guidances but promotes use of existing international guidances and best practices in Priority Work Areas (PWA)
- Advanced Therapies PWA:
  - Developed Strategic Roadmap document to guide effort
  - Establishing first CoEs in this area: candidate institutions are Duke-National University of Singapore (Singapore) and Northeastern University (Boston)
  - Draft Core Curriculum for future CoEs to work from to be piloted in training programs and adjusted as appropriate

Regulatory Information Exchanges

- "Cluster" discussions
  - Under confidentiality arrangements
  - Originally created with EMA alone, expanded over the years to include other confidential partners (e.g., Canada, Japan)
  - Discussion can include: Guidance under development; Policy perspectives; Clinical trial design & endpoints; Scientific advice; Adverse events; Submissions
  - Gene therapy discussions fall within Advanced Therapy Medicinal Products Cluster primarily, though at times also within Oncology or Rare Disease Clusters
- Bilaterals: Senior leadership meetings with counterparts
- *Ad hoc* exchanges

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

Advanced Manufacturing Technology and Vaccines

- Modernization of vaccine production process to incorporate advanced manufacturing technologies could improve agility to respond to existing and emerging pathogens
- Plans for internal research program and collaborations with federal partners initially focused on influenza vaccine
  - Optimize cell lines for production
  - Improve yield of recombinant technology
  - Opportunities to apply continuous manufacturing concepts

Advanced Manufacturing Technology and Cell and Gene Therapies

- Lack of capacity for manufacture of lentiviral and adeno-associated virus (AAV) vectors is limiting clinical development
- Process of production in current cell lines is still not able to meet demand despite some improvement over past few years
- Plans for CBER laboratory research programs and collaborations with academic and public private partners to advance field
  - Improved cell lines for vector production
  - Advanced manufacturing technologies

Future directions for Advanced Manufacturing within CBER

- Internal workgroup on advanced manufacturing
- Develop CBER research programs to improve understanding of advanced manufacturing for vaccines and cell and gene-based therapies
- Promote the creation of more modern Domestic Manufacturing
  - Recently published BAA soliciting proposals to support regulatory science and innovation. Target areas relevant to advanced manufacturing of complex biologics include support for novel and improved materials and manufacturing methods as well as new analytical methods

https://www.fbo.gov/spg/HHS/FDA/DCASC/FDABAA-19-00123/listing.html

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

FDA Patient Engagement Initiatives*

Initiative	FDA-led Patient-Focused Drug Development (PFDD) Meetings	Externally-led PFDD Meetings	NORD MOU Pilot Listening Sessions	Patient Engagement Collaborative (PEC)	Patient Engagement Advisory Committee (PEAC)	Patient Representative Program (PRP)
Purpose	Public meetings that systematically obtain the patient perspective on specific diseases and their treatments	To allow patient organizations to identify and organize patient-focused collaborations to generate public input on other disease areas, using the process established through FDA-led PFDD meetings as a model	Pilot listening sessions in rare diseases to inform FDA staff of disease and treatment burden in rare diseases	A forum to discuss and share experiences on patient engagement in medical product development and regulatory discussions	Provides advice to the Commissioner or designee, on complex issues relating to medical devices, the regulation of devices, and their use by patients in a public advisory committee meeting	FDA Patient Representative ℠ consultants provide direct input to inform the Agency's decision-making associated with medical products for drugs, biologics, and medical devices in a public advisory committee meeting or as part of agency-directed assignments
Medical Product Type Covered	Biologics, Drugs	Biologics, Drugs	Biologics, Devices, Drugs	Biologics, Devices, Drugs	Devices	Biologics, Devices, Drugs

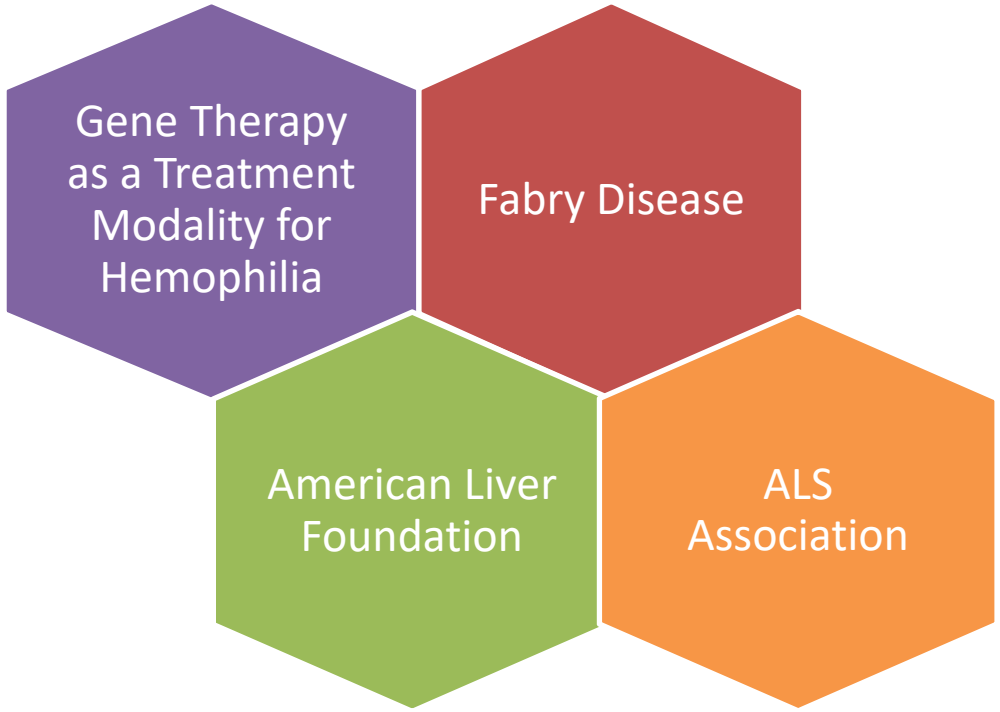
*This list is not inclusive of all FDA Patient Engagement Initiatives.

Complete table available at https://www.fda.gov/ForPatients/PatientEngagement/ucm611467.htm

Rare Disease Listening Sessions

- FDA Patient Affairs Staff (PAS) in partnership with National Organization for Rare Diseases (NORD) (pilot program)
  - Inform regulatory decision making
  - Provide a starting point to inform early stage research & development
  - Educate review staff about rare diseases or specific segments of non-rare diseases
  - Help patients and their advocates understand the FDA's mission and work

Rare Disease Listening Sessions



Public reports: https://wwwfda.gov/ForPatients/PatientEngagement/ucm625092.htm

Gene Therapy as a Treatment Modality for Hemophilia

October 23, 2018

Topics Discussed:

- Risks and benefits of gene therapy
- Safety monitoring
- Measuring success
- Other considerations

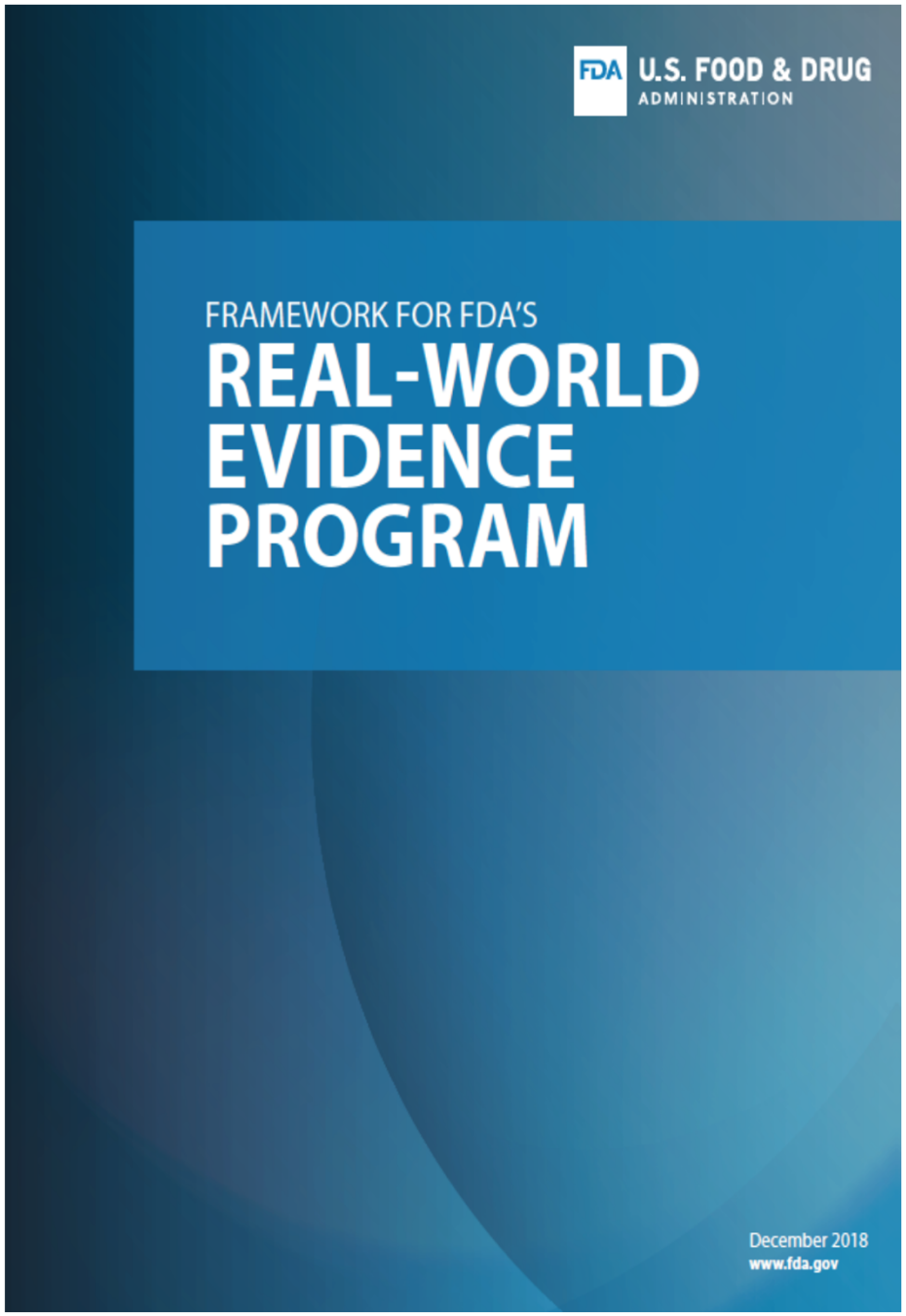
Participates:

- 7 patients and caregivers who are segments of the following groups:
  - adults with hemophilia enrolled in a clinical trial
  - adults with hemophilia not enrolled in a clinical trial
  - caregivers to children with hemophilia

21st Century Cures Deliverables

- FDA shall establish a program to evaluate the potential use of real world evidence (RWE) to:
  - Help support approval of a new indication for a drug approved under section 505(c)
  - Help satisfy post-approval study requirements
- Program will be based on a framework that was to be issued by 2018

Real world evidence means data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than *traditional clinical trials*



- Intended for drug and biological products
- Outlines FDA's plan to implement the RWE program
- Multifaceted program
  - Internal processes
  - Guidance development
  - Stakeholder engagement
  - Demonstration projects

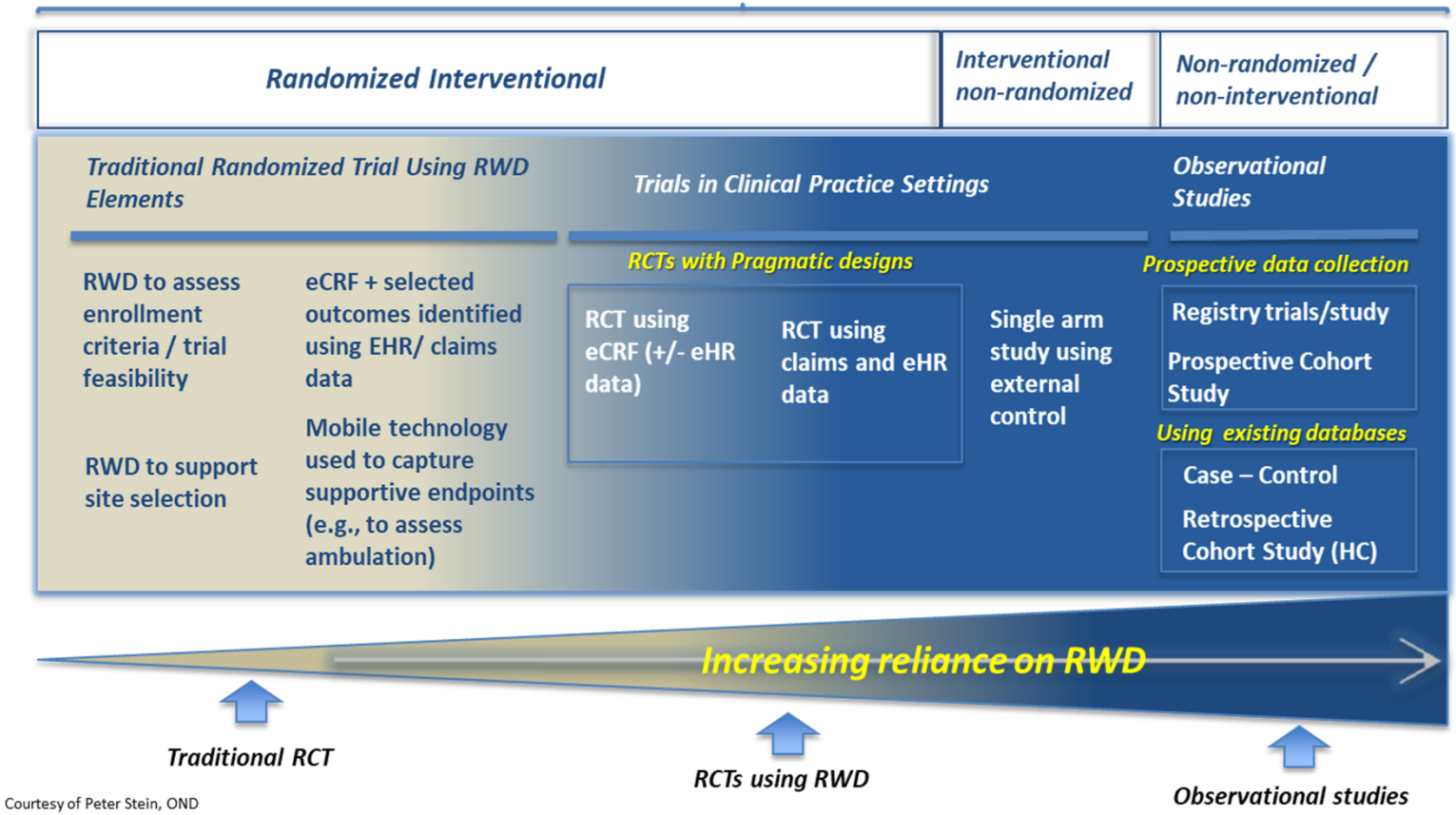
https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RealWorldEvidence/UCM627769.pdf

Scope of the RWE Program

Evaluates the potential use of RWE to support changes to labeling about drug product effectiveness, including:

- Adding or modifying an indication, such as a change in dose, dose regimen, or route of administration
- Adding a new population
- Adding comparative effectiveness or safety information

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



Courtesy of Peter Stein, OND

INTERACT Program

INitial Targeted Engagement for Regulatory Advice on CBER producTs

- To further encourage interaction with sponsors and replace the pre-pre-IND meeting process across the Center
- Details of requesting a meeting at:

https://www.fda.gov/BiologicsBloodVaccines/ResourcesforYou/Industry/ucm611501.htm

CBER Strategic Priorities FY2019

- Timely regulatory advice and product approvals
- Cell and gene therapy guidance documents
- Compliance and enforcement plan for cell therapies
- Advanced manufacturing for biologic products
- Global regulatory framework for advanced therapies
- Recruitment and retention of critical staff

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)**
  Email: industry.biologics@fda.gov
- **Follow us on Twitter**
  https://www.twitter.com/fdacber


FDA
U.S. FOOD & DRUG
ADMINISTRATION