

Update from the Center for Biologics Evaluation and Research (CBER): Progress Advancing the Development of Complex Biologic Products

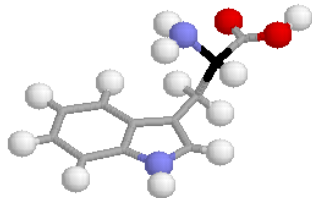
Peter Marks, M.D., Ph.D.

FDLI 2018

Outline

- Products regulated
- Regenerative medicine update
- Gene therapy
- Center priorities

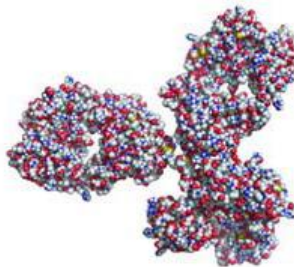
Complexity of Therapeutics



One subunit of a protein

10^2 Atoms

L-tryptophan
Small Molecule Drug



Protein composed of about
1100 subunits

10^5 Atoms

IgG antibody molecule
Protein Biologic



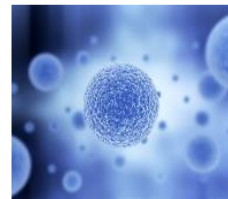
Cell composed of about
 3.6×10^6 proteins

10^{14} Atoms

Mesenchymal stem cell
Cellular Biologic

Products Regulated by CBER

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



Regenerative Medicine

A field with great promise that includes a variety of innovative products

- Cell therapies, including genetically modified cells
- Gene therapies producing durable effects
- Therapeutic tissue engineering products
- Human cell and tissue products
- Certain combination products

Some Regenerative Medicine Products



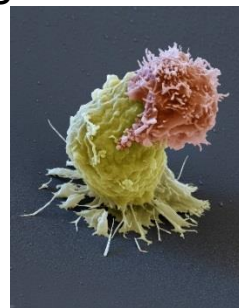
Bioengineered skin



Bioengineered blood vessel



Bioengineered bladder



Red-colored cell is a
T cell

Yellow-colored cell is a
cancer cell

Chimeric antigen receptor-T cell



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

- Section 351 of the Public Health Service Act
 - License needed to distribute in interstate commerce
 - Product must be safe, pure, potent
 - Suspension/revocation power, recall authority
- Section 361 of the Public Health Service Act
 - Authorizes FDA to issue and enforce regulations necessary to prevent introduction, transmission, or spread of communicable diseases from foreign countries into the US, or interstate

Two Regulatory Tiers for HCT/Ps

1. Drugs, devices, biological products (351 HCT/Ps)
 - Regulated under authority of section 361 and section 351 of Public Health Service Act and/or the Federal Food, Drug, and Cosmetic Act
2. 361 HCT/P (meet criteria to be kicked down)
 - Regulated solely under authority of section 361
 - Subject to “Tissue Regulations” (21 CFR Part 1271)
 - *Premarket review and approval not required*

Section 361 HCT/Ps

To be regulated solely under section 361 of the PHS Act, HCT/Ps must meet the following criteria (21 CFR Part 1271.10(a)):

1. Minimally manipulated (MM)*;
2. Intended for homologous use (HU)** only;
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

* Defined in § 1271.3(f)

** Defined in § 1271.3(c)

Objectives of Suite of Regenerative Medicine Guidance Documents

- Clarify existing regulations to make it simpler for sponsors to determine if they need to obtain premarket authorization for their products
- Expedite the development and review of innovative regenerative medicine therapies



Regenerative Medicine Guidance Suite

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 – Draft
4. Expedited Programs for Regenerative Medicine Therapies for Serious Conditions – Draft

Regenerative Medicine Advanced Therapy Designation (RMAT)

- To expedite the development and review of regenerative medicine advanced therapies
 - Applies to certain cell therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products
 - Genetically modified cell therapies and gene therapies producing durable effects included

RMAT Designation Provisions

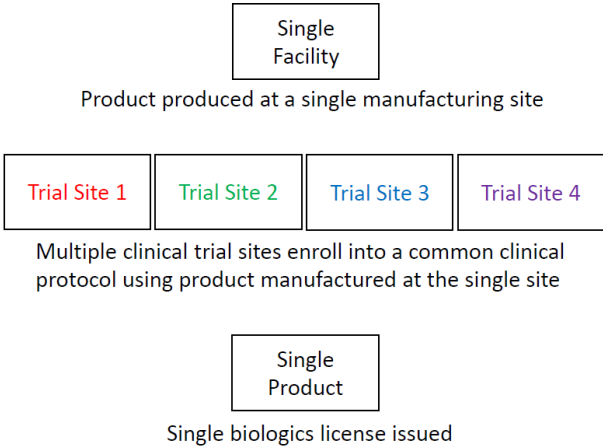
- Products must be intended for serious or life-threatening diseases or conditions
- Preliminary clinical evidence must indicate potential to address unmet medical needs in that condition
- FDA will reply to designation requests with 60 days
- Designated products are eligible as appropriate for priority review and accelerated approval

RMAT Accelerated Approval Provisions

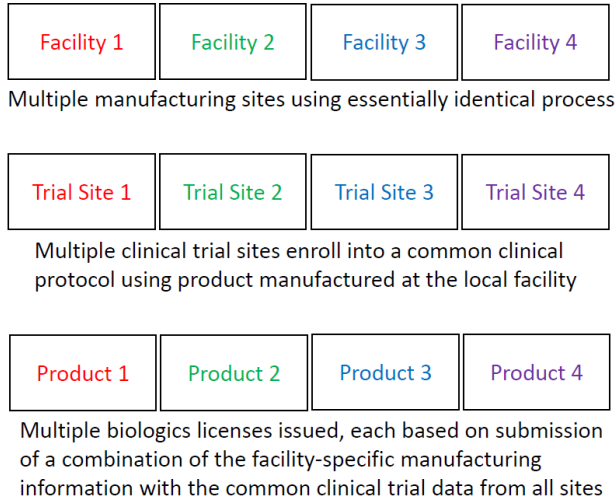
- Post-approval requirements can be fulfilled as appropriate through submission of
 - Clinical evidence, clinical studies, patient registries or other sources of real world evidence such as electronic health records
 - Collection of larger confirmatory datasets as agreed upon
 - Post-approval monitoring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

Innovative Development Program for Regenerative Medicine Products

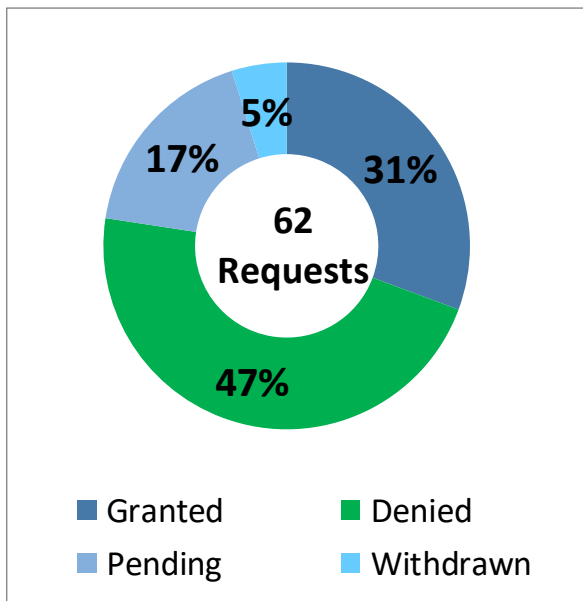
Traditional Development of a Biologic Product



Alternative Development of a Biologic Product



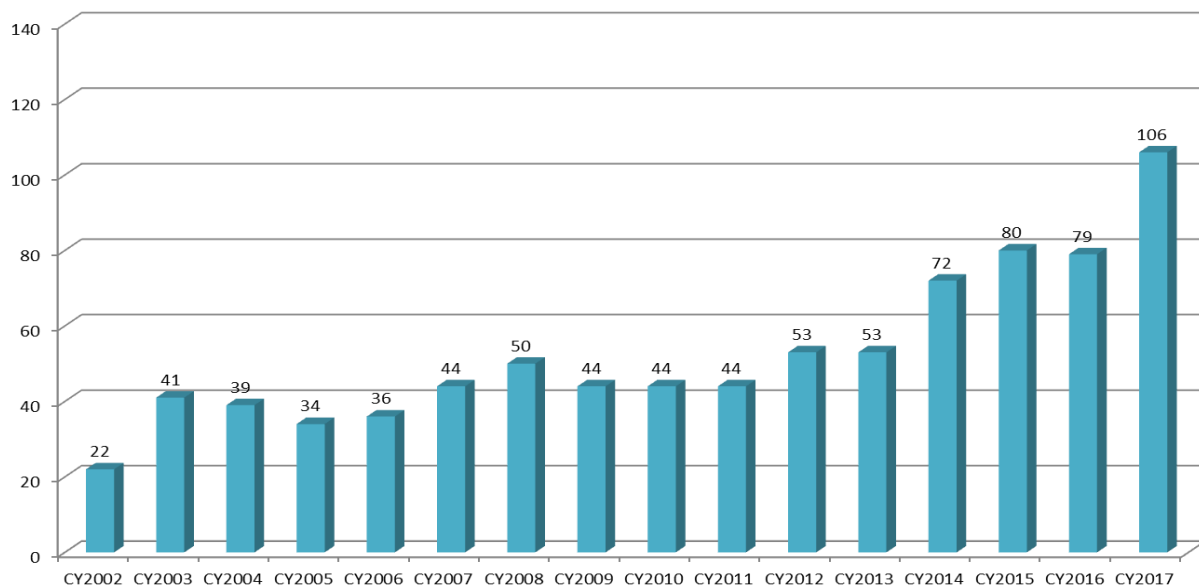
RMAT Designations Granted



Data as of April 30, 2018

- 19 products granted designation
- 14 of the 19 products have Orphan Product designation
- 6 of the 19 products have Fast Track designation
- Most are cellular therapy products or cell-based gene therapy products

Investigational New Drug Applications Gene Therapy Products, CY 2002-2017



Developments in Gene Therapy: Genome Editing



- FDA regulates somatic and germline gene modifications used as therapeutics in humans
 - Includes modification of cells prior to administration and the direct administration of gene therapy vectors
 - Somatic cell versus germline editing relevant
 - By law FDA cannot currently accept an investigational or marketing application for a product that involves heritable genetic modification



Two Cell-Based Gene Therapies Approved in 2017

- Tisagenlecleucel (KYMRIAHA): indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse
- Axicabtagene ciloleucel (YESCARTA): indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy

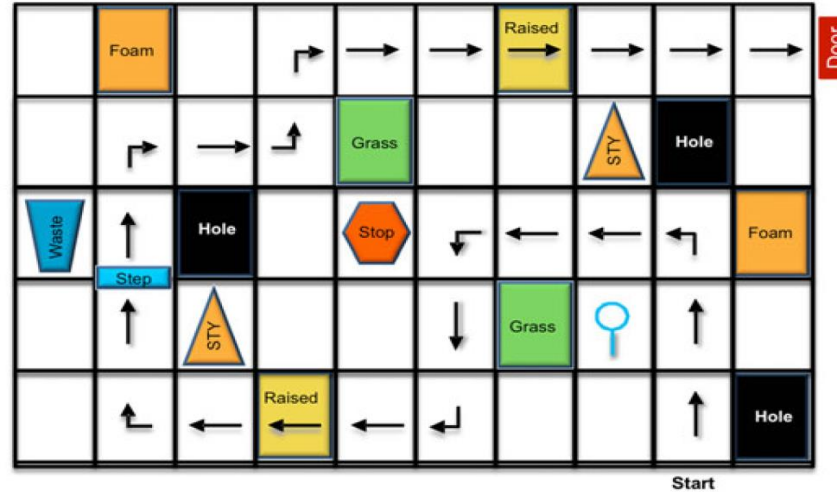


One Directly Administered Gene Therapy Approved in 2017

- Voretigene neparvovec-rzyl (LUXTURNA): indicated for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy. Patients must have viable retinal cells as determined by the attending physician(s).
 - Novel endpoint used for approval developed by sponsor with input from FDA

Multi-Luminance Mobility Test

Negotiating a path with obstacles at different light levels



Scoring based on time and accuracy

Illuminance (lux)	Luminance (cd/m ²)	Corresponding environment
1	0.32 mesopic vision	Moonless summer night; or indoor nightlight
4	1.3 mesopic vision	Cloudless summer night with half moon; or outdoor parking lot at night
10	3.2 mesopic vision	60 min after sunset in a city setting; or a bus stop at night
50	15.9 photopic vision	Outdoor train station at night; or inside of illuminated office building stairwell
125 [†]	39.8 photopic vision	30 min before cloudless sunrise; or interior of shopping mall, train or bus at night
250 [‡]	79.6 photopic vision	Interior of elevator, library or office hallway
400	127.3 photopic vision	Office environment; or food court

Challenges in the Development of Advanced Therapies

- Need for novel approaches to clinical development
 - Often have limited patient populations for clinical trials
 - Employ principles of patient focused drug development
 - Advance planning for clinical trials
- Transition from pilot scale to commercial manufacturing can be challenging
 - Consider scalable manufacturing processes

Challenges in the Development of Advanced Therapies

- Need for standards for the reproducible production of regenerative medicine products such as cellular therapies
- Lack of capacity for manufacture of lentiviral and adeno-associated virus (AAV) vectors is limiting clinical development

Potential Manufacturing Solutions for Advanced Therapies on the Horizon

- Modular manufacturing facilities
 - Scalable pre-built for biotechnology manufacture
- Continuous manufacturing applied to biologics



Select Scientific Priorities for 2018

- Facilitating the development of standards for use in regenerative medicine in collaboration with National Institutes of Health (NIH) and the National Institute of Standards and Technology (NIST)

Select Scientific Priorities for 2018

- Maintaining expertise in rapidly emerging and evolving technologies such as genome editing
- Plans for CBER laboratory research programs and collaborations with partners to advance field
 - Improved cell lines for vector production
 - Programs in continuous manufacturing

Select Regulatory Priorities for 2018

- Continue to work with sponsors of regenerative medicine products to submit investigational new drug or biologics license applications when appropriate
- Continue to pursue compliance and enforcement actions

Select Regulatory Priorities for 2018

- Publish suite of draft guidance documents related to the manufacturing of gene therapy products
- Publish suite of draft guidance documents covering key principles of clinical development for gene therapy products

Key Messages

- Advanced therapy products are now a reality
- CBER looks forward to facilitating public health by
 - Helping to individualize product development
 - Working to overcome limitations in manufacturing
 - Providing input and collaboration on novel endpoints
 - Encouraging the use of innovative clinical trial designs



U.S. FOOD & DRUG
ADMINISTRATION