

Regenerative Medicine and the Changing Regulatory Landscape

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Gene Therapy

CRISPR-Cas9

- Inspired by genetic defense mechanisms found in bacteria
- Cas9 is an enzyme guided to a specific location in the genome to cut cellular DNA so that bits of DNA can be added/removed
- Guide RNA is a small piece of pre-designed RNA sequence inside a longer RNA scaffold. The scaffold binds to DNA and the pre-designed sequence “guides” Cas9 to cut a specific part of the genome
- Cell recognizes the damage and tries to repair it. Scientists use the DNA repair machinery to add, activate, delete, or suppress genes
- As of the end of February 2018, there is one registered clinical study in the U.S.
 - UPenn will use CRISPR-Cas9 to modify immune cells, prompting them to attack three different types of cancer (multiple myeloma, melanoma and/or two types of sarcoma)

Gene Therapy

CAR-T Cell Therapy

- The FDA has approved its first gene-altering leukemia treatment, Novartis' Kymriah, for children and young adults with an aggressive type of leukemia
 - Kymriah is made individually for each patient and given only once
 - The therapy turns a patient's cells into a "living drug", and trains them to recognize and attack the disease when reintroduced. white blood cells, called T-cells, are removed from a patient's bloodstream at an approved medical center, frozen, and shipped to Novartis for genetic engineering and multiplying. It is then frozen again and shipped back to the medical center to be dripped into the patient. The whole process is expected to take 22 days
 - While the drug costs \$475,000 per treatment, if a patient doesn't respond to treatment within the first month, there is no charge
- Shortly thereafter, the FDA also approved a similar therapy, Gilead's Yescarta
 - The therapy costs \$373,000 per treatment
- As of the end of February 2018, there are 164 CAR-T registered clinical studies

Federal Funding

- FDA Commissioner Scott Gottlieb has been quoted as saying that there are currently more than 550 types of experimental gene therapies being studied.
- Congress has taken steps to prevent funding of certain gene therapy technologies:
 - The Consolidated Appropriations Act of 2017 contained a provision that prohibits the FDA from using appropriated funds to notify sponsors or acknowledge receipt of a submission for an exemption to carry out investigational clinical research that:
 - Uses a drug or biological; and
 - Involves a human embryo that was created or modified to include a heritable genetic modification.
 - The Consolidated Appropriations Act of 2018 contains carryover language from the 2017 bill, forbidding funding from going to research on the editing of human embryos to include a heritable genetic modification

Stem Cells

- **Adult stem cells**
 - Can be found throughout the body, and found as unspecialized cells among specialized cells in tissues and organs, as well as in umbilical cord blood and peripheral blood. An adult stem cell can either divide to make more adult stem cells, or differentiate to produce some, or all, of the major specialized types of the tissue or organ
- **Human embryonic stem cells (hESC)**
 - Come from human embryos that develop from eggs that have been fertilized *in vitro*. hESC's can develop into any specialized cell type in the body
- **Induced pluripotent stem cells (iPS)**
 - Generated by reprogramming adult cells that have already differentiated into a specific cell. After programming, iPS cells are able to develop into and specialized cell type in the body
- They are capable of surviving over long periods and can divide to make additional stem cells. They may also help repair the body by dividing to replenish cells that are damaged by disease, injury, or aging
- They are unspecialized (“blank slates” that can become specific types of cells) but can develop into specialized cell types, or cells that do specific work in the body

Gene and Stem Cell Therapies

FDA Regulation

- In November 2017, FDA published two final guidance documents that are part of a comprehensive policy framework:
 1. *Regulatory Considerations for Human Cell, Tissues, and Cellular and Tissue-Based products: Minimal Manipulation and Homologous Use*
 - Intended to provide clarity in the determination of whether HCT/Ps are subject to FDA's premarket review requirements
 2. *Same Surgical Procedures Exception: Questions and Answers Regarding the Scope of the Exception*
 - Intended to provide clarity as to whether an establishment may qualify for an exception from the requirements under Part 1271 by meeting the exception in 21 CFR 127.15(b)
- In November 2017, FDA published two new draft guidances:
 1. *Expedited Programs for Regenerative Medicine Therapies for Serious Conditions*
 - Describes several programs, such as Fast Track designation and Breakthrough Therapy designation, that are available to sponsors of regenerative medicine therapies, and information about the requirements for, and benefits of, the new RMAT designation program that was created by the 21st Century Cures Act.
 2. *Evaluation of Devices Used with Regenerative Medicine Advanced Therapies*
 - Required by section 3034 of the 21st Century Cures Act. Provides the agency's current thinking about concepts related to the evaluation of devices used in the recovery, isolation and delivery of RMATs.

FDLI Annual Conference: Regenerative Medicine and the Changing Regulatory Landscape

Julia C. Tierney, J.D.

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Food and Drug Administration

May 2018

Regulation of Human Cells, Tissues & 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 Comprehensive Regenerative Medicine Policy Framework

- 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 approval of safe and effective innovative regenerative medicine therapies and associated devices



Comprehensive Regenerative Medicine Policy Framework – 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 HCT/Ps: 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 (RMAT) Designation

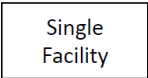
- Established by the 21st Century Cures Act to help expedite development and review of regenerative medicine advanced therapies (RMATs)
- RMAT designation provides
 - all breakthrough therapy features, including early interactions to discuss any potential surrogate or intermediate endpoints
 - possible priority review and accelerated approval (if eligible)
 - statutory flexibility with regard to accelerated approval and post-approval requirements

Regenerative Medicine Advanced Therapy (RMAT) Designation

- A drug is eligible for designation if:
 - It is a regenerative medicine therapy
 - Includes cell therapies, genetically modified cells, gene therapies producing durable effects, therapeutic tissue engineering products, human cell and tissue products, or any combination product using such therapies or products
 - It 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

Innovative Development Program for Regenerative Medicine Therapies

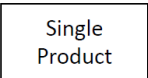
Traditional Development of a Biologic Product



Product produced at a single manufacturing site

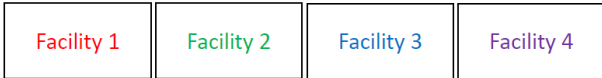


Multiple clinical trial sites enroll into a common clinical protocol using product manufactured at the single site



Single biologics license issued

Alternative Development of a Biologic Product



Multiple manufacturing sites using essentially identical process



Multiple clinical trial sites enroll into a common clinical protocol using product manufactured at the local facility



Multiple biologics licenses issued, each based on submission of a combination of the facility-specific manufacturing information with the common clinical trial data from all sites



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FDLI Conference May 2018

Michael J. Werner

Partner, Holland & Knight, LLP

FDA's RM Policy Framework

What does it do?

- » *Protects patients by maintaining the FDA's high safety and efficacy standards.*
- » *Provides product developers with the necessary regulatory clarity via details and specific examples of how these regulations will apply to specific product types.*
- » *Provides clarity around how FDA will implement its new RMAT designation.*

Why is it needed?

- » *Protect patients*
- » *Industry needed further clarity on how FDA planned to regulate RM products, and which kinds of products required regulatory approval.*
- » *Other nations (incl UK, Japan, Canada), recognizing the immense value of these products, have established special RM regulatory provisions. The U.S. could fall behind its economic competitors if it did not take specific steps to support the field.*

- » **Regenerative Medicine Advanced Therapy (RMAT) Designation** creates a program for designation of regenerative medicine advanced therapies.
- » **Included in the 21st Century Cures Act (passed Dec 2016)**
 - For the first time in the U.S., a specific RM / AT technology product designation.
 - Optimizes FDA's approval pathways for RM / AT products – similar to FDA's Breakthrough Therapy designation, or other expedited approval programs.
 - Maintains the FDA's high approval standards for product safety and efficacy.
- » **Product sponsor benefits:**
 - Guaranteed interactions with the FDA.
 - Eligibility for priority review and accelerated approval.
 - Flexibility in the number of clinical sites used and the possibility to use patient registry data and other sources of “real-world” evidence for post-approval studies (pending FDA approval).

RMAT Designation Provisions

- » Defines 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

Regenerative Medicine Advanced Therapies (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
 - Differs from AA pathway under 506(c) which does not state that approval may be based on data obtained from a meaningful number of sites
 - Also differs from AA pathway under 506(c) which says postapproval study requirements may only be met through “appropriate post-approval studies to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical benefit.”

- » *Enacted in December 2016 as part of the 21st Century Cures Act and designed to acknowledge the importance and unique characteristics of RM technologies and provide for expedited approval without weakening FDA safety and efficacy standards.*

- » *Implementation:*
 - *In early 2017, FDA published application instructions**
 - *FDA confirms the gene therapies qualify for RMAT in late 2017*
 - *16 products have publicly announced they have received the designation (as of late April 2018); incl 2 gene therapy products*

» * Available here: <https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm537670.htm>

» ** Available here: <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm573443.htm>

RMAT vs Breakthrough

<p>Eligible if:</p> <ul style="list-style-type: none">• <i>Regenerative Medicine Therapy, and</i>• <i>Intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; and</i>• <i>Preliminary clinical evidence indicates [it] has the potential to address unmet medical needs</i>	<p>Eligible if:</p> <ul style="list-style-type: none">• <i>Intended to treat a serious condition; and</i>• <i>Preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies</i>

RMAT allows earlier interaction with OTAT to facilitate an efficient development program

- *i.e. early general agreement on evidence generation plan through to BLA and for long-term follow-up post-approval, including early discussion on endpoints and the type of real world evidence that could support program*

Public Statement by Dr. Gottlieb

Commissioner statement on August 28, 2017:

*“In addition, the FDA will continue to work closely with industry to find other ways to aid in the effort to bring novel therapies to patients as quickly, and as safely, as possible. One of these will include our continued commitment to **fully implement** the Regenerative Medicine Advanced Therapy designation.*

*This pathway enables regenerative cell therapies to access the FDA’s existing expedited programs to help foster the development and approval of these novel products. Among other things, we plan to include **certain gene therapy products that permanently alter tissue and produce a sustained therapeutic benefit** as part of the products that **will meet the definition of being eligible to come under the pathway enabled by **RMAT****. This is part of our **broader commitment** to pursue efforts that will **advance innovation** in this space. We encourage sponsors who are seeking FDA approval of their product to consider this pathway.”*

RMAT Draft Guidance – Published late 2017

- » Draft implementation guidance issued; provides clarity and support
- » Further clarity and information to support use of designation:
 - FDA should further clarify the benefits of RMAT designation regarding post-approval requirements, especially versus other expedited programs
 - FDA should publish metrics on the time between when RMAT designation was granted and when initial BLA approval is granted
 - FDA should publish a summary of why products were deemed ineligible for the designation.
- » Another issue for industry: FDA should consider expanding the type of meetings feasible for regenerative medicine therapies to “portfolio and/or platform” meetings.
 - Portfolio and/or platform meetings would be very helpful for companies developing several regenerative medicine therapies for ultra-rare diseases; expediting the development of each program by identifying synergies between them

Other Regulatory Guidance

- » *Ensure that implementation of FDA's regulatory framework provides sponsors with clear, predictable, and consistently applied rules to support product development.*
- » *FDA issued final guidance re: minimal manipulation and homologous use*
 - *Provide greater clarity about application of FDA regulations and FDA decision-making criteria*
 - *Risk-based approach*
 - *36 month period for companies to work with FDA to determine if BLA is required; enforcement discretion for certain products that are subject to the FDA's premarket review under the existing regulations, but are not currently meeting these requirements. Except for those products that pose a potential significant safety concern.*
 - *But, although the guidance on minimal manipulation mentions the Tissue Reference Group (TRG), it does not provide any information about the TRG's decision-making process*
- » *FDA enforcement actions re: "bad actors"*

Other Regulatory Issues

- » Industry looking for more guidance on CMC, labeling, and other issues as they related to cell and gene therapy products
- » Industry supports FDA actions that encourage and exercise flexibility in the development and use of standards to facilitate CBER-regulated medical product development and a more efficient evaluation of regulatory submissions.
- » FDA signaled development of disease-specific guidance for gene therapy products; hemophilia in 2018
- » FDA to continue Right to Try
 - Not workable for gene therapies, especially single administration

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