

FDA Regenerative Medicine Policy Framework and Advanced Therapy Designation

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This article discusses the policy framework established by the US Food and Drug Administration (FDA) for the regulation of regenerative medicine and advanced therapies. The four guidance documents supporting regenerative medicine regulation are summarized against the background of FDA's regulation of human cells, tissues and cellular and tissue-based products.

Introduction

In November 2017, FDA published a comprehensive Regenerative Medicine Policy Framework to stimulate innovation and support access to potentially transformative safe and effective treatments. A suite of four guidance documents provides updated clarification on what products are regulated as drugs, devices and/or biologics using a risk-based approach:

1. *Final Guidance on “Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous use”*{1}
2. *Final Guidance on “Same Surgical Procedure Exception Under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception”*{2}
3. *Draft Guidance on “Expedited Programs for Regenerative Medicine Therapies for Serious Conditions”*{3}
4. *Draft Guidance on “Evaluation of Devices Used With Regenerative Medicine Advanced Therapies”*{4}

The first guidance addresses the interpretation of the terms “minimal manipulation” and “homologous use,” while the second provides greater clarity around the “same surgical procedure” exception. The two other guidance documents relate to the implementation of the “Regenerative Medicine Advanced Therapy” (RMAT) Designation introduced by the “21st Century Cures Act.”{5} The first of these highlights expedited programs that may be available

for RMATs and the second describes FDA's intention to simplify and streamline the regulatory requirements for devices used in the recovery, isolation and delivery of RMATs.

Background

Human cells, tissues and cellular and tissue-based products (HCT/P) are “articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion or transfer into a human recipient” as defined in 21 CFR 1271.3(d).{6} In 2005, FDA implemented a tiered, risk-based approach to HCT/P regulation due to their unique nature. During the development of the risk-based regulatory approach, questions regarding: the transmission of communicable disease and the potential for contamination during the processing and preservation of tissue integrity played a major role to safeguard public health. Based on the potential risk, tissues are either regulated under Section 361 of the *Public Health Service Act (PHS Act)*{7} (361 tissues) or under Section 361 and Section 351 of the *PHS Act* (351 tissues):

- Section 361 establishes FDA's authority to regulate products to prevent the introduction and spread of communicable diseases. Together with Title 21 of the Code of Federal Regulations (CFR) 1271, the regulations explain which HCT/Ps do not require premarket approval and determine any registration, manufacturing and reporting steps required.
- Any product not falling into the criteria for 361 tissues listed in 21 CFR 1271.10{8} or eligible for exception under 21 CFR 1271.15,{9} will be regulated by Section 361 and Section 351 of the PHS Act as well as Part 1270{10} and Part 1271{11} of the *Federal Food, Drug and Cosmetic Act (FD&C Act)*;^{12} the latter requiring premarket approval of the HCT/P as a drug, biologic or device.

Minimal Manipulation and Homologous Use

The two final guidances aim to clarify the various criteria used in the determination if an HCT/P fulfils the criteria to be regulated as 361 tissue.

The “regulatory considerations for human cells, tissues and cellular and tissue-based products: minimal manipulation and homologous use”^{13} guidance addresses the minimal manipulation and homologous use criteria specified in 21 CFR 1271.10 (a)(1) and 21 CFR 1271.10(a)(2).^{14}

21 CFR 1271.10 provides the criteria for HCT/Ps regulated solely under Section 361 of the *PHS Act* and 21 CFR 1271 as follows:

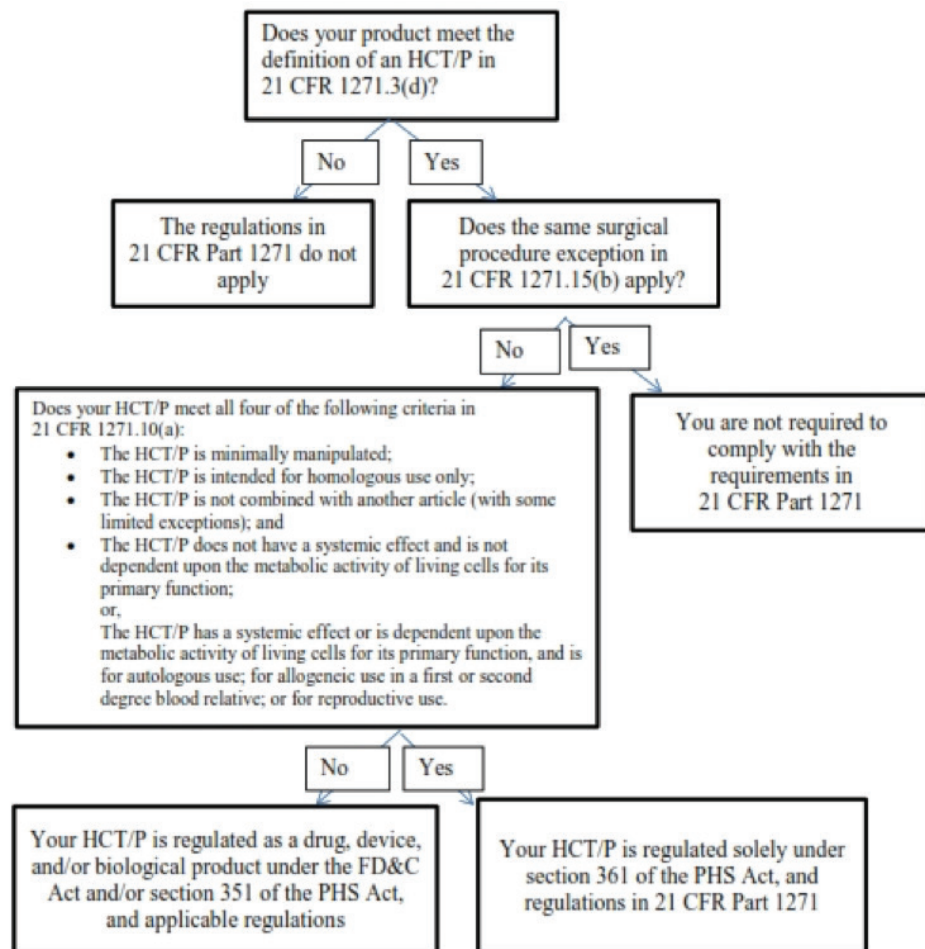
1. The HCT/P is *minimally manipulated*.
2. *The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent.*
3. *The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving or storage agent does not raise new clinical safety concerns with respect to the HCT/P.*
4. *Either:*
 - The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function or
 - The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and
 - is for autologous use
 - is for allogeneic use in a first-degree or second-degree blood relative or
 - is for reproductive use

According to 21 CFR 1271.3 (f),^{15} minimal manipulation is defined as any processing that does not alter: the relevant characteristics relating to the tissues' utility for reconstruction, repair or replacement for structural tissues and the relevant biological characteristics of cells or tissue that are non-structural. If there is no information showing that the processing does not alter the relevant characteristics, the HCT/P will be regarded as “more than minimally manipulated” and will require premarket approval.

As noted in 21 CFR 1271.3(c), “homologous use” is defined as the repair, reconstruction, replacement or supplementation of a recipient’s cells/tissues with a HCT/P performing the same basic function(s) in the recipient as the donor.

This guidance contains a flow chart to determine the regulation of a particular HCT/P and further information in a question-and-answer format. This was developed based on the many questions received from stakeholders to clarify the application of these conventions. The guidance provides a discussion of structural versus non-structural tissues and how each might be affected by processing. It also provides a detailed discussion of the various terms within the definition for homologous use. Each section is supplemented by specific examples.

Figure 1. Flowchart Illustrating the Application of the Criteria in 21 CFR 1271.15(b) and 1271.10(a){16}



Same Surgical Procedure

The “same surgical procedure exception under 21 CFR 1271.15(b): questions and answers regarding the scope of the exception”{17} guidance provides FDA’s current thinking on the “same surgical procedure exception” described in 21 CFR Part 1271.15(b){18} in a question-and-answer format. The guidance does not address any other exceptions. It has long been discussed how the following exception should be applied:

“You are not required to comply with the requirements of this part if you are an establishment that removes HCT/Ps from an individual and implants such HCT/Ps into the same individual during the same surgical procedure.”

What constitutes a same surgical procedure? What if autologous cells are implanted multiple times?

The criteria to apply for the exception are:

1. HCT/P must be removed and implanted into the same individual (i.e., autologous use).
2. Implantation must be conducted in the same surgical procedure.
3. HCT/P must remain in their original form (must remain “such HCT/P”)

“Same surgical procedure” generally means the removal of an HCT/P and implantation back into the same patient in a single operation at the same establishment (e.g., autologous skin grafting). There are limited circumstances where an HCT/P may be removed and where implantation occurs a few days later. However, generally the same institution must conduct the implantation as shipping may increase the risk of contamination. Guidance is provided for various procedures. The only HCT/P manipulations that would support the third criterion of an HCT/P to remain “such HCT/P” as defined in the guidance are rinsing, cleansing, sizing and shaping. Some processing considered minimal manipulation under 21 CFR 1271.10(a){19} may cause the HCT/P no longer to be regarded as “such HCT/P” and this exception would no longer apply.

FDA also published two draft guidance documents intended to stimulate innovation and address some of the requirements under the *21st Century Cures Act*.{20}

Expedited Programs for RMATs

The draft guidance, “*Expedited Programs for Regenerative Medicine Therapies for Serious Conditions*”{21} addresses all five expedited programs available:

1. **Fast-Track Designation:** investigational products for serious conditions with preliminary evidence for addressing an unmet medical need qualify for actions facilitating the development program and expedited review including rolling submission.
2. **Breakthrough Therapy Designation (BTD):** a therapy intended to treat a serious condition with preliminary clinical evidence of significant improvement over existing treatments on at least one clinical endpoint may qualify for all fast-track benefits plus FDA guidance on efficient product development and a commitment for senior management involvement.
3. **Regenerative Medicine Advanced Therapy (RMAT) Designation:** the RMAT designation was implemented under Section 3033 in the 21st Century Cures Act for products that are regenerative medicine advanced therapies, intended to treat, modify, reverse or cure a serious condition with available clinical evidence for addressing an unmet medical need. Benefits of receiving the designation include all those of the fast-track and BTD with additional early interactions and alternative options to fulfil post-approval requirements. Products also may be eligible for priority review and accelerated approval. To date, 15 products have been reported to have received RMAT designation (Table 1).
4. **Priority Review Designation:** priority review designation may be given to a product holding fast-track, BTD and/or RMAT designation if supported by clinical data. The designation shortens the Center for Biologics Evaluation and Research (CBER) timeframe to six months.
5. **Accelerated Approval:** accelerated approval based on surrogate or alternative endpoints is available for therapies that treat a serious condition with an extended disease course where a long period of time would be required to measure a clinical benefit if such therapy is for a serious condition and provides a meaningful benefit over existing therapies. Generally, post-approval confirmatory studies will be required.

For additional information on expedited programs in general (one to five), FDA released a guidance in May 2014.{23} This guidance applies to all drugs and biologics and also provides a tabular overview of the requirements and benefits of these expedited programs available for all types of therapies. The current draft guidance addresses more specifically considerations for the development of regenerative medicines including trial design and the use of alternative and/or experimental endpoints to determine a clinical benefit when traditional endpoints may not be specific enough.

The consultation period for this guidance closed in February 2018 and the comments received from 13 organizations and companies involved in regenerative medicine therapy development have been posted online.^{24} In addition to requests for refining some definitions (e.g., consistency in using regenerative medicine advanced therapy, interpretation of serious disease that is non-life-threatening) the main discussion point was the level of clinical evidence required for obtaining the designation and ways to achieve such. The commentators particularly asked about clarification and examples of the level of clinical evidence needed for breakthrough designation and RMAT designation and how this could be collected. To receive breakthrough therapy designation, the preliminary clinical evidence must indicate “that the product may demonstrate substantial improvement over available therapies on one or more clinically significant endpoints.”^{25} To obtain RMAT designation, the preliminary clinical evidence should demonstrate “the potential of a regenerative medicine therapy to address unmet medical needs.”^{26}

The stakeholders that commented also requested better distinction between the benefits of the breakthrough therapy designation and the RMAT designation. Particularly whether there would be an added benefit of obtaining breakthrough therapy designation in addition to the RMAT designation if this was already granted.

An additional concern noted was the maintenance of RMAT designation throughout development and necessary manufacturing changes. The guidance states “it is essential that the preliminary clinical evidence be generated using the regenerative medicine therapy,” which raised concerns about any necessary adjustments throughout the development program to accommodate any increase in the scale of the product.

The RMAT Designation Application^{27}

The sponsor submits the RMAT designation request either with an initial Investigational New Drug application (IND) or with an IND amendment at any time to the CBER. Requests must be clearly labeled in bold capital letters with “**REQUEST FOR REGENERATIVE MEDICINE ADVANCED THERAPY DESIGNATION.**” If the request is submitted with an initial IND, an additional label with “**INITIAL INVESTIGATIONAL NEW DRUG SUBMISSION**” is required.

The RMAT designation request generally contains the following:

- rationale for the new drug meeting the regenerative medicine definition
- discussion supporting the indicated disease or condition as being serious
- summary of risks and benefits of any currently available therapies
- description of the unmet medical need potentially addressed
- preliminary clinical evidence supporting the potential to address the unmet medical need for the serious condition

Preliminary clinical supporting the potential of a regenerative medicine to address an unmet medical need may not always be generated from prospective clinical trials, but also may come from studies using historical controls or retrospective studies. CBER assesses factors including “the rigor of data collection, the nature and meaningfulness of the outcomes, the number of patients or subjects, the number of sites contributing to the data and the severity, rarity or prevalence of the condition.”^{28} Although some examples are listed in the guidance, stakeholders noted during the commenting period that better clarification on the type and extent of preliminary clinical data required for a successful designation request would be beneficial.

FDA will make a decision on the request within 60 days from receipt. However, designation requests for INDs that are inactive or on clinical hold will not be accepted. Similarly, a pending designation request will not be further processed should an IND be placed on hold during the 60-day review period.

There are currently (as of end of March 2018) 15 products that have been reported to be RMAT designated (**Table 1**). According to statistics released by FDA for the period 13 December 2016 to 30 September 2017, approximately one third of the requests are granted.^{29} Of 31 requests received during that time, 17 were rejected, two withdrawn and 10 granted with two requests outstanding at the end of September 2017.

Table 1: RMAT Designated Products Listed in the Public Domain

Humacyl [®]	human acellular ves- sels	kidney failure (vas- cular access for hemodialysis)	20 March 2017	Fast-track 2014	Phase III
RVT-802	apply allogeneic thy- mus tissue to restore some immune function	DiGeorge syn- drome	17 April 2017	Orphan Drug 2017 Breakthrough Therapy 2017 Rare Pediatric Disease 2017	Phase III
jCell	human retinal progeni- tor cells release neu- rotrophins to poten- tially rescue diseased retinal cells	developmental retinitis pigmen- tosa	2 May 2017	-	Phase IIb
Ixmyelocel-T	autologous multice- llular therapy of mesen- chymal stromal cells and macrophages to repair damaged tissue	serious cardiovas- cular disease	10 May 2017	Fast-track 2017	Phase II
Stratagraft [®]	autologous skin tissue	complex skin defects due to thermal burns	18 July 2017	Orphan Drug 2012	Phase III
ATIR101 [™]	adjunctive immune- therapeutic of donor lymphocytes	blood cancers	20 Septem- ber 2017	Orphan Drug 2014	Phase III marketing authori- zation application submit- ted in the EU/2017
AST-OPC1	oligodendrocyte pro- genitor population de- rived from embryonic human stem cells	spinal cord injury	2 October 2017	Orphan Drug 2016	Phase I/II
MultiStem	bone marrow and other nonembryonic stem cells based on MAPC [®] technology	ischemic stroke	5 October 2017	Sakigake (Ja- pan) 2016	Phase III
LentiGlobin	autologous hematopoi- etic stem cells ex vivo transduced to express a functional beta- globin gene	severe sickle cell disease	October 2017	Orphan Drug (EU) 2014 Orphan Drug (US) 2014 Fast-track 2014	Phase I/II
JCAR017	CD19 directed CAR-T cell product	r/r aggressive large B-cell Non- Hodgkin Lym- phoma	1 November 2017	Orphan Drug (EU) 2017 Orphan Drug (US) 2016 Breakthrough Therapy 2016 PRIME (EU) 2016	Phase II – Phase III planned for 2018
CEVA101	autologous bone marrow-derived stem cells	traumatic brain injury	8 November 2017	-	Phase II
MPC-150-IM	mesenchymal precu- sor cells	heart failure patients with left ventricular systolic dysfunction and ventricular assist device	21 December 2017	-	Phase III

EB-101	gene-corrected autologous cell therapy	recessive dystrophic epidermolysis Bullosa	29 January 2018	Orphan Drug (EU) 2017 Orphan Drug (US) 2017 Breakthrough Therapy 2017 Rare Paediatric Disease 2017	Phase I/II – Phase III planned for 2018
CAP-1002	allogeneic Cardio-sphere-Derived Cells (CDCs)	duchenne muscular dystrophy	5 February 2018	Orphan Drug 2015 Rare Paediatric Disease 2017	Phase II
AmnioFix® Injectable	micronized amniotic tissue	osteoarthritis of the knee	9 March 2018	-	Phase IIb

Eleven products obtained other designations including but not limited to fast-track, breakthrough (see other expedited programs above) and rare pediatric disease designation as noted in the column “other designations/year” in **Table 1**. Rare pediatric diseases affect individuals from birth until 18 years of age and affect less than 200,000 persons in the US. By far the most common is the orphan drug designation (eight products) for products to treat, diagnose or prevent rare diseases or disorders affecting fewer than 200,000 people in the US.

About half the products already have progressed quite far through the development program with eight products currently in or with planned Phase III trials. Only the Asterias Biotherapeutics and BlueBird Bio products are at an early development stage not having progressed beyond Phase I/II yet, at time of writing. It should be expected that more early stage products will receive designation going forward as sponsors can take advantage of the program earlier in their clinical development program. Sponsors applying for the designation at a later stage in development can still make use of some of the benefits of the designation. However, the earlier a sponsor can enter the program the greater the benefit to the overall clinical development program.

Medical Devices Used With RMATs

The final draft guidance, “*Evaluation of Devices Used With Regenerative Medicine Advanced Therapies*,”^{30} was mandated by Section 3034 of the 21st Century Cures Act to advise sponsors on the regulatory evaluation of devices used in the “recovery, isolation or delivery of regenerative medicine advanced therapies.” “For the purpose of this guidance only, recovery means obtaining cells or tissues from a human donor, isolation is processing that results in selection, separation, enrichment or depletion of recovered cells or tissues that will become components of the final product and delivery refers to any method by which an RMAT is introduced onto or into the body of a human recipient, for example, infusion, injection, topical application, or inhalation.”

Generally, the regulatory pathway for a device varies depending on the technology employed and the intended use of the device. These will be further defined based on characteristics and conditions of use of the associated RMAT and the role the device plays in the final product.

The premarket pathway of a specific device depends on its classification in Section 513 *FD&C Act*, which establishes three classes (I—general controls, II—general and special controls and III—premarket approval - devices) based on the risk of a particular device and the controls needed to provide a reasonable assurance of safety and effectiveness. The guidance provides an overview of regulatory pathways to achieve marketing authorization including premarket notification (510(k)), de novo classification, premarket approval, humanitarian device exemption and considerations for combination products. The characteristics of cells in a cell-based RMAT will determine the characteristics of the delivery device needed (e.g., cell size, bore of needle/catheter and robustness of cells, shear force possible) and will be important in the determination of whether a particular device can obtain marketing authorization for a use limited to a specific RMAT or if a broader use can be obtained. If an RMAT has characteristics and requirements that allow for

administration with a general class of devices, that RMAT may be approved on its own with appropriate labeling for the use of such device.

Comments on this draft guidance^{31} generally welcomed that combination RMAT will be evaluated in a single application and found it useful. The evaluation of manufacturing or processing devices within the realm of the Biologics License Application (BLA) generated questions on which devices/equipment would be included, how the use of novel tools would be handled, particularly if they may not strictly be regarded as devices and also on the need for testing.

The potential for accelerated approval of a device for use in RMATs in addition to the first-time use of an RMAT was welcomed, but also generated questions around whether this would only apply to the same sponsor which created the RMAT or if FDA plans to release certain data that could be useful for subsequent use applications.

Conclusion

The guidance documents described herein, support a risk-based, flexible regulatory approach to help support innovation with the potential to bring novel treatment options to market faster. The development of advanced therapies has increased over the past number of years and many new products with varying degrees of complexity are now in the development pipeline. The newly aligned focus aims to bring into play a clearer definition and framework for HCT/Ps and designated regenerative medicine advanced therapies and how these can be specifically tailored for “best fit” clinical development and patient access.

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