

FDA Releases Comprehensive Regulatory Framework for Regenerative Medicine

November 21, 2017

Food, Drugs, and Devices

In a July 7, 2017 post to the FDA Voice blog, FDA Commissioner Scott Gottlieb announced that FDA would be releasing a “comprehensive regulatory framework” for regenerative medicine products.¹ On November 16, 2017, FDA issued four guidance documents outlining certain aspects of that framework. This alert summarizes each of the guidance documents and highlights significant issues.

Final Guidance

- Regulatory Considerations for Human Cell, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use (“Minimal Manipulation and Homologous Use Guidance”)
- Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception (“Same Surgical Procedure Guidance”)

Draft Guidance

- Expedited Programs for Regenerative Medicine Therapies for Serious Conditions (“Regenerative Medicine Expedited Programs Draft Guidance”)
- Evaluation of Devices Used with Regenerative Medicine Advanced Therapies (“Device Draft Guidance”)

FDA is accepting comments on the two draft guidance documents for a 90-day period, which ends on February 15, 2018.

The final guidance documents are intended to provide manufacturers with additional clarity in determining which (if any) FDA requirements apply to given human cells, tissues, and cellular and tissue-based products (HCT/Ps). The Regenerative Medicine Expedited Programs Draft Guidance provides information about pre-existing expedited programs that may apply to HCT/Ps, as well as the new Regenerative Medicine Advanced Therapies (RMAT) designation

¹ See Scott Gottlieb, *How FDA Plans to Help Consumers Capitalize on Advances in Science*, FDA VOICE (July 7, 2017), <https://blogs.fda.gov/fdavoices/index.php/2017/07/how-fda-plans-to-help-consumers-capitalize-on-advances-in-science/>. Commissioner Gottlieb offered a more detailed preview of the framework on August 28, 2017. See Statement from FDA Commissioner Scott Gottlieb, M.D. on the FDA’s new policy steps and enforcement efforts to ensure proper oversight of stem cell therapies and regenerative medicine (Aug. 28, 2017), <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm573443.htm>.

created by the 21st Century Cures Act.² The Device Draft Guidance was required under the 21st Century Cures Act to provide clarity on FDA's evaluation of devices used in the recovery, isolation, and delivery of RMATs.

The Commissioner's August 28 statement promised a "comprehensive policy framework that will more clearly describe the rules of the road for this new field" and that would provide product developers a more efficient process for obtaining FDA approval. It also emphasized the need for "bright lines" and "appropriate oversight." More specifically, the framework would "establish clearer lines around when these regenerative medicine products have sufficient complexity to fall under the agency's current authority, and then define an efficient process for how these products should be evaluated for safety and effectiveness." Regarding oversight, the Commissioner announced that FDA would implement "a compliance policy that, with the exception of outliers potentially harming public health in a significant way right now, will give current product developers a very reasonable period of time to interact with the FDA in order to determine if they need to submit an application for marketing authorization and to come into the agency and work on a path toward approval."

The suite of guidance documents issued on November 16 provides additional clarity around key concepts for determining whether HCT/Ps require premarket approval, whether they qualify for an exception from regulation under Part 1271, and how FDA intends to exercise enforcement discretion to allow manufacturers to come into compliance. The guidance also addresses the Commissioner's commitment to "developing a novel approach to FDA approval that we believe will allow very small product developers to gain all the benefits of FDA approval through a process that is minimally burdensome and less costly" through its implementation of the RMAT designation.

Minimal Manipulation and Homologous Use Guidance

The Minimal Manipulation and Homologous Use Guidance finalizes two separate draft guidances on those topics issued by FDA in December 2014 and October 2015, respectively.³ Minimal manipulation and homologous use are two parts of the four-part test within FDA's tiered, risk-based approach to regulating HCT/Ps.⁴ HCT/Ps are defined as "articles containing or

² Pub. L. 114-255, § 3033, 130 Stat. 1033, 1101 (2016).

³ See Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products; Draft Guidance for Industry and Food and Drug Administration Staff (December 2014) (Minimal Manipulation Draft Guidance); Homologous Use of Human Cells, Tissues, and Cellular and Tissue-Based Products; Draft Guidance for Industry and FDA Staff (October 2015) (Homologous Use Draft Guidance). It also incorporates certain aspects of previously issued draft guidance on adipose tissue. See "Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) from Adipose Tissue: Regulatory Considerations; Draft Guidance for Industry" (Adipose Draft Guidance) (December 2014). Other guidance on adipose tissue has been incorporated into the final Same Surgical Procedure Guidance. The adipose tissue material in these two final guidance documents supersedes the Adipose Draft Guidance from December 2014, which is now withdrawn. The Minimal Manipulation and Homologous Use Guidance also supersedes the September 2006 guidance document, Minimal Manipulation of Structural Tissue (Jurisdictional Update). Minimal Manipulation and Homologous Use Guidance, at 2.

⁴ The other two criteria are that (1) the HCT/P is not combined with another article (subject to certain exceptions); and (2) either (a) it has no systemic effect and is not dependent upon the metabolic activity of living cells for primary function; or (b) it has a systemic effect or is dependent upon the metabolic activity of living cells for primary function but is for autologous use, allogeneic use in close blood relative,

consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.”⁵ The four-part test determines whether an HCT/P is regulated solely under section 361 of the PHS Act and 21 C.F.R. Part 1271 (often referred to as a “361 HCT/P”) on the one hand, or as a drug, biologic, or device on the other.⁶ If an HCT/P meets the four criteria, it is a 361 HCT/P and is thereby exempt from investigational new drug application (IND) and premarket review and approval requirements.

The main goal of the Minimal Manipulation and Homologous Use Guidance is to provide clarity on what kinds of manipulation and use would satisfy those two criteria. The final guidance generally maintains the positions set forth in the draft guidances and elaborates on certain areas, including through additional examples. The guidance also announces FDA’s intention to exercise enforcement discretion as to the IND and premarket approval (biologic license application (BLA)) requirements for certain HCT/Ps under certain limited circumstances, for 36 months. FDA’s stated enforcement priorities are described below.

Minimal Manipulation

According to the guidance, to assess whether an HCT/P is no more than minimally manipulated, first a manufacturer must determine if the HCT/P is structural tissue or if it is cells or nonstructural tissue. Different definitions of minimal manipulation apply to each. Minimal manipulation of structural tissue “means that the processing of the HCT/P does not alter the original relevant characteristics of the tissue relating to the tissue’s utility for reconstruction, repair, or replacement.”⁷ Minimal manipulation of cells or nonstructural tissues “means that the processing of the HCT/P does not alter the relevant biological characteristics of cells or tissues.”⁸ Structural tissues generally are those “that physically support or serve as a barrier or conduit, or connect, cover, or cushion in the donor.”⁹ Cells or nonstructural tissues “are generally those that serve predominantly metabolic or other biochemical roles in the body such as hematopoietic, immune, and endocrine functions.”¹⁰

The guidance recognizes that HCT/Ps may perform multiple functions. FDA also recognizes that structural tissue generally contains cells. Nevertheless, the guidance states that for purposes of the regulatory framework, HCT/Ps must be classified as structural or nonstructural.¹¹ Although the guidance does not directly explain how to classify tissues with multiple functions, it provides one potentially instructive example:

or reproductive use. 21 C.F.R. § 1271.10(a). For additional background on the regulatory framework, see our September 16, 2016 alert, “FDA Holds Public Hearing and Seeks Comment on Draft Guidances Concerning Regulation of HCT/Ps” (available [here](#)).

⁵ 21 C.F.R. § 1271.3(d) (providing examples of HCT/Ps as well as articles that are not considered HCT/Ps).

⁶ See 21 C.F.R. § 1271.10(a). If an HCT/P does not qualify for any of the 1271.15 exceptions and does not satisfy the four criteria under 1271.10(a), it is regulated as a drug, device, and/or biological product under the FDCA and/or section 351 of the PHS Act, and applicable regulations, and premarket review is required. See Minimal Manipulation and Homologous Use Guidance, at 3.

⁷ *Id.* at 6 (citing 21 C.F.R. § 1271.3(f)(1)).

⁸ *Id.* (citing 21 C.F.R. § 1271.3(f)(2)).

⁹ *Id.* at 7.

¹⁰ *Id.* at 13.

¹¹ See *id.* at 7.

While adipose tissue has multiple functions, because it is predominantly composed of adipocytes and surrounding connective tissues that provide cushioning and support to the body, FDA considers adipose tissue to be a structural tissue for the purpose of applying the HCT/P regulatory framework.¹²

Next, a manufacturer should identify the original relevant characteristics of the structural tissue, or the relevant biological characteristics of the cells or nonstructural tissues, before assessing whether processing alters those characteristics. In both types of HCT/Ps, the relevant characteristics generally include the properties of the tissue or cells that contribute to its function or functions.¹³ For structural tissues, a characteristic is “original” if it exists in the donor, and is “relevant” if it “could have a meaningful bearing on the tissue’s utility for reconstruction, repair, or replacement.”¹⁴ Such characteristics could include “strength, flexibility, cushioning, covering, compressibility, and response to friction and shear.”¹⁵ For cells and nonstructural tissues, examples of relevant characteristics include “differentiation and activation state, proliferation potential, and metabolic activity.”¹⁶

According to the guidance, altering an HCT/P’s original characteristics “raises increased safety and effectiveness concerns for the HCT/P because there would be less basis on which to predict the product’s function after transplantation.”¹⁷ Therefore, the minimal manipulation determination “is based on the effect of manufacturing on those characteristics of the HCT/P as the HCT/P exists in the donor and not based on the intended use of the HCT/P in the recipient.”¹⁸

The guidance refers to a number of types of processing¹⁹—changing size or shape, removing cells from structural tissue, changing the physical state, storage, and isolating cells—and describes how each would affect whether an HCT/P is minimally manipulated. For each processing type, the guidance also provides many examples involving different types of cells and tissues—including bone, amniotic membrane, skin, adipose tissue, cartilage, ligament, and hematopoietic stem/progenitor cells—in each case articulating the relevant characteristics. For example the guidance states that the “[o]riginal relevant characteristics of bone relating to its utility to support the body and protect internal structures include strength, and resistance to compression.”²⁰ Similarly, it states that “[t]he original relevant characteristics of skin relating to its utility to serve as a protective covering generally include its large surface area, keratinized, water-resistant epithelial layer (epidermis), and dense, strong, and flexible connective tissue layer (dermis).”²¹ The guidance does not, however, provide significant guidance on how

¹² See *id.* at 8.

¹³ See *id.* at 6.

¹⁴ *Id.* at 9.

¹⁵ *Id.*

¹⁶ *Id.* at 14.

¹⁷ *Id.* at 6.

¹⁸ *Id.*

¹⁹ “Processing” means “any activity performed on an HCT/P, other than recovery, donor screening, donor testing, storage, labeling, packaging, or distribution, such as testing for microorganisms, preparation, sterilization, steps to inactivate or remove adventitious agents, preservation for storage, and removal from storage” as well as “cutting, grinding, shaping, culturing, enzymatic digestion, and decellularization.” *Id.* at 7 (citing 21 C.F.R. § 1271.2(ff)).

²⁰ *Id.* at 9 (Example 10-1).

²¹ *Id.* at 10 (Example 10-4).

manufacturers should determine the original relevant characteristics of other HCT/Ps, other than to consider the “properties of that tissue in the donor that contribute to the tissue’s function or functions.”²²

Having identified the original relevant characteristics of various structural tissues, the examples in the guidance then discuss how different types of processing do, or do not, constitute more than minimal manipulation of those tissues. For example, the guidance states that grinding bone into bone chips and particles is minimal manipulation “because the processing does not alter the bone’s original relevant characteristics relating to its utility to support bodily structures.”²³ By contrast, grinding and lyophilizing amniotic membrane and packaging it as particles would be more than minimal manipulation “because the processing alters the original relevant characteristics of the HCT/P relating to its utility to serve as a barrier.”²⁴

The minimal manipulation analysis can be particularly challenging for HCT/Ps created by extracting cells from structural tissue. Structural and nonstructural or cell-based HCT/Ps are assessed under similar standards (whether the relevant characteristics of the tissue/cell are altered). But where the process involves isolating cells from structural tissue, FDA applies the minimal manipulation definition for structural tissue, “regardless of the method used to isolate the cells.” FDA’s thinking is that the classification of the HCT/P “is based on the characteristics of the HCT/P as it exists in the donor, prior to recovery and any processing that takes place.”²⁵ In particular, FDA identifies stromal vascular fraction—considered a potential source of adipose-derived stromal/stem cells—as an example where the structural tissue definition applies, and the processing to isolate the cells is considered more than minimal manipulation because it alters the characteristics of the adipose tissue related to its utility to provide providing cushioning and support.²⁶

Relatedly, the guidance addresses whether removing cells from structural tissue is considered minimal manipulation of the remaining structural tissue. This must be assessed for each type of tissue a manufacturer processes, because “[w]hile some structural tissues may undergo processing that alters the cellular or extracellular matrix components without altering the original relevant characteristics of the tissue, *the same processing* may alter the original relevant characteristics of a different structural tissue.”²⁷ This is consistent with FDA’s position that processing to change the size or shape of structural tissue may or may not be minimal manipulation depending on whether it alters the original relevant characteristics of the structural tissue.²⁸

Homologous Use

To satisfy the homologous use prong of the four-part test, an HCT/P must be “intended for homologous use only, as reflected by the labeling, advertising, or other indications of the

²² *Id.* at 9.

²³ *Id.* at 9 (Example 10-1b).

²⁴ *Id.* at 10 (Example 10-2b).

²⁵ *Id.* at 13.

²⁶ See *id.* Stromal vascular fraction was discussed at length at the public hearing. See generally, Transcript, Part 15 Hearing: Draft Guidances Relating to the Regulation of Human Cells, Tissues, or Cellular or Tissue-Based Products (Sept. 12, 2016) (available [here](#)).

²⁷ *Id.* at 11 (emphasis added). The guidance provides examples involving removal of cells from adipose tissue, amniotic membrane, and skin. See *id.*

²⁸ See *id.* at 9.

manufacturer's objective intent."²⁹ In assessing this part of the test, FDA will first determine the intended use and then apply the definition of homologous use.³⁰

The final guidance states FDA's position on determining a manufacturer's objective intended use. Specifically, FDA will determine objective intent based on "the expressions of the manufacturer or its representatives" and/or "the circumstances surrounding the distribution of the article."³¹ Examples include "labeling, claims, advertising matter, or oral or written statements by the manufacturer or its representatives."³² Consistent with the draft guidance, FDA requires that to satisfy the homologous use prong of the four-part test, labeling, advertising, or other indications of objective intent must refer to *only* homologous uses and not any other uses.³³

The manufacturer's intended use must meet the definition of homologous use. FDA regulations at 21 C.F.R. § 1271.3(c) define homologous use to mean "the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor." The guidance explains that FDA generally considers an HCT/P to be for homologous use when it is used to repair, reconstruct, replace, or supplement recipient cells or tissues (whether or not identical to the donor cells or tissues), if they perform one or more of the same basic functions in the recipient as the cells or tissues performed in the donor.³⁴ It also reaffirms FDA's thinking that "[i]f an HCT/P is intended for use as an unproven treatment for a myriad of diseases or conditions, the HCT/P likely is not intended for homologous use only."³⁵

To determine if a use is homologous, a manufacturer must first identify whether the HCT/P is being used to "repair, reconstruct, replace, or supplement" recipient cells or tissues.³⁶ The guidance provides examples of each type of activity and notes that they are not mutually exclusive functions.³⁷ Then a manufacturer must consider what are the basic functions of the HCT/P in the donor. FDA explains that "basic function" means "what it does from a biological/physiological point of view, or is capable of doing when in its native state."³⁸ Again emphasizing that the analysis is based on the HCT/P as it exists in the donor, the guidance explains that clinical effects of the HCT/P in the recipient generally do not qualify as basic functions unless they are also attributed to the HCT/P in the donor.³⁹ The guidance suggests that it should be straightforward to identify the "basic" (*i.e.*, "commonly attributed to the HCT/P as it exists in the donor") function(s): "Basic functions are well understood; it should not be necessary to perform laboratory, pre-clinical, or clinical studies to demonstrate a basic function or functions for the purpose of applying the HCT/P regulatory framework."⁴⁰

²⁹ 21 C.F.R. § 1271.10(a)(2)

³⁰ Minimal Manipulation and Homologous Use Guidance, at 4.

³¹ *See id.* at 21.

³² *Id.*

³³ *See id.* at 20.

³⁴ *Id.* at 15.

³⁵ *See id.*

³⁶ *See id.* at 16.

³⁷ *See id.*

³⁸ *Id.*

³⁹ *See id.* at 16-17.

⁴⁰ *See id.* at 16.

Nevertheless, one change between the draft and final guidance suggests that there may be some flexibility and discretion in making this “basic function” determination. The draft guidance indicated that because the basic function of breast tissue is lactation, and lactation is not a basic function of adipose tissue, that using HCT/Ps from adipose tissue for breast augmentation would not be homologous use.⁴¹ In the final guidance, the example was revised to state that using adipose tissue “for transplantation into the subcutaneous areas of breast for reconstruction or augmentation procedures . . . is homologous use because providing cushioning and support is a basic function of adipose tissue.”⁴² This change appears to recognize that breast tissue has a basic function other than lactation, and resolve the concern that the draft guidance would have called into question the status of reconstructive surgeries, which are not intended to restore lactation.

As with minimal manipulation, the guidance provides a number of examples of whether various HCT/Ps—including hematopoietic stem/progenitor cells, amniotic membrane, adipose tissue, skin, bone, pancreatic islets—perform the same basic function in the recipient as it does in the donor. Three principles that emerge from these examples are particularly important. First, the HCT/P is not required to perform all of the basic functions in the recipient that it performed in the donor in order to qualify as homologous use.⁴³ Conversely, however, “any of the basic functions that the HCT/P is expected to perform in the recipient must be a basic function the HCT/P performed in the donor.”⁴⁴ Second, an HCT/P does not need to be used in the same anatomic location in the recipient as where it existed in the donor, as long as it performs the same basic function(s) as it did in the donor.⁴⁵ Finally, FDA appears to extend a principle from the guidance’s minimal manipulation analysis when assessing HCT/Ps extracted from structural tissue. The basic function of the structural tissue, rather than the extracted cells, is what is relevant for assessing homologous use. For example, in assessing whether the intended use of hematopoietic stem/progenitor cells from bone marrow is homologous, the guidance compares that intended use of the cells in the recipient to the basic function(s) of bone marrow in the donor.⁴⁶

Enforcement Discretion and Priorities

For a 36 month period ending on November 16, 2020, FDA plans to exercise enforcement discretion with respect to the IND and pre-market approval requirements for HCT/Ps that do not

⁴¹ See Adipose Tissue Draft Guidance, at 5 (Example B-3).

⁴² Minimal Manipulation and Homologous Use Guidance, at 19. The final guidance notes that some breast augmentation or reconstruction procedures may qualify for the same surgical procedure exception, which is discussed below. See *id.*

⁴³ *Id.* at 16. For example, an acellular dermal product used for supplemental support, protection, reinforcement, or covering for a tendon is homologous use even though the product does not perform the basic function of skin serving as a water-resistant barrier:

“Example 20-1: The basic functions of skin include covering, protecting the body from external force, and serving as a water-resistant barrier to pathogens or other damaging agents in the external environment. The dermis is the elastic connective tissue layer of the skin that covers, provides support and protects the body from mechanical stress.

a. An acellular dermal product is used for supplemental support, protection, reinforcement, or covering for a tendon. This is homologous use because in both anatomic locations, the dermis provides support and protects the soft tissue structure from mechanical stress.” *Id.* at 19-20.

⁴⁴ *Id.* at 16.

⁴⁵ *Id.* at 19.

⁴⁶ See *id.* at 17 (Example 19-1c).

meet the four-part test for 361 HCT/Ps. This enforcement discretion is intended to allow manufacturers to prepare an IND or premarket application if needed.⁴⁷ It is important to recognize, however, that this enforcement discretion is limited. Specifically, FDA intends to exercise this enforcement discretion only if “the HCT/P is intended for autologous use and its use does not raise reported safety concerns or potential significant safety concerns.”⁴⁸

FDA also intends to prioritize enforcement based on risk. Factors it will take into consideration include: “whether the product is for non-autologous (allogeneic) use and the route and site of administration.”⁴⁹ Reiterating its concern about the predictability of an HCT/P’s behavior in the recipient, FDA reasons that “HCT/Ps that are 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, are also more likely to raise significant safety concerns than HCT/Ps intended for homologous use.”⁵⁰ FDA also expresses the concern that patients may use such products instead of approved products that have been found safe and effective through the NDA or BLA process.⁵¹

Same Surgical Procedure Guidance

The Same Surgical Procedure Guidance finalizes the draft guidance on the same topic that was issued in October 2014. Like the Minimal Manipulation and Homologous Use Guidance, this guidance incorporates information on adipose tissue from the now-withdrawn Draft Adipose Guidance.⁵² We addressed the draft Same Surgical Procedure Guidance and Draft Adipose Tissue Guidance in our September 16, 2016 alert, “FDA Holds Public Hearing and Seeks Comment on Draft Guidances Concerning Regulation of HCT/Ps” (available [here](#)). The final guidance retains much from the draft, and adds a few new questions and answers.

21 C.F.R. § 1271.15(b) Exception

An establishment is not required to comply with the requirements of Part 1271 if it is “an establishment that removes HCT/Ps from an individual and implants such HCT/Ps into the same individual during the same surgical procedure.”⁵³ To qualify for the exception, three criteria must be met:

1. The establishment must remove and implant the HCT/Ps into the same individual from whom they were removed (autologous use);
2. The implanted HCT/Ps must be the same HCT/Ps that were removed (*i.e.*, they must remain “such HCT/Ps”; and
3. The HCT/Ps must be implanted within the same surgical procedure.⁵⁴

The rationale for this exception is that “autologous cells or tissues that are removed from an individual and implanted into the same individual without intervening processing steps beyond

⁴⁷ *Id.* at 21.

⁴⁸ *Id.*

⁴⁹ *Id.*

⁵⁰ *See id.*

⁵¹ *Id.*

⁵² *See* Same Surgical Procedure Guidance, at 1.

⁵³ *Id.* at 2.

⁵⁴ *Id.* at 4.

rinsing, cleansing, sizing, or shaping, raise no additional risks of contamination and communicable disease transmission beyond that typically associated with surgery.”⁵⁵ FDA considers this to be a narrow exception.⁵⁶

The final Same Surgical Procedure Guidance provides an explanation of the relationship between the same surgical procedure exception and the four-part test under 1271.10(a) described above for determining if an HCT/P is regulated solely under Part 1271. 21 C.F.R. § 1271.15 provides several exceptions from the requirements in Part 1271. If an HCT/P does not qualify for any of those exceptions, then the manufacturer must apply the four-part test in 1271.10(a) to determine whether the HCT/P is regulated solely under section 361 of the PHS Act and Part 1271, or alternatively regulated as a drug, biologic, and/or medical device. In other words, if an establishment qualifies for the Same Surgical Procedure exception, it is not subject to FDA regulation and does not need to evaluate whether it meets the four-part test under 1271.10(a).

Meaning of “Such HCT/P”

The Same Surgical Procedure Guidance emphasizes that to qualify for the exception, the HCT/P must remain “such HCT/P” (*i.e.*, in its original form) after the surgical procedure in question. This standard is stricter than the standard for minimal manipulation under the four-part test. Consistent with the draft guidance, the final guidance explains that “[g]enerally, the only processing steps that will allow an HCT/P to remain ‘such HCT/P’ are rinsing, cleansing, sizing, and shaping.”⁵⁷ Any other processing steps, even if considered minimal manipulation, generally will cause the HCT/P to no longer be “such HCT/P,” and therefore outside of the scope of the same surgical procedure exception.⁵⁸ In support of this limitation, FDA reasons that “[p]rocessing of the autologous HCT/P raises safety concerns, such as contamination and cross-contamination, beyond those typically associated with surgery.”⁵⁹

The final guidance offers further information on what level of processing can allow an HCT/P to remain “such HCT/P,” including examples of permissible sizing and shaping.⁶⁰ For example, FDA distinguishes between adipose tissue that is centrifuged to remove debris and extracellular fluid, from adipose tissue that is processed to isolate cellular components.⁶¹ The tissue in the first example remains “such HCT/P,” while the tissue in the second example does not, and therefore would not qualify for the exception.

“Same Surgical Procedure”

The final guidance maintains FDA’s pre-existing position that “[g]enerally . . . procedures consisting of more than a single operation are not considered the same surgical procedure.”⁶² However, it goes on to state that establishments that perform (a) craniotomy or craniectomy with subsequent implantation of the bone flap to reverse the cranial defect, or (b) parathyroidectomy with subsequent implantation of a portion of the tissue to preserve parathyroid function, may

⁵⁵ *Id.* at 3.

⁵⁶ *Id.*

⁵⁷ *Id.* at 5.

⁵⁸ *Id.*

⁵⁹ *Id.* at 7.

⁶⁰ *Id.* at 7-8.

⁶¹ *Id.*

⁶² *Id.* at 5.

qualify for the “same surgical procedure” exception even though removal and implantation of the applicable HCT/P takes place several days apart.⁶³ In those cases, however, no processing or manufacturing steps other than rinsing, cleansing, labeling, and temporary storage may be performed in the intervening period.⁶⁴

The exception allowing multiple procedures typically applies only when the removal and implantation occur at the same establishment.⁶⁵ However, FDA does not intend to object if an HCT/P is shipped to another establishment for reimplantation under very limited circumstances for craniotomy, craniectomy, or parathyroidectomy procedures.⁶⁶ In those cases, reimplantation at another establishment must be medically necessary, and precautions must be taken to protect the HCT/P from contamination and cross-contamination. It is unclear from the final guidance whether procedures other than the specified craniotomy, craniectomy, and parathyroidectomy procedures could qualify for the same surgical procedure exception if it is necessary for the reimplantation of the HCT/P to be performed at a different establishment.

Expedited Programs for Regenerative Medicine Therapies for Serious Conditions Draft Guidance

In the Regenerative Medicine Expedited Programs Draft Guidance, FDA provides its recommendations for the expedited development of regenerative medicine therapies intended to treat serious or life-threatening diseases or conditions. In so doing, it expands upon the existing guidance for Expedited Programs for Serious Conditions – Drugs and Biologics, dated May 2014 (2014 Expedited Programs Guidance) and explains how the programs addressed in that guidance apply to regenerative medicine therapies. It also attempts to clarify certain aspects of the new RMAT Designation, which Congress created as part of the recently enacted 21st Century Cures legislation.

Regenerative medicine therapies⁶⁷ intended to treat serious conditions are eligible for all of FDA’s expedited programs: fast track designation, breakthrough designation, RMAT designation, accelerated approval, and priority review.⁶⁸ The Regenerative Medicine Expedited Programs Draft Guidance briefly describes the pre-existing programs, and summarizes several of the applicable terms: “serious disease or condition,” “unmet medical need,” “surrogate endpoint,” “intermediate clinical endpoint,” and “clinically significant endpoint.”⁶⁹ Readers should consult the 2014 Expedited Programs Guidance for more information on these programs and detailed explanations of the key terms.

⁶³ *Id.*

⁶⁴ *Id.* at 5-6.

⁶⁵ *Id.* at 6 (noting that shipping the HCT/P raises additional safety concerns).

⁶⁶ *Id.*

⁶⁷ Section 506(g)(8) of the FDCA defines “regenerative medicine therapy” as “cell therapy, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products, except for those regulated solely under section 361 of the Public Health Service Act and part 1271 of title 21, Code of Federal Regulations.”

⁶⁸ Regenerative Medicine Expedited Programs Draft Guidance, at 2.

⁶⁹ *Id.* at 3. The draft guidance uses “condition” and “disease” interchangeably, and “serious condition” refers to any serious or life-threatening disease or condition, or serious aspect of a disease or condition.

RMAT Designation

The Regenerative Medicine Expedited Programs Draft Guidance also addresses RMAT designation, which is the newest expedited program applicable to regenerative medicine therapies. Congress specifically provided for expedited development and review of RMATs by adding section 506(g) to the Federal Food, Drug, and Cosmetic Act (FDCA) in December 2016.⁷⁰ CBER may grant RMAT designation to an investigational drug if (1) the drug “meets the definition of regenerative medicine therapy,” (2) the drug “is intended to treat, modify, reverse, or cure a serious condition,” and (3) “preliminary clinical evidence indicates that the regenerative medicine therapy has the potential to address unmet medical needs for such condition.”⁷¹

RMAT designation has several features in common with fast track and breakthrough therapy designations, and also some noteworthy differences. Like breakthrough therapy designation, RMAT designation requires preliminary clinical evidence. In contrast, fast track designation may be based on preclinical or clinical data. Breakthrough therapy designation also has stricter qualifying criteria than RMAT designation. As the Regenerative Medicine Expedited Programs Draft Guidance points out, breakthrough therapy designation requires preliminary clinical evidence indicating that the drug may demonstrate *substantial improvement on a clinically significant endpoint over available therapies*.⁷² RMAT designation requires only that preliminary evidence indicate that the drug has the *potential to address unmet medical needs* for the serious disease or condition.⁷³

The Regenerative Medicine Expedited Programs Draft Guidance provides FDA’s views on the kinds of preliminary clinical evidence that are required to demonstrate the potential of a regenerative medicine therapy to address unmet medical needs. In general, clinical investigations should be “specifically conducted to assess the effects of the therapy on a serious condition.”⁷⁴ Particularly in the early stages of development, CBER may be willing to accept evidence from investigations other than prospective clinical trials with a concurrent control.⁷⁵ Examples of other types of studies that may be acceptable in some cases include “studies with appropriately chosen historical controls” or “well-designed retrospective studies or clinical case series that provide data systematically collected by treating physicians.”⁷⁶ The draft guidance emphasizes that clinical evidence must be generated using the regenerative medicine therapy being developed, not a related product.⁷⁷

CBER will consider several factors in assessing the sufficiency of preliminary clinical evidence in support of RMAT designation. Those factors include: “the rigor of data collection; the nature and meaningfulness of the outcomes; the number of patients or subjects, and the number of sites, contributing to the data and the severity, rarity, or prevalence of the condition.”⁷⁸ As noted

⁷⁰ *Id.* at 2.

⁷¹ *Id.* at 5.

⁷² *Id.* at 8 (table).

⁷³ *Id.*

⁷⁴ *Id.* at 6.

⁷⁵ *Id.*

⁷⁶ *Id.*

⁷⁷ *See id.*

⁷⁸ *Id.*

above, unlike breakthrough designation, RMAT designation does not require a showing that the drug⁷⁹ may offer a substantial improvement over available therapies.

The draft guidance provides procedural guidance for sponsors seeking RMAT designation. A sponsor may apply for RMAT designation by submitting a request to CBER with a new IND or in an IND amendment. Requests should include a concise summary of supporting information, including:

- A rationale for the investigational new drug meeting the definition of a regenerative medicine therapy;
- A discussion to support that the disease or condition, or the aspect of the disease or condition, that the product is intended to treat is serious;
- A summary of the risks and benefits associated with any therapies currently available for the condition;
- A description of the unmet medical need that the regenerative medicine product has the potential to address; and
- The preliminary clinical evidence showing that the product has the potential to address a specified unmet medical need for this serious condition.⁸⁰

Accelerated Approval

The Regenerative Medicine Expedited Programs Draft Guidance explains how FDA's accelerated approval program will be applied to RMAT designated products. As added by the Cures Act, FDCA section 506(g) makes clear that products that have been granted RMAT designation are eligible for accelerated approval. However, the statute applies a revised set of eligibility criteria as compared to the criteria available for accelerated approval for other products. Under FDCA section 506(c), FDA may grant accelerated approval based on a showing of an effect on (a) a surrogate endpoint that is reasonably likely to predict clinical benefit, or (b) an "intermediate clinical endpoint."⁸¹ RMAT products may qualify for accelerated approval based on (1) "previously agreed-upon surrogate or intermediate endpoints that are reasonably likely to predict long-term clinical benefit," or (2) "reliance upon data obtained from a meaningful number of sites, including through expansion to additional sites, as appropriate."⁸²

The draft guidance attempts to explain the second option, and what qualifies as a "meaningful" number of sites. Specifically, CBER "expect[s] that the determination of whether the number of investigational sites, even if limited, is 'meaningful' will depend on whether the evidence of effectiveness is likely to be affected by a site-specific or investigator-specific bias, such that any conclusions regarding the product's effectiveness could not be reliably generalized to other sites."⁸³ CBER also anticipates that this will be a case-by-case determination in the BLA

⁷⁹ With respect to expedited programs, the draft guidance uses "drug" or "drug products" to refer to human drugs, including drugs that are biological products, unless otherwise specified. See *id.* at 4. "As a general matter, however, th[e] guidance addresses regenerative medicine therapies regulated by CBER as biological products under the FD&C Act, section 351 of the PHS Act (42 U.S.C. 262), and applicable regulations." *Id.*

⁸⁰ See *id.* at 7.

⁸¹ 21 U.S.C. §356(c).

⁸² Regenerative Medicine Expedited Programs Draft Guidance at 9.

⁸³ *Id.*

review.⁸⁴ There remain a number of questions as to how this will work in practice, and the determination appears to be highly discretionary.

The draft guidance also discusses requirements for post-approval confirmatory studies for RMAT products that receive accelerated approval. FDCA section 506(g) specifies that sponsors of RMAT products may satisfy the accelerated approval confirmatory study requirement through, as appropriate:

- The submission of clinical evidence, clinical studies, patient registries, or other sources of real world evidence such as electronic health records;
- The collection of larger confirmatory data sets as agreed upon during product development; or
- Post-approval monitoring of all patients treated with such therapy prior to approval of the therapy.⁸⁵

The draft guidance makes clear that FDA will determine the type of evidence required to satisfy the confirmatory study requirement on a case-by-case basis. It also articulates some of the considerations that CBER will use for making this determination. These include “the nature of the product and its administration, the evidence supporting marketing approval, the nature and magnitude of the intended benefit, the size of the target population, and the feasibility of obtaining confirmatory evidence.”⁸⁶

Clinical Development Considerations

Because regenerative medicine therapies are often developed to treat serious and rare diseases, the draft guidance makes clear that CBER intends to “work with sponsors and encourage flexibility in clinical trial design.”⁸⁷ This includes, for example, willingness to find novel endpoints, as well as innovative clinical trial designs.⁸⁸ In his August 28, 2017 statement, Commissioner Gottlieb recognized the costs of innovation and FDA registration trials for small companies developing regenerative medicine therapies. As a result, he stated that FDA “will also be developing a novel approach to FDA approval that we believe will allow very small product developers to gain all the benefits of FDA approval through a process that is minimally burdensome and less costly.”⁸⁹

The Regenerative Medicine Expedited Programs Draft Guidance articulates one such novel approach. Specifically, for regenerative medicine therapies for “more common diseases,” CBER states that it may be appropriate for multiple clinical sites to participate in a multi-center trial “with the intent of sharing the combined clinical trial data to support BLAs from each of the individual centers/institutions.”⁹⁰ Each such site would use a common manufacturing protocol and product quality testing specifications. Each center/institution could then submit a BLA that

⁸⁴ *Id.*

⁸⁵ *Id.* at 10.

⁸⁶ *Id.*

⁸⁷ *Id.*

⁸⁸ *See id.* at 11.

⁸⁹ *See* Statement from FDA Commissioner Scott Gottlieb, M.D. on the FDA’s new policy steps and enforcement efforts to ensure proper oversight of stem cell therapies and regenerative medicine (Aug. 28, 2017), <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm573443.htm>.

⁹⁰ Regenerative Medicine Expedited Programs Draft Guidance, at 11.

relied on both that center/institution's data from its own site(s) as well as on combined data from all the sites that participated in the trial.⁹¹

Evaluation of Devices Used with RMATs Draft Guidance

The last of the four new guidances, and the second draft guidance, lays out FDA's current thinking on evaluation of devices used in the recovery, isolation, or delivery of RMATs.⁹²

The Device Draft Guidance is limited in scope. Specifically, it applies only to devices that are used solely for the recovery, isolation, or delivery of an RMAT. Devices that are used for additional functions beyond recovery, isolation or delivery are not within the scope of the Device Draft Guidance. For example, FDA states that a scaffold combined with a cellular product generally would not fit within the scope of the Device Draft Guidance because such scaffolds usually provide more than a delivery function, including physical support and/or reinforcement in or on the body. The Device Draft Guidance provides the following definitions:

- *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.⁹³

The 21st Century Cures Act directed FDA to issue guidance addressing, among other topics, "what, if any, intended uses or specific attributes would result in a device used with a regenerative therapy product to be classified as a class III device."⁹⁴ But the Device Draft Guidance provides little specific guidance as to how devices used in the recovery, isolation, or delivery of RMATs will be classified or reviewed. Indeed, the Device Draft Guidance states that "at this time" the agency is "unable to provide a definitive list of intended uses or specific attributes that would result in a standalone device used with an RMAT being classified as a Class III device, but have instead addressed this requirement by providing information about characteristics of Class III devices."⁹⁵

In evaluating the appropriate review pathway for a device used in recovery, isolation, or delivery of an RMAT, FDA plans to rely on the same general approaches it applies to other devices. The Device Draft Guidance states that "[t]he appropriate regulatory evaluation pathway for devices used in the recovery, isolation, or delivery of RMATs and for Center jurisdiction for such devices may vary depending upon the devices' technological characteristics intended uses."⁹⁶ It then goes on to provide a detailed summary of FDA's general approach to device classification and premarket review.⁹⁷ The Device Draft Guidance does address regulation of RMATs and devices

⁹¹ *Id.*

⁹² Device Draft Guidance.

⁹³ *Id.* at 4.

⁹⁴ Pub. L. 114-255, § 3034, 130 Stat. 1033, 1103 (2016).

⁹⁵ Device Draft Guidance, at 2 n.2.

⁹⁶ *Id.* at 5.

⁹⁷ *Id.* at 6.

intended for use in recovery, isolation, or delivery of an RMAT as combination products. The Device Draft Guidance states that RMAT-based combination products (like combination products generally) will most often be reviewed under a single application. This approach is consistent with section 503(g) of the FDCA (as amended by the 21st Century Cures Act⁹⁸), which states that FDA shall conduct the premarket review of a combination product under a single application “whenever appropriate.” In the case of devices covered by the Device Draft Guidance, this typically will be a BLA evaluated by CBER.⁹⁹ However, FDA also notes that some such devices, including certain general use devices (such as surgical tools, syringes, apheresis collection devices, and catheters), may be evaluated independently as stand-alone devices using traditional medical device applications.¹⁰⁰ Separate marketing applications may also be appropriate where the device may ultimately be labeled for use with multiple RMATs that have similar characteristics and administration requirements.¹⁰¹

Finally, the Device Draft Guidance discusses factors that FDA will consider in evaluating whether marketing authorization for a device should be limited to use with a specific RMAT or the device can obtain marketing authorization for a broader use. Given the diversity of potential RMAT products, FDA discusses a broad range of potentially relevant factors. For example, FDA notes that in the case of cell-based products, “the interaction between cells and a delivery device can have an impact on critical characteristics, such as cell viability, differentiation potential, activation state and ability to respond to stimuli after administration.”¹⁰² FDA points to additional factors such as cell size and sensitivity to shearing forces that can impact “the potential utility of a given delivery device with a specific RMAT.”¹⁰³ The Device Draft Guidance advises that it may be necessary to repeat testing to assess interactions of each new device-RMAT combination because cellular products can possess extremely variable sensitivities to physical and chemical stimuli.¹⁰⁴ On the other hand, FDA acknowledges that a RMAT may be approved on its own with appropriate labeling for use with a general class of devices (e.g., conventional syringe) or a subset of delivery devices with defined characteristics, if the RMAT is determined to have characteristics and use requirements that would allow it to be administered with such devices without compromising the safety and efficacy of the RMAT.¹⁰⁵

Comments on Draft Guidance Documents

FDA is accepting comments on the draft guidance documents until February 15, 2018. Instructions for submitting comments are available in the Federal Register notices announcing availability of the draft guidance documents.¹⁰⁶

⁹⁸ Pub. L. 114-255, § 3038, 130 Stat. 1033, 1105 (2016).

⁹⁹ Device Draft Guidance, at 10.

¹⁰⁰ *Id.*

¹⁰¹ *Id.*

¹⁰² *Id.* at 11.

¹⁰³ *Id.*

¹⁰⁴ *Id.*

¹⁰⁵ *Id.*

¹⁰⁶ 82 Fed. Reg. 54385 (Nov. 17, 2017) (Regenerative Medicine Expedited Programs Draft Guidance) and 82 Fed. Reg. 54349 (Nov. 17, 2017) (Device Draft Guidance).

If you have any questions concerning the material discussed in this client alert, please contact the following members of our Food, Drugs, and Devices practice:

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