

# FDA Holds Public Hearing and Seeks Comment on Draft Guidances Concerning Regulation of HCT/Ps

September 16, 2016

Food, Drugs, and Devices

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On September 12 and 13, 2016, the U.S. Food and Drug Administration (FDA) held a two-day public hearing to obtain input on four draft guidance documents issued by the agency concerning human cells, tissues, and cellular and tissue-based products (HCT/Ps).<sup>1</sup> The draft guidances (collectively, the “HCT/P Draft Guidances”) covered by the hearing were:

- Same Surgical Procedure Exception Under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception (October 2014) (“Same Surgical Procedure Draft Guidance”);
- Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (December 2014) (“Minimal Manipulation Draft Guidance”);
- Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) from Adipose Tissue: Regulatory Considerations (December 2014) (“Adipose Tissue Draft Guidance”); and
- Homologous Use of Human Cells, Tissues, and Cellular and Tissue-Based Products (October 2015) (“Homologous Use Draft Guidance”).

During the hearing, industry stakeholders, physicians, researchers, and patient advocates voiced their opinions about the HCT/P Draft Guidances and emphasized the importance of preserving access to innovative cell therapies while simultaneously protecting patients. FDA is accepting comments on the HCT/P Draft Guidances until September 27, 2016.<sup>2</sup>

To help interested parties that are considering submitting comments to any of the HCT/P Draft Guidances, this client alert summarizes each of the guidance documents, highlights significant areas of discussion during the public hearing, and provides insights on potential areas for further discussion with the agency.

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<sup>1</sup> See 81 Fed. Reg. 23661, 23661 (Apr. 22, 2016). FDA previously had announced a 1-day public hearing for April 13, 2016, but postponed it due to considerable interest in the public hearing and to give stakeholders additional time to provide comments to the agency.

<sup>2</sup> See 81 Fed. Reg. 23664, 23664 (Apr. 22, 2016).

## Background

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In February 1997, FDA announced a new framework for the regulation of HCT/Ps, which sought to provide “a unified approach to the regulation of both traditional and new products.”<sup>3</sup> FDA acknowledged that the then-existing approach to the regulation of HCT/Ps was fragmented and unclear, leading to both industry and FDA reviewer confusion. A report discussing the proposed regulatory approach, “Reinventing the Regulation of Human Tissues,” was produced in conjunction with Vice President Al Gore’s National Performance Review. Therein, FDA explained that “[a]lthough [HCT/Ps] are often the result of the newest technologies, the concepts and procedures under which they are regulated were developed many years ago, and sometimes are ill-suited for their purpose.”<sup>4</sup> The new framework, which would regulate HCT/Ps based on a tiered, risk-based approach, “would maintain or improve protection of the public and increase public confidence in these new technologies, while permitting significant innovation to go forward unfettered by unnecessary regulatory requirements.”<sup>5</sup>

HCT/Ps are “articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.”<sup>6</sup> Under 21 C.F.R. Part 1271, FDA employs the aforementioned tiered, risk-based approach to regulating HCT/Ps, where the level of regulation applicable to the product is proportional to the product’s degree of risk. FDA regulates higher risk HCT/Ps as drugs, biologics, or medical devices. Such products are subject to the IND/IDE requirements to conduct clinical trials, and the premarket review and approval/clearance requirements applicable to traditional drugs, biologics, and devices. Lower risk HCT/Ps, however, are exempt from these requirements. Such products frequently are referred to as “361 HCT/Ps” because FDA regulates them solely pursuant to section 361 of the Public Health Service Act (PHSA), which gives FDA authority to promulgate regulations to control the spread of communicable diseases.

FDA will consider an HCT/P to be “low risk,” and therefore regulated as a 361 HCT/P, if it meets all of the following criteria:

- It is minimally manipulated;
- It is intended for homologous use only;
- It is not combined with another article (subject to certain exceptions); and
- Either

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<sup>3</sup> FDA, [Proposed Approach to Regulation of Cellular and Tissue-Based Products](#), at 6 (Feb. 28, 1997) [hereinafter HCT/P Regulation Proposed Approach] (last accessed Sept. 14, 2016). See also FDA, [Proposed Approach to Regulation of Cellular and Tissue-Based Products; Availability and Public Meeting](#), 62 Fed. Reg. 9721, 9722 (Mar. 4, 1997) (announcing document’s availability and public meeting).

<sup>4</sup> FDA, [Reinventing the Regulation of Human Tissue](#) (Feb. 1997) (last accessed Sept. 14, 2016).

<sup>5</sup> *Id.* See also FDA, Final Rule, Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing, 66 Fed. Reg. 5447, 5447 (Jan. 19, 2001) (“The goal of the new approach is to improve protection of the public health without imposing unnecessary restrictions on research, development, or the availability of new products.”).

<sup>6</sup> 21 C.F.R. § 1271.3(d).

- It has no systemic effect and is not dependent upon the metabolic activity of living cells for primary function; or
- 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, or reproductive use.<sup>7</sup>

As noted above, a low-risk product will be regulated solely under section 361 of the PHSA, and FDA's implementing regulations at 21 C.F.R. Part 1271, unless it qualifies for an exception. For example, Part 1271 specifically exempts establishments from complying with the requirements of Part 1271 if the HCT/P is removed from an individual and then implanted into the same individual during the same surgical procedure.<sup>8</sup> Such products are not subject to any regulation by FDA.

FDA has established a body known as the Tissue Reference Group (TRG) to "assist in making jurisdictional decision and applying consistent policy to [HCT/Ps]."<sup>9</sup> The TRG is composed of three employees from the Center for Biologics Evaluation and Research (CBER) and three employees from the Center for Devices and Radiological Health (CDRH). A manufacturer may submit a description of its HCT/P product to the TRG for purposes of receiving an advisory opinion as to whether FDA would regulate the product as a 361 HCT/P.<sup>10</sup> A manufacturer is not required, however, to seek a TRG opinion. Many manufacturers simply place their HCT/Ps on the market based on a self-determination that their products meet the requirements to be regulated as 361 HCT/Ps.<sup>11</sup>

Each year since 1998, the TRG publishes a report detailing the recommendations the group made during the previous fiscal year concerning the application of the 361 HCT/P criteria to particular products, as well as other issues pertaining to the regulations in Part 1271. Over the past several years, in the vast majority of cases the TRG has declined to classify products as 361 HCT/Ps. In most cases, this determination is made on the basis that the product is (a) not intended for homologous use, or (b) more than minimally manipulated. Accordingly, what FDA considers to be homologous use and minimal manipulation are critical to the determination of what types of products might qualify for regulation as 361 HCT/Ps. Thus, FDA's recently released guidance documents on homologous use and minimal manipulation, both of which were discussed at the public hearing, are of critical importance.

## Homologous Use Draft Guidance

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FDA's regulations at 21 C.F.R. § 1271.3 define homologous use as "the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs

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<sup>7</sup> *Id.* § 1271.10(a).

<sup>8</sup> *Id.* § 1271.15(b).

<sup>9</sup> HCT/P Regulation Proposed Approach, *supra* note 3, at 16.

<sup>10</sup> A manufacturer may also submit a request for designation to the Office of Combination Products (OCP) to obtain a formal classification of HCT/P, or contact OCP to obtain an informal classification. *Adipose Tissue Draft Guidance*, at 10.

<sup>11</sup> See HCT/P Regulation Proposed Approach, *supra* note 3, at 18, 19.

the same basic function or functions in the recipient as in the donor.”<sup>12</sup> In the Homologous Use Draft Guidance, FDA provides guidance on its interpretation of this definition and its components (i.e., “same basic function or function” and “repair, reconstruction, replacement, or supplementation”). In the guidance document, FDA explains that it:

consider[s] an HCT/P to be for homologous use when it is used to repair, reconstruct, replace, or supplement:

- Recipient cells or tissues that are identical (e.g., skin for skin) to the donor cells or tissues, and perform one or more of the same basic functions in the recipient as the cells or tissues performed in the donor; or,
- Recipient cells that may not be identical to the donor’s cells, or recipient tissues that may not be identical to the donor’s tissues, but that perform one or more of the same basic functions in the recipient as the cells or tissues performed in the donor.<sup>13</sup>

FDA notes that if an HCT/P “is intended for use as an unproven treatment for a myriad of diseases or conditions, the HCT/P is likely not intended for homologous use only.”<sup>14</sup> The Homologous Use Draft Guidance provides several examples of what is, and what is not, homologous use for various tissues and cells under 21 C.F.R. Part 1271, including for tissues such as pericardium, corneal tissue, veins and arteries, amniotic membrane, and skin, and cells including hematopoietic stem/progenitor cells and pancreatic islets.

### **“Same Basic Function or Functions”**

Because the regulatory definition of “homologous use” references cells or tissues that perform the “same basic function or functions” in the recipient as in the donor, FDA’s interpretation of the term “same basic function” is important. According to FDA, “the same basic function or functions” refers to the basic functions the HCT/P performs in the donor and would be expected to perform in the recipient following the transfer. Thus, a homologous use for a structural tissue would be to perform a structural function (e.g., serve as a barrier or conduit) in the recipient, and a homologous use for a cellular or nonstructural tissue would be a metabolic or biochemical function (e.g., hematopoietic, immune, or endocrine function) in the recipient. Performing the same basic function or functions does not require that the HCT/P be used in the same anatomical location in the recipient as the donor. For example, the TRG has determined that decellularized allogeneic fascia lata—the deep fascia of the thigh—and pericardium—the membrane enclosing the heart—used as wound coverings for defects in dura mater—the

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<sup>12</sup> 21 C.F.R. § 1271.3(c). The Homologous Use Draft Guidance explains that repair “generally means the physical or mechanical restoration of tissues,” reconstruction “generally means surgical reassembling or re-forming,” replacement “generally means substitution of a missing tissue or cell,” and supplementation “generally means to add to, or complete[.]” Homologous Use Draft Guidance, at 4. Because these functions are not mutually exclusive, an HCT/P can perform one or more of the repair, reconstruction, replacement, or supplementation functions for a given intended use. *Id.*

<sup>13</sup> Homologous Use Draft Guidance, at 3.

<sup>14</sup> *Id.*, at 4.

outermost membrane surrounding the brain and spinal cord—is homologous use, and such products can be regulated as a 361 HCT/P.<sup>15</sup>

### **Determining Whether an HCT/P is Intended for Homologous Use**

According to FDA regulation, whether an HCT/P is intended for homologous use only is determined by its labeling, advertising, or other indications of the manufacturer’s objective intent.<sup>16</sup> Tracking the language in 21 C.F.R. § 201.128 on the meaning of “intended uses” for drugs, FDA explains that a manufacturer’s objective intent is determined by the manufacturer’s or its representatives’ expressions, or the circumstances surrounding the distribution of the article, and “may be shown by the circumstances that the article is, with the knowledge of the manufacturer or its representatives, offered and used for a purpose for which it is neither labeled nor advertised.”<sup>17</sup> The precise nature of what FDA can look to in order to determine a manufacturer’s objective intent has been subject to some controversy and is not further addressed in the Homologous Use Draft Guidance.

### **Issues Raised by the Homologous Use Draft Guidance**

The Homologous Use Draft Guidance raises critical questions about how to define an HCT/P’s basic function(s) and the intended function(s) of the HCT/P in the recipient. Stakeholders may wish to seek clarification on some of these points. For example, FDA’s draft guidance is silent as to how to determine the basic function(s) of a specific HCT/P, even though the definition plays a crucial role in evaluating whether a product’s intended use is homologous use. Indeed, FDA’s descriptions of specific structural tissues vary across the HCT/P Draft Guidances.<sup>18</sup> This discrepancy in scope and specificity could lead to confusion and inconsistent application of the regulations. Additionally, as a few speakers mentioned during the public hearing, stakeholders may benefit from FDA broadening the scope of the guidance to address other cellular therapies—such as those derived from totipotent and pluripotent stem cells—and explaining what the agency considers to be the “basic function” of these cells and how such a determination is made. Furthermore, FDA indicates that a determination of homologous use is not possible if there is “insufficient evidence” to support a particular proposed basic function of a cell or tissue.<sup>19</sup> FDA does not address, however, what level of evidence is necessary to substantiate a claimed basic function, or what an HCT/P establishment must demonstrate to support the claimed basic function. Stakeholders may benefit from the agency addressing these

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<sup>15</sup> See FDA, [TRG FY 2008 Update](#) (last accessed Sept. 14, 2016). Although the TRG opinion does not provide a detailed analysis, the Homologous Use Draft Guidance states that one of the basic functions of pericardium in the donor is to “serve as a covering,” which makes pericardium intended to be used as a wound covering for dura mater defects homologous use. Homologous Use Draft Guidance, at 4.

<sup>16</sup> 21 C.F.R. § 1271.10(a)(2).

<sup>17</sup> Homologous Use Draft Guidance, at 7.

<sup>18</sup> *Compare id.*, at 5-6 (explaining that the basic functions of amniotic membrane include “covering, protecting, serving as a selective barrier for the movement of nutrients between the external and in utero environment, and to retain fluid in utero”) and Minimal Manipulation Draft Guidance, at 5 (explaining amniotic membrane “serves as a covering”).

<sup>19</sup> Homologous Use Draft Guidance, at 5.

issues, among others raised by the Homologous Use Draft Guidance, prior to finalizing the guidance document.

## Minimal Manipulation Draft Guidance

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The Minimal Manipulation Draft Guidance offers FDA's current thinking on the requirement that the HCT/P be "minimally manipulated" to qualify as a 361 HCT/P. FDA's regulations provide two definitions of minimal manipulation—one for structural tissue, and one for cells or nonstructural tissue. According to that regulation, minimal manipulation of structural tissue means "processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement."<sup>20</sup> Minimal manipulation of cells or nonstructural tissue means "processing that does not alter the relevant biological characteristics of cells or tissues."<sup>21</sup> Central to both definitions of minimal manipulation is the level of processing of the HCT/P. In FDA's regulations, "processing" is defined as "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."<sup>22</sup> In the draft guidance, FDA adds that "[p]rocessing also generally includes cutting, grinding, shaping, culturing, enzymatic digestion, and decellularization."<sup>23</sup>

### "Main Function" of the HCT/P

In the draft guidance, FDA states that it will determine the "main function" of the HCT/P in order to determine whether the HCT/P is a structural tissue or cellular/nonstructural tissue, and therefore which definition of minimal manipulation applies.<sup>24</sup> The HCT/P's "main function" should be based on the HCT/P's function in the donor, not the recipient. FDA explains that structural tissues are generally those that "physically support or serve as a barrier or conduit, or connect, cover, or cushion[,] while cells or nonstructural tissue "serve predominantly metabolic or other biochemical roles in the body such as hematopoietic, immune, and endocrine functions."<sup>25</sup> The Minimal Manipulation Draft Guidance provides that if cells are isolated from a structural tissue, the definition of minimal manipulation for structural tissue applies.<sup>26</sup>

### Original Relevant Characteristics of Structural Tissue

To determine whether the processing of structural tissue satisfies the minimal manipulation requirement, FDA's draft guidance explains that a manufacturer should evaluate "whether the processing alters an original relevant characteristic of the tissue relating to the tissue's utility for

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<sup>20</sup> 21 C.F.R. § 1271.3(f)(1).

<sup>21</sup> *Id.* § 1271.3(f)(2).

<sup>22</sup> *Id.* § 1271.3(ff).

<sup>23</sup> Minimal Manipulation Draft Guidance, at 4.

<sup>24</sup> *Id.*

<sup>25</sup> *Id.*

<sup>26</sup> *Id.*, at 8.

reconstruction, repair, or replacement as structural tissue.”<sup>27</sup> An original characteristic for structural tissue is one that is present in the tissue in the donor. A characteristic is relevant “if it could have a meaningful bearing on the tissue’s utility for reconstruction, repair, or replacement.”<sup>28</sup> Relevant characteristics include strength, flexibility, cushioning, covering, compressibility, and response to friction and shear. FDA notes that processing steps that alter the original relevant characteristics of one type of tissue, such as grinding or fragmentation, may not alter the original relevant characteristics of another. The agency provides several examples of structural tissue (e.g., bone, skin, blood vessel, tendon, or ligament) and processing scenarios, both mechanical and chemical, to illustrate the application of the regulatory framework to structural tissues.

FDA acknowledges that structural tissue may be composed of both an extracellular matrix and cellular components, and explains that separation of the tissue into components in which the relevant characteristics relating to reconstruction, repair, or replacement are not altered would generally be deemed minimal manipulation.<sup>29</sup> If these characteristics are altered, however, more than minimal manipulation has occurred. FDA also explains that if cells are isolated from a structural tissue to produce a cellular therapy product, the definition of minimal manipulation for structural tissues—not cells—will apply.<sup>30</sup>

### **Relevant Biological Characteristics of Cells or Nonstructural Tissue**

According to the Minimal Manipulation Draft Guidance, examples of cells or nonstructural tissues include reproductive cells or tissues (e.g., oocytes), amniotic fluid, parathyroid glands, and pancreatic tissue, among others.<sup>31</sup> The relevant biological characteristics of cells or nonstructural tissues “generally include the properties of the cells or nonstructural tissue in the donor that contribute to the cells or tissue’s function or functions.”<sup>32</sup> Processing that alters these functions would generally be considered more than minimal manipulation. According to the Minimal Manipulation Draft Guidance, differentiation and activation state, proliferation potential, and metabolic activity are all examples of relevant biological characteristics.<sup>33</sup>

### **Issues Raised by the Minimal Manipulation Draft Guidance**

Stakeholders may be interested in commenting on how an HCT/P’s “main function” is, or should be, determined—or, as stakeholders observed during the public hearing, whether this new concept is more appropriate for notice and comment rulemaking than introduction in a guidance

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<sup>27</sup> *Id.*, at 5.

<sup>28</sup> *Id.*

<sup>29</sup> *Id.*

<sup>30</sup> *Id.*, at 8.

<sup>31</sup> *Id.*

<sup>32</sup> *Id.*, at 9.

<sup>33</sup> *Id.*



document.<sup>34</sup> As noted above, determination of an HCT/Ps main function is critical to a determination of which of the two definitions of “minimal manipulation” will apply. Stakeholders may also wish to encourage FDA to reconsider its position that if cells are isolated from a structural tissue to produce a cellular therapy product, the definition of minimal manipulation for structural tissues will apply—particularly given FDA’s broad definition of structural tissues. During the public hearing, several stakeholders spoke to the need for FDA to reconsider this approach. Additionally, for structural tissues, FDA’s standard for determining whether a characteristic is “relevant” may be ambiguous (i.e., “[a] structural tissue characteristic is ‘relevant’ if it *could* have a meaningful bearing on the tissue’s utility for reconstruction, repair, or replacement”) (emphasis added). Stakeholders may benefit from FDA clarifying how it will determine whether the “meaningful bearing” threshold has been met, and should consider whether to urge FDA to adopt a more concrete standard than “could” when determining a characteristic’s relevancy. Finally, similar to the Homologous Use Draft Guidance, FDA states that “if information does not exist to show that the processing meets the definition of minimal manipulation,” the HCT/P cannot qualify as a 361 HCT/P.<sup>35</sup> Stakeholders may want FDA to clarify what information must be shown to avoid this categorical exclusion.

## Adipose Tissue Draft Guidance

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FDA’s Adipose Tissue Draft Guidance provides recommendations to adipose tissue HCT/P manufacturers for compliance with 21 C.F.R. Part 1271 and, as applicable, section 351 of the PHSa and the FDCA. FDA explains that it considers adipose tissue to be a structural tissue, as it is “a connective tissue that stores energy in the form of lipids, insulates the body, and provides cushioning and support for subcutaneous tissues and internal organs.”<sup>36</sup> Adipose tissue is composed of clusters of adipocytes, among other cells, which are surrounded by a reticular fiber network and interspersed with small blood vessels.<sup>37</sup>

### Application of Criteria in 21 C.F.R. § 1271.10(a) to Adipose Tissue

In the guidance document, FDA discusses the application of the minimal manipulation and homologous use criteria to HCT/Ps derived from adipose tissue. For example, FDA explains that isolating non-adipocyte or non-structural components from adipose tissue “is generally considered more than minimal manipulation . . . because the connective tissue and structural components of the adipose tissue are entirely removed . . . thereby altering the original relevant characteristics relating to the tissue’s utility for reconstruction, repair, or replacement.”<sup>38</sup> This interpretation aligns with FDA’s position in the Minimal Manipulation Draft Guidance that the definition of minimal manipulation for structural tissues will apply if cells are isolated from a

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<sup>34</sup> The term “main function” does not appear in the agency’s 1998 proposed rule on Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products, 63 Fed. Reg. 26744 (May 14, 1998), which FDA cites in support of this concept.

<sup>35</sup> Minimal Manipulation Draft Guidance, at 3.

<sup>36</sup> Adipose Tissue Draft Guidance, at 1-2.

<sup>37</sup> *Id.*, at 1.

<sup>38</sup> *Id.*, at 3.



structural tissue to produce a cellular therapy product.<sup>39</sup> FDA explains that processing of adipose tissue that would constitute minimal manipulation includes aliquoting, rinsing, removal of microscopic debris, and freezing.<sup>40</sup>

In terms of homologous use, FDA's draft guidance states that using an adipose tissue HCT/P to repair, reconstruct, replace, or supplement a subcutaneous adipose tissue defect would satisfy this requirement. FDA provides several examples applying the homologous use criteria to adipose tissue HCT/Ps. For example, according to the draft guidance, using these HCT/Ps to "cosmetically fill voids in the subcutaneous space in the face or hands" would be homologous use, whereas using these HCT/Ps for "breast augmentation" would not.<sup>41</sup> FDA also addresses the exceptions that may exempt an adipose tissue HCT/P manufacturer from being subject to FDA regulation—including the same surgical procedure exemption.

Additionally, the Adipose Tissue Draft Guidance discusses the regulatory requirements under the PHSA and FDCA for an adipose tissue HCT/P that does not meet the criteria in 21 C.F.R. § 1271.10(a). These include the need to register as an establishment and to obtain an IND and effective biologics license. The guidance document identifies additional resources for manufacturers who might have questions about how their adipose tissue HCT/P would be regulated and what they need to do to comply with applicable regulations.

### Issues Raised by the Adipose Tissue Draft Guidance

With respect to the Adipose Tissue Draft Guidance, stakeholders may wish to comment on how FDA reached its definition of the basic function of adipose tissue and its components, as well as the intended function of the adipose tissue HCT/Ps in recipients, as detailed in various examples in the guidance document. In particular, stakeholders may wish to highlight potential inconsistencies in the agency's approach. For example, the draft guidance explains that "using HCT/Ps from adipose tissues for breast augmentation would generally be considered a non-homologous use" because "[t]he basic function of breast tissue is to produce milk (lactation) after childbirth."<sup>42</sup> The draft guidance reaches this conclusion even though it explains that adipose tissue, among other things, "provides cushioning and support for subcutaneous tissues and internal organs" and simultaneously acknowledges that "the breast is composed of lobes of glandular tissue and branching ducts, *interspersed with fat and ligaments that support the breast and give it shape . . .*"<sup>43</sup> During the public hearing, stakeholders also urged FDA to reconsider its position that the definition of minimal manipulation for structural tissues applies if cells are isolated from adipose tissue to produce a cellular therapy product. Finally, stakeholders may want to encourage the agency to adopt a more flexible approach to the processing steps that may be undertaken and still satisfy the minimal manipulation requirement, or qualify for the same surgical procedure exception, with respect to HCT/Ps derived from adipose tissue.

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<sup>39</sup> See Minimal Manipulation Draft Guidance, at 8.

<sup>40</sup> Adipose Tissue Draft Guidance, at 4.

<sup>41</sup> *Id.*, at 5.

<sup>42</sup> *Id.*, at 5.

<sup>43</sup> *Id.*, at 1, 5 (emphasis added).

## Same Surgical Procedure Draft Guidance

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As noted above, HCT/Ps that are removed from an individual and implanted into the same individual during the “same surgical procedure” are exempt from FDA regulation.<sup>44</sup> In its Same Surgical Procedure Draft Guidance, FDA explains that it considers the exception to be a narrow one. According to the draft guidance, for the exception to apply, an HCT/P establishment must: (1) remove and implant the HCT/Ps into the same individual (autologous use); (2) implant the HCT/Ps within the same surgical procedure; and (3) maintain the original form of the HCT/Ps so that they constitute “such HCT/Ps.”<sup>45</sup> FDA asserts that “even manufacturing steps considered minimal manipulation . . . will typically cause the HCT/P to no longer be ‘such HCT/P’ under [the same surgical procedure exception], unless the HCT/P is only rinsed, cleaned, sized, or shaped.”<sup>46</sup>

For the most part, FDA explains that “same surgical procedure” refers to a single surgical procedure in which an HCT/P is taken from a donor and implanted back into that donor. Specifically, the draft guidance states that “procedures that involve an incision or instrumentation (e.g., incision or surgical technique) during which an HCT/P is removed from and implanted into the same patient within a single operation performed at the same establishment” qualify for the exception.<sup>47</sup> The draft guidance identifies limited circumstances, however, where surgical removal and implantation of the HCT/P may occur several days apart and still constitute the “same surgical procedure.” In this scenario, the HCT/P may be “rinsed or cleansed and temporarily stored after being labeled pending implantation” and still qualify for the exception. As examples, FDA’s draft guidance points to craniotomy with subsequent implantation of the bone flap to reverse the cranial defect, and parathyroidectomy with subsequent implantation of part of the tissue to preserve parathyroid function.<sup>48</sup> FDA indicates that it must be the same establishment that removes and implants the autologous HCT/P, whereas shipping the HCT/P to another establishment for temporary storage renders the establishment ineligible for the exception.<sup>49</sup>

Stakeholders may benefit from further clarification of how FDA determines which procedures consisting of more than one operation may qualify for the exception, and whether the list of such procedures provided in the draft guidance is finite. Additionally, to be eligible for the exception, FDA limits the processing of the HCT/P permitted by the establishment to “rinsing, cleansing, or sizing, or certain manufacturing steps” of the tissue.<sup>50</sup> Stakeholders may wish to clarify which manufacturing steps would be permitted. Furthermore, stakeholders may want to encourage the agency to expand the scope of permissible processing steps and/or consider a more flexible approach that can accommodate emerging processing techniques and related technological

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<sup>44</sup> 21 C.F.R. § 1271.15(b).

<sup>45</sup> Same Surgical Procedure Draft Guidance, at 3.

<sup>46</sup> *Id.*, at 3, note 4.

<sup>47</sup> *Id.*, at 4.

<sup>48</sup> *Id.*

<sup>49</sup> *Id.*, at 4-5.

<sup>50</sup> *Id.*, at 5.

improvements. Certain stakeholders at the public hearing also encouraged FDA to more broadly apply the “same surgical procedure” exception, given that surgical centers already have procedures in place to prevent the spread of communicable diseases.

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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