June 2, 2015

Division of Dockets Management (HFA–305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852


Submitted electronically at www.regulations.gov

Dear Madams and Sirs:

The American Association of Tissue Banks Tissue Policy Group (AATB TPG) submits these additional comments to the guidance document titled Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products: Draft Guidance for Industry and Food and Drug Administration Staff (December 2014) (draft guidance). The American Association of Tissue Bank’s (AATB’s) Tissue Policy Group (TPG), LLC (AATB TPG) includes Chief Executive Officers and senior regulatory personnel from U.S. tissue banks that process donated human tissue. The purpose of the AATB TPG is to drive public policy in furtherance of the adoption of laws and regulations that foster the safety, quality and availability of donated tissue. The AATB TPG’s membership is responsible for the vast majority of tissue available for transplantation within the U.S. While the AATB has previously commented on this draft guidance, these comments are focused on providing specific counterpoints to some of the other comments submitted to the docket.

As part of our overall discussion with the Food and Drug Administration (FDA or agency), the AATB and the AATB TPG have requested that the FDA provide more certainty, not less, with regard to the regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps). By doing so, the AATB and the AATB TPG believe that there will be further innovation and improved patient care. The Association and the AATB TPG has requested, and will continue to request, clear guidance related to the current good tissue practices and manufacturing arrangements.¹

To enhance that clarity, the AATB TPG would like to ensure that the FDA is aware of key issues related to manufacturing and complexity of HCT/Ps, the new regulatory approach proposed by the draft guidance, the need for notice and comment rulemaking, and the lack of premarket clearance for HCT/Ps.

I. KEY POLICY STATEMENTS

Despite the issues raised by other commenters, the AATB TPG continues to assert the following:

• 361 HCT/Ps can be manufactured products, and such products can have complex interactions in the body,
• The draft guidance does propose a new regulatory approach,
• Notice and comment rulemaking is required, and
• Existing regulations do not contemplate premarket clearance for 361 HCT/Ps.

II. 361 HCT/Ps CAN BE MANUFACTURED PRODUCTS

The implication that FDA did not intend for HCT/Ps to be “manufactured” is without foundation. FDA’s own regulations refer to the manufacture of HCT/Ps and include a definition of “manufacture.” According to the preamble to the Establishment Registration and Listing final rule, the manufacture of HCT/Ps is “an umbrella term to capture the many different actions that HCT/P establishments might take in preparing HCT/Ps for use.”

There is simply no basis for the assertion that FDA has objected to HCT/Ps that are manufactured or mass-produced. Human tissue is complex, and it works in complex ways. An HCT/P’s eligibility for marketing as a Section 361 product in no way turns on the complexity of the interaction between the HCT/P and the patient. The criteria for marketing an HCT/P as a Section 361 product include minimal manipulation and homologous use.

III. THE DRAFT GUIDANCE DOES PROPOSE A NEW REGULATORY APPROACH

A product’s homologous use can only properly be determined based on science, not by the narrow, new regulatory concept of “main function.” In other words, the AATB TPG supports a regulatory framework in which the 361 standard applies only to tissues that offer a recipient the same basic functionality the tissues could provide in a donor. Our fundamental objections are that Section 361 products should not be arbitrarily limited to a single use under the new “main function” test and that a new test cannot be imposed in the tissue industry via guidance given that the test is at odds with FDA’s current regulations.

Further, our focus is on the fact that tissues can have multiple homologous uses notwithstanding the distinction between structural and non-structural tissues in the regulations. But, even

assuming *arguendo* that we embraced the main function test, the draft guidance provides no rationale to support the disparate treatment of HCT/Ps subjected to the same or similar processing—e.g., grinding of bone versus grinding of amniotic tissue. On the one hand, the draft guidance asserts that amniotic tissue cannot be ground or micronized under Section 361 because it could affect tensile strength, which is vital to its alleged “main function” as a structural tissue. On the other hand, however, the draft guidance asserts that even though the “main function” of bone is clearly structural, grinding/micronizing bone does not alter the relevant characteristics of compressibility and strength and therefore constitutes minimal manipulation.³ It is not clear to us how these positions can be reconciled, and the disparity suggests the new “main function” test will not be applied uniformly, which is yet another reason this process must be subject to the rigors of notice-and-comment rulemaking. In short, the agency’s thinking appears to be shifting for some HCT/Ps but not for others and not even for all HCT/Ps in the same class without any scientific rationale. That disparate treatment is problematic under the federal Administrative Procedure Act (APA) because disparate treatment of similar products is *per se* arbitrary and capricious.⁴

The draft guidance, if implemented, would thus represent a significant change in the manner in which FDA regulates many HCT/Ps and determines which HCT/Ps may be subject to greater regulation. Such a fundamental change in the scope and application of a regulatory regime constitutes a substantive rulemaking that can only properly be accomplished, if at all, through notice and comment rulemaking.

### IV. NOTICE AND COMMENT RULEMAKING IS REQUIRED

The AATB TPG is aware that recent court rulings have noted that interpretative rules do not require notice and comment, while “substantive” rules do. The AATB TPG continues to assert that these guidance documents promulgate substantive rules. As evidenced by previous letters submitted to the FDA, the AATB TPG is disappointed that the FDA:

- opted not to re-iterate or expand upon a list of processing steps that would be considered minimal manipulation;
- failed to address processing steps that improve safety or enhance the original relevant characteristics;
- added a completely new concept (i.e., “main function”), which is not grounded in regulation;
- inappropriately narrowed the function or functions of an HCT/P to only one function;
- failed to provide key definitions related to non-structural or cellular tissues (e.g., provides no examples of “main function” for tissue types that are non-structural or cellular, does not

³ See Minimal Manipulation Draft Guidance, Example 8-1, page 7.
provide the FDA’s current thinking with respect to cell incubation and the use of culture media and growth factors, etc.);

- altered the presumption of classification (i.e., FDA clarified that the agency intends to employ a presumption that any processing will amount to more than minimal manipulation unless information exists—as demonstrated by the manufacturer—to show that the processing meets the definition of minimal manipulation);

- provided inconsistent statements related to acellularization/decellularization (e.g., with respect to amnion, adipose tissue, and cardiovascular tissue, as detailed in pp. 21-24 of our February 23, 2015 comments to the docket); and,

- failed to address what does or does not constitute alteration of original relevant characteristics of structural tissues. The FDA has outlined the relevant characteristics for a specific tissue category, which will, in most cases, be applied across the board by the agency in addressing the question of minimal manipulation. As such, certain processes will almost always alter the original relevant characteristics of a tissue and will virtually always amount to more than minimal manipulation if performed on a certain type of tissue. Therefore, if that is the intent of the FDA, then the guidance could be enhanced with key examples related to this topic.

And, most importantly, as part of this process, the FDA seems to be making sweeping policy changes which can have much broader ramifications. For instance, these draft guidance documents potentially result in the de facto re-classification of a series of HCT/Ps – namely:

- **Ground amnion.** In Example 7-1, FDA states: “Original relevant characteristics of amniotic membrane to serve as a membranous barrier generally include the tissue’s physical integrity, tensile strength, and elasticity. . . . A manufacturer grinds and lyophilizes amniotic membrane and packages it as a powder. The HCT/P generally is considered more than minimally manipulated because the processing alters the membrane’s physical integrity, tensile strength, and elasticity that allow it to serve as a membranous barrier.” Even assuming the FDA is correct that the grinding process (i.e., micronization/ particularization) alters the tissue’s utility as a barrier, the guidance does not explain how the grinding process alters the tissue’s utility as an anti-inflammatory and anti-scarring agent, or for wound healing. Were it not for FDA’s limited view of the function of amniotic tissue as a covering, there would have no basis for considering the grinding process to be more than minimal manipulation, especially since the process is used for several other tissue types, including skin, dermis, and bone.

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• **Amnion for wound healing and other purposes (e.g., inflammation, scar tissue reduction).** The FDA states in the draft guidance document that the “main function” of amniotic membrane in the donor is to serve as a covering, which results in the conclusion that amniotic membrane is a structural tissue. The draft guidance document ignores the fact that amniotic membrane is a complex tissue, and has many functions in the donor -- both “structural” and “nonstructural.” For example, the FDA has recognized through the RFD process that anti-scarring and anti-inflammation are homologous uses of amniotic membrane. These functions are clearly “nonstructural.” The FDA’s conclusion that anti-scarring and anti-inflammation are homologous uses necessarily includes a determination that amniotic membrane has anti-scarring and anti-inflammation functionality in the donor. The draft guidance document provides no explanation of why these functions of amniotic membrane in the donor are not considered the “main function.” In addition, the FDA has also previously recognized that non-decellularized amniotic membrane may be marketed solely under Section 361 of the PHS Act when intended for use in wound healing. The FDA’s 2005 letter to OKTOS Surgical Corp. states: “FDA has recognized that amniotic membrane that has not been dehydrated or decellularized may be used for wound repair and wound healing.” The conclusion that wound repair and wound healing is a Section 361 use for amniotic membrane necessarily includes a conclusion that wound repair and wound healing is a basic function of amniotic membrane in the donor. This finding by the FDA has been confirmed in the literature. Importantly, in the letter to OKTOS, the FDA applied the definition of minimal manipulation applicable to cells and nonstructural tissue to amniotic membrane because it was considering how the cells in amniotic membrane “mediate wound repair and wound healing.”

• **Acellular Dermal Matrixes (ADMs) for abdominal wall repair and breast reconstruction.** The FDA describes the “main function” of skin to be “provides a barrier to retain moisture and

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6 FDA’s Letter to Bio-Tissue, November 2001
7 The definition of homologous use is “the repair, reconstruction, replacement or supplementation of the recipient’s cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor.” 21 CFR 1271.3(c).
8 Letter to OKTOS Surgical Corp., June 23, 2005
10 FDA’s letter to OKTOS misstates the definition of minimal manipulation of cells and nonstructural tissue by referring to the “original relevant biological characteristics,” but the reference to 21 CFR 1271.3(f)(2) clarifies the Agency’s intent to rely on the nonstructural tissue definition.
protect from infection and/or the external environment” (emphasis added). Thus, it is not clear if ADMs (while generally considered 361 HCT/Ps) are still appropriate for interior applications, such as abdominal wall repair and breast reconstruction. For abdominal wall repair, a 2011 review published in the Journal of Plastic, Reconstructive & Aesthetic Surgery\(^\text{11}\) titled “Outcomes after abdominal wall reconstruction using acellular dermal matrix: A systematic review” noted that “the most common indications for the use of ADM were abdominal wall reconstruction in a surgical field at high risk for infection (i.e., contaminated, dirty wounds) and complex or recurrent abdominal hernias.” With respect to breast reconstructive surgery, with increasing frequency, surgeons are electing to use ADMs to assist with tissue expander or implant-based primary breast reconstruction. Of the approximately 86,000 breast reconstructions performed in the United States in 2009, about 57,000 (roughly 65%) were tissue expander-implant–based breast reconstructions.\(^\text{12}\) The introduction of ADM has provided surgeons with alternative means of obtaining sufficient vascularized soft tissue to cover the implant, thereby alleviating some complications. Several authors, including Salzberg\(^\text{13}\) and Spear,\(^\text{14,15}\) have reported enhanced outcomes with breast reconstruction utilizing ADMs, citing increased fill volumes and improved aesthetic outcomes. According to a recent review article,\(^\text{16}\) principal advantages include the potential enhancement of cosmesis in breast reconstruction, amelioration of late or irradiation-induced contracture, improved long-term correction of complications following aesthetic revisionary surgery and cost-savings imparted by the direct-to-implant breast reconstruction model.

- **Adipose for breast augmentation and reconstruction.** In Example B-3, FDA states: “Adipose tissue is recovered and processed for injection into the breast, as reflected by the labeling, advertising, or other indications of the manufacturer’s objective intent, for non-implant breast augmentation. 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; and nerves, blood vessels, and lymphatic tissues. The basic function of breast tissue is to produce milk (lactation) after childbirth. Because this is not a basic function of adipose tissue, using HCT/Ps from adipose tissues for breast augmentation would generally be considered a


\(^{12}\)http://emedicine.medscape.com/article/1851090-overview


\(^{16}\)http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3383551/
non-homologous use.” The fact that adipose tissue does not produce milk is irrelevant to the use of the tissue for breast reconstruction. Breast reconstruction using adipose is performed to provide additional padding, cushioning and shape to the breast, not to provide the patient with additional milk production capabilities. In addition, such an interpretation of the “basic function” of breast tissue (only for lactation) is inconsistent with other governmental positions which support breast augmentation or breast reconstruction in women who are not likely to rely upon such breast tissue for lactation, including Medicare coverage of breast reconstruction surgeries in women who are post-menopausal as well as insurance coverage of breast augmentation coverage for transgendersed individuals. Finally, it is inconsistent with Federal law (Public Law 105-277), which requires insurance coverage for breast reconstruction post-mastectomy or lumpectomy irrespective of the woman’s childbearing status. While FDA’s example focused on breast augmentation, given the reliance of a “basic function” of breast related to lactation, adipose tissue used for breast reconstruction would likely also be limited.

- **Mesenchymal Stem Cells (MSCs) from adipose tissue.** In Example 10-1, FDA states: “Original relevant characteristics of adipose tissue, a structural tissue, to pad and cushion against shocks generally include its bulk and lipid storage capacity. A manufacturer recovers adipose tissue by tumescent liposuction and processes the adipose tissue to isolate cellular components, commonly referred to as stromal vascular fraction, which is considered a potential source of adipose-derived stromal/stem cells. The HCT/P generally is considered more than minimally manipulated because the processing breaks down and eliminates the structural components that provide cushioning and support, thereby altering the original relevant characteristics of the HCT/P relating to its utility for reconstruction, repair, or replacement.” Therefore, despite the fact that MSCs, whether they are derived from cord blood, peripheral blood, adipose, amnion, or other sources are (by definition) the same, the FDA’s interpretation is that the extraction of cell components from adipose tissue (because those are classified solely as structural tissues) results in a more than minimally manipulated MSC product, while extraction of those same MSCs from peripheral blood (which are classified solely as nonstructural tissues) results in a potentially minimally manipulated product. For
reasons which are scientifically unclear, the FDA seems to be creating a regulatory hurdle for adipose-derived MSCs (requiring them to be regulated as more than 361 HCT/Ps), while simultaneously allowing peripheral blood derived MSCs (at least under certain conditions) to be regulated as 361 HCT/Ps. It is unclear as to why the FDA believes that, from a regulatory standpoint, the source of the MSCs is most important, rather than the "relevant biological characteristics" (the key regulatory requirement for nonstructural tissues).

• Decellularized adipose tissue. With respect to adipose tissue, the FDA also defines the tissue as a structural tissue and further states that its "main function" is that it "provides padding and cushioning against shocks and stores fat." As noted above, the draft guidance document generally states that "extraction or separation of cells from structural tissues in which the remaining structural tissue's relevant characteristics relating to the reconstruction, repair, or replacement remain unchanged generally would be considered minimal manipulation," but departs from this general statement when it comes to adipose tissue. The draft guidance document provides two examples relating to the removal of cells from adipose tissue. In the first example, 7-3, the draft states that removal of cells from adipose tissue "alters the HCT/Ps ability to provide padding and cushioning." The second example is particularly problematic. The draft guidance document states that when cells are isolated from structural tissue, the definition of minimal manipulation applicable to structural tissue should be applied to the cells. Thus, according to the draft guidance document in example 10-1, if cells are isolated from adipose tissue, and the cells are intended to be the HCT/P, the cells are more than minimally manipulated because removing the cells alters the remaining adipose tissue's ability to provide cushioning and support. Evidently, according to the draft guidance document, the only cells that could be considered minimally manipulated are derived from structural tissue with original characteristics that are not altered by the cell separation or are derived from nonstructural tissue. No scientific basis is provided for this limitation on the kinds of cells that may be considered minimally manipulated. Moreover, this is an entirely new interpretation of the regulations that should not be implemented via a guidance document, but rather should be subject to notice and comment. The FDA's interpretation that the extraction of cell components from adipose tissue results in a more than minimally manipulated product is especially concerning as it is related to the extraction of mesenchymal stem and stromal cells (MSCs). By way of background, MSCs are found in virtually all organs of the body. Bone

23See p. 5.
24Example 10-1: Original relevant characteristics of adipose tissue, a structural tissue, to pad and cushion against shocks generally include its bulk and lipid storage capacity. A manufacturer recovers adipose tissue by tumescent liposuction and processes the adipose tissue to isolate cellular components, commonly referred to as stromal vascular fraction, which is considered a potential source of adipose-derived stromal/stem cells. The HCT/P generally is considered more than minimally manipulated because the processing breaks down and eliminates the structural components that provide cushioning and support, thereby altering the original relevant characteristics of the HCT/P relating to its utility for reconstruction, repair, or replacement.
marrow-derived MSCs (BM-MSCs) were discovered first, and the bone marrow was considered the main source of MSCs for clinical application. Subsequently, MSCs have been isolated from various other sources with the adipose tissue, serving as one of the alternatives to bone marrow. Adipose tissue-derived MSCs (ASCs) can be more easily isolated. This approach is safer, and also, considerably larger amounts of ASCs can be obtained compared with the bone marrow. Despite minor differences between these MSC populations, ASCs seem to be as effective as BM-MSCs in clinical application, and, in some cases, may be better suited than BM-MSCs. Thus, once again, the FDA is narrowing the definition of minimal manipulation and not allowing "cell separation" to be considered minimal manipulation for this tissue category. And, by doing so, FDA is inappropriately limiting the appropriate clinical application of those products.

- **Fresh osteochondral grafts stored in fetal bovine serum as well as cryopreserved allograft heart valves, conduit tissue grafts, and vessels such as allograft arteries and veins with fetal calf serum.** In examining the two FDA outlined circumstances between two similar cell categories within Example 12-1, the main difference is the cell incubation, which results in the tissue being more than minimally manipulated. Thus, the FDA's rationale seems to be that any cell incubation likely results in cell expansion; and, as such, results in a more than minimally manipulated HCT/P. The AATB encourages the agency to further expand upon the agency's current thinking with respect to cell incubation and the use of culture media and growth factors. In doing so, the AATB encourages the Agency to adopt the standard for cell expansion (as described by Freshney 2005) as maximizing the cell proliferation rate through repeated passaging to maintain optimal cellular density so that the cells remain constantly in

Note: The AATB acknowledges that, per 21 CFR §1271.3(d)(4), “Minimally manipulated bone marrow for homologous use and not combined with another article (except for water, crystalloids, or a sterilizing, preserving, or storage agent, if the addition of the agent does not raise new clinical safety concerns with respect to the bone marrow)” is not considered a 361 HCT/P and is, instead, receives oversight from the Health Resources and Services Administration. However, it is important, in this context, to highlight the similarities of MSCs, despite their origin and regulatory framework.

Example 12-1: Relevant biological characteristics of hematopoietic stem/progenitor cells generally include the ability to repopulate the bone marrow by self-renewal and by differentiating along myeloid and lymphoid cell lines.

a. A manufacturer performs cell selection on a mobilized peripheral blood apheresis product to obtain a higher concentration of hematopoietic stem/progenitor cells for transplantation. The HCT/P would generally be considered minimally manipulated because the cell-selected peripheral blood stem cells are not altered with regard to their relevant biological characteristics relating to repopulating the bone marrow.

b. A manufacturer of a placental/umbilical cord blood product performs cell selection and incubates the selected cells in a laboratory vessel containing culture media and growth factors to achieve large numbers of cells capable of long-term repopulation of the bone marrow. This HCT/P derived from cord blood would generally be considered more than minimally manipulated because the processing affects the production of intracellular or cell-surface proteins and other markers of cell lineage, activation state, and proliferation, thereby altering the cells’ relevant biological characteristics of multipotency and capacity for self-renewal.

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[26](http://www.ncbi.nlm.nih.gov/pubmed/22468918)

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28*Culture of Cells for Tissue Engineering*, edited by Gordana Vunjak-Novakovic and R. Ian Freshney

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exponential growth (“log phase”). In addition, we urge the agency to clarify that storage of HCT/Ps with fetal bovine serum or fetal calf serum is not considered “incubation with culture media and growth factors.” By providing such clarification, the agency will be protecting a long-standing practice for the storage of fresh osteochondral grafts with fetal bovine serum, as well as cryopreserved allograft heart valves, conduit tissue grafts, and vessels such as allograft arteries and veins with fetal calf serum.

- **Fresh and cryopreserved skin used for burn patients, fresh cartilage grafts used for repair of cartilage defects, osteoarticular allografts used in limb preservation procedures, and cancellous bone containing live cells.** FDA’s draft guidance documents seem to indicate that products which contain both structural tissues as well as cells are generally considered more than minimally manipulated because the HCT/P is dependent upon the metabolic activity of living cells for its primary function. This is primarily elucidated from question D in the adipose guidance document examining questions related to whether stem cells from adipose tissue (cells) seeded onto a bone scaffold (structural tissue) would give rise to a more than minimally manipulated HCT/P. This statement is contradictory to agency practice, given that the following tissue products containing live cells and a structural component have been safely regulated as 361 HCT/Ps for decades: fresh and cryopreserved skin used for burn patients; fresh cartilage grafts used for repair of cartilage defects; osteoarticular (OA) allografts used in limb preservation procedures and cancellous bone containing live cells. More recently, subsequent to discussions with the FDA related to an

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32. Note: Such cells are not from the original structural tissue but another tissue source, given that FDA’s draft guidance states that “[s]tructural tissue is composed of structural components and cells, and those cells are part of the structural tissue. . . “
33. If the HCT/P from adipose tissue has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and is not intended for autologous use or use by a first- or second-degree blood relative, then it does not meet the criteria in 21 CFR 1271.10(a) for regulation solely under section 361 of the PHS Act and the regulations in Part 1271. Autologous use is the implantation, transplantation, infusion, or transfer of human cells or tissue back into the individual from whom the cells or tissue were recovered (21 CFR 1271.3(a)).

**Example D-1:** Adipose tissue is recovered from an unrelated allogeneic donor. Stem cells are isolated from that adipose tissue and seeded onto a bone scaffold for repair of pathologically or surgically created bony voids. The manufacturer advertises the stem cells as contributing to the primary function of filling, augmenting, or repairing the bone void by giving rise to osteoblasts, which mineralize the allograft and increase its durability; this function depends on the metabolic activity of the cells. The HCT/P from adipose tissue is dependent upon the metabolic activity of living cells for its described primary function of repairing the bone void and it is not intended for autologous use or allogeneic use in a first- or second-degree blood relative. Therefore, the HCT/P would generally be considered not to meet the criteria in 21 CFR 1271.10(a) for regulation solely under section 361 of the PHS Act and the regulations in Part 1271.
Untitled Letter (issued in October 2013), according to an SEC filing, Osiris is currently marketing a 361 HCT/P Ovation OS, which includes structural components (i.e., bone matrix), as well as nonstructural components (i.e., bone supportive growth factors, viable MSCs and osteoblasts, and growth factors). Therefore, the AATB urges the FDA to withdraw the position that cells seeded into a scaffold results in a more than minimally manipulated product.

Further, for some of these HCT/Ps, prior to issuing the draft guidance, the FDA issued Untitled Letters focused on whether such HCT/Ps should be considered 361 HCT/Ps. The AATB TPG remains concerned that FDA’s actions were inappropriate, given that the FDA had not issued guidance or regulations which provided regulatory certainty regarding the classification of the product(s) prior to issuing the Untitled Letters.

If finalized in the current form, despite its assertions to the contrary, this guidance document does establish a binding norm for the regulated industry because it imposes significant new obligations. As the FDA acknowledges in the draft guidance document, if an HCT/P does not meet the criteria for minimal manipulation established in 21 CFR 1271.10(a), it does not qualify for exemptions under Part 1271, and will regulated as a drug, medical device and/or biologic product under entirely different statutory schemes, i.e., the FDCA and/or Section 351 of the PHSA. Therefore, while the guidance opens with standard language regarding the fact that it is “non-binding,” the substance of the guidance effectively up-classes certain HCT/Ps into regulatory categories subject to premarket approval and other, additional regulatory requirements. As such, even as the guidance claims to set forth no legal obligations, it does exactly that through its reclassification of certain HCT/Ps. The fact that the agency intends to reclassify these products is supported by its recent use of Untitled Letters, as described above. In addition, by expanding the meaning of “minimal manipulation” to rely upon the “main function” to determine whether a tissue category is considered structural or nonstructural, coupled with the interpretation that such designation applies across all products from the tissue category, the FDA has imposed a new limitation on a right (and obligation) established under the HCT/P regulations, 21 CFR 1271. As previously discussed, such determination not only erodes the regulatory term “homologous use” but also has far-reaching implications for a variety of tissue categories and products currently available to patients.

Further, as previously asserted, the AATB TPG is concerned that FDA's interpretation of the Part 1271 regulation, e.g., definition of minimal manipulation, is arbitrary and capricious and inconsistent with the plain meaning and historical application of the regulation.

Even if the FDA does not agree with the AATB TPG’s assertion related to these guidance documents being substantive rules, the lack of a definitive legal requirement under the

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36 [http://www.osiris.com/ovationOS](http://www.osiris.com/ovationOS)
Administrative Procedures Act (APA) for notice-and-comment rulemaking does not preclude the FDA from opting to perform notice-and-comment rulemaking under these circumstances. The AATB TPG notes that, given the numerous draft guidance documents related to the classification of HCT/Ps (namely, Draft Guidance for Industry: Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception,37 Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products: Draft Guidance,38 and Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) from Adipose Tissue: Regulatory Considerations; Draft Guidance39, as well as the proposal to issue an additional guidance -- Draft Guidance for Industry: Homologous Use of Human Cells, Tissues, and Cellular and Tissue Based Products40), the FDA is indicating that there is a substantial amount of clarity/guidance required for these products. It should do so with a public workshop and notice and comment rulemaking, so that FDA will have the benefit of a wide range of views and information.

V. EXISTING REGULATIONS DO NOT CONTEMPLATE PREMARKET CLEARANCE FOR 361 HCT/PS

While others have suggested a premarket clearance for 361 HCT/Ps, this request ignores the express language of Section 361, which limits FDA regulatory authority under the statute to regulation of only those products that present a risk of communicable disease. If the FDA were to establish a presumption that a tissue product is not a Section 361 HCT/P absent confirmation from the Tissue Reference Group (TRG) that the product meets the criteria of Section 1271.10, this would, in effect, create a premarket notification process, which would be an unnecessary burden on the tissue industry and would delay the availability to patients of demonstrably safe and valuable products. A premarket review or clearance process was not contemplated by FDA when it exempted certain products from Biologics License Applications (BLAs) under 21 C.F.R. part 1271.

VI. CONCLUSION

As previously outlined, the AATB TPG believes that 361 HCT/Ps can be manufactured products; the draft guidance does propose a new regulatory approach; notice and comment rulemaking is required; and finally premarket clearance for 361 HCT/Ps is not contemplated under the existing regulatory paradigm. The AATB TPG stands ready and willing to assist the FDA with its deliberations in any way that the FDA deems appropriate.

Respectfully,

[Signature]

Tom Cycyota
AATB TPG Chair

Cc:  Karen Midthun, MD; Celia Witten, MD, PhD; Mary Malarkey; Lori J. Churchyard; Melissa Segal; Angela Krueger; Leigh Hayes; Pauline Cottrell