COALITION OF

# Wound Care Manufacturers

February 23, 2015

Ms. Leslie Kux
Associate Commissioner for Policy
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

**In Re: Docket No. FDA-2014-D-1696-0001: Comments to the Draft Guidance Document Titled Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products: Draft Guidance for Industry and Food and Drug Administration Staff (December 2014)**

*Submitted electronically at [www.regulations.gov](http://www.regulations.gov)*

Dear Ms. Kux:

The Coalition of Wound Care Manufacturers ("Coalition") is submitting the following comments in response to the FDA draft guidance document on "***Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products: Draft Guidance for Industry and Food and Drug Administration Staff* (December 2014)".** The Coalition represents leading manufacturers of wound care products used by Medicare beneficiaries for the treatment of wounds including those products that are subject to provisions contained in this Guidance. As such we have a particular interest in this draft document and we offer our specific comments below.

The Coalition has three very specific areas of concern:

## Period of Time to Comment is Too Short

First, while we appreciate the opportunity to offer our comments, we are very disappointed in the short amount of time that the FDA allowed to respond to this very dense document that is so critical to wound care stakeholders. The Coalition has treated writing our comments to this draft very seriously, and has convened conference calls, conversations and emails with our member organizations to ensure that all stakeholders' input has been included. Since we still do not believe there has been enough time to give this important document the careful consideration that it needs, we are submitting these comments, but intend to supplement our filing as we receive more information from our members. Again, the time frame for public comment given the complexity and complete overhaul of tissue regulations is far too short.

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## Draft Guidance is Inappropriate – Proposed Regulation Should Have Been Issued

Second – Utilizing a draft guidance document rather than a proposed regulation is inappropriate. This guidance document is a significant departure from current law and as such a formal proposed regulation should have been issued which is more appropriate given the significant implications and changes to current regulations. A guidance document is just that – guidance. Yet, the significant changes that this document proposes renders it more than just guidance. This document not only proposes changes in the way that tissue products are and will be regulated, but also adds new requirements and introduces new terminology all within the guise of a guidance document.

Under the approach outlined in the draft guidance document, the FDA has suggested that specific tissues have specific relevant characteristics independent of their use. As such, it is likely that many HCT/P products will be considered more than minimally manipulated – a key component in the regulations - and, thus, subject to regulation beyond section 361 of the PHS and 21 C.F.R. Part 1271, irrespective of how they are processed. As such, this draft guidance document could render more HCT/Ps subject to regulation as drugs, devices, or biologics under Section 351 of the PHS Act, the FDCA, and the applicable regulations. These products would be subject to the more stringent regulatory requirements as a result.

Given the expanded definition of minimal manipulation to rely upon the "main function" in order to determine whether a tissue type is considered structural or nonstructural imposes new limitations under the current 21 CFR Part 1271 regulation. As such, this draft guidance should have been issued in accordance with the notice-and-comment proceedings required by the APA. Section 553 of the APA requires the publication of proposed agency rules be followed by a period of time for consideration and comment by the public. A notice-and-comment period is not required if an agency issues an interpretive rule or general statement. This guidance document is not an interpretive rule nor is it a general statement. Rather it is a material change to an existing regulation with additional requirements being imposed.

The Coalition offers the following recommendations:

- The FDA should meet with affected stakeholders either through workshops or public meetings
- The FDA should withdraw this guidance document and issue a proposed rule
- Address the following issues within the proposed rule:
    - Provide the scientific basis for the various tissue categories (e.g., selection of skin versus dermis or epidermis);
    - Provide a scientific accounting of the function or functions of all tissue categories;
    - Provide the scientific rationale for selecting one of the functions as the main function for each of the tissue categories;

- Provide the scientific rationale for shifting the focus of the utility of the tissue from its function in the recipient to the function in the donor;
- Provide the scientific rationale for "locking in" only one main function for a tissue category and not examining how it is utilized in the recipient; and
- Provide the distinction between the term "main function" and the term "homologous use."

**Substantive Concerns Due to Regulatory Departure**

Finally, as there is a significant departure from what has been regulated in the past, the Coalition has several substantive concerns with the FDA guidance document as written including adding a new criterion for HCT/Ps to meet in order to be regulated solely under section 361 of the Public Health Service Act. Specifically, we have issues with the following: The FDA introduces a broad expansion of the definition of minimal manipulation through the use of the new term "main function" - which is inconsistent with the Administrative Procedures Act (the APA), has broad, far-reaching ramifications for a variety of tissue types and has no regulatory basis, and changes the requirements for HCT/Ps which renders some of the current requirements useless.

Under current regulations, an HCT/P is regulated solely under section 361 of the PHS Act and the regulations in his part if it meets all of the following criteria:

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

The FDA issued these HCT/P regulations to provide a comprehensive, risk-based framework for the regulation of these products. The FDA established the HCT/P

regulatory framework, in essence, to carve out categories of HCT/Ps that present a low risk of communicable disease transmission. HCT/Ps that meet the criteria above are implicitly considered safe enough for their intended homologous use to justify their being regulated solely as 361 HCT/Ps based on these criteria in the regulations. The specific criteria have been outlined in the regulations since September, 2006. The HCT/Ps that meet the criteria established in 21 C.F.R. Part 1271 are regulated solely under §361 of the PHS Act (i.e., "361 HCT/Ps") and are not required to be licensed, approved, or cleared prior to their introduction into interstate commerce. Furthermore, as part of the final rule establishing the framework for the regulation of HCT/Ps, the FDA included examples of minimal manipulation.

However, in the guidance document, FDA does not provide examples, essentially reduces the significance of homologous use and introduces a new term, "main function," which is not introduced or defined as part of the regulatory framework under 21 CFR §1271. The "main function" is a critical new element for determining whether a HCT/P is deemed by FDA to be "structural" or "non-structural." Given that the draft guidance also implies that any such categorization is permanent, despite the potential clinical application of the HCT/P, this new definition and subsequent identification of the particular main function for a HCT/P has far-reaching effects and is not scientifically or clinically correct.

By regulation, homologous use "means 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**". There are two key elements of the regulatory definition of homologous use which are lost in this draft guidance: (1) the definition clearly infers that a single 361 HCT/P may have more than one function; and (2) the application of the use having similar function or functions within the recipient and donor.. However in the draft guidance document, the FDA implies that HCT/Ps have only 1 function. This is simply not correct. Many HCT/Ps have more than one function. For example- with skin, the FDA has defined main function as "provides a barrier to retain moisture and protect from infection and/or the external environment. However, other functions and/or inherent characteristics of skin include the following:

- Reduces microbial contamination of wounds
- Tissue expander to allow for enhanced fill volume, greater aesthetic outcome
- Protect abdominal contents and restore functional support
- Provides augmentation of tendon and rotator cuff repairs
- Provides a filler for congenital and trauma induced defects
- Provides a flap for guided tissue regeneration in the mouth
- Abdominal Wall Repair
- Breast reconstruction
- Burn
- Hand reconstruction
- Dental procedures

- Wound Care
- Rotator Cuff repair

The FDA also changes how "minimal manipulation" is determined. Under current law, whether an HCT/P is considered to be more than "minimally manipulated" is determined by the tissue's function **in the recipient**. Thus, for structural tissue, the analysis is concerned with the effects that processing has on the "tissue's utility for reconstruction, repair, or replacement". The draft guidance, however, analyzes minimal manipulation in terms of the "main function" of the HCT/P. It focuses on the main function of the HCT/P, **in the donor**. We do not understand why the FDA would change the location of the tissue function. This is a clear departure from the current regulatory framework under 21 CFR §1271.

Furthermore, the main function eliminates the regulatory significance of "homologous use". Under the FDA's draft guidance interpretation that only the "main function" is relevant for the definition of "minimal manipulation," it is unclear how or why one would need to separately apply the definition of "homologous use." Thus, by significantly expanding the scope of "minimal manipulation" by adding the term "main function," the draft guidance, in effect, alters the impact of "homologous use," which has been in the regulation as a requirement for HCT/Ps for years.

As a result the Coalition offers the following recommendations:

- Abandon the concept of "main function" which inappropriately limits the processing steps allowable for a minimally manipulated HCT/P and instead re-iterate an updated list of processing steps which will be considered minimally manipulated for all HCT/Ps.
- If the FDA decides it needs to move forward with minimum function then the Coalition recommends that the FDA:
    - For all HCT/Ps, examine the function that such HCT/P would have in the recipient and determine whether such HCT/P is structural or non-structural based on function in the recipient, not on a predetermined function outlined by the FDA for all HCT/Ps which fall within a tissue category.
    - If,the FDA is unwilling to examine the proposed function of the HCT/P in the recipient and maintains its tissue categories, then the FDA should, at the very least, clarify that:
        - Amnion has a "main function" which incorporates its wound healing, anti-inflammatory, and anti-scarring benefits; and
        - Skin is comprised of two key layers – dermis and epidermis. While the FDA's "main function" for skin is appropriate for the epidermis, the main function for dermis should incorporate its connective properties.

Finally, the draft guidance document does not repeat or retain a list of processing steps

which would be defined as minimal manipulation. And, in fact, the FDA seems to have eliminated some of the previously named processing steps from those that could be performed and still be considered minimal manipulation for some HCT/Ps, as well as create a new presumption that products are not considered 361 HCT/Ps unless the manufacturer can prove that the HCT/P meets the definition. Furthermore, the FDA does not provide procedures that are considered minimal manipulation. This lack of transparency is unacceptable. The FDA should be able to provide clarity to manufacturers and as such, the Coalition recommends that the FDA:

- re-state its previous list of procedures that are considered minimal manipulation and expand the list to include acellularization or decellularization, sterilization using any validated technique, and drying.
- withdraw its presumption that a manufacturer must prove that a product meets the definition of a 361 HCT/P and instead provide clarity regarding the agency's views related to the classification of products and, like other medical products, review the classification of a HCT/P on a case-by-case basis. Should the FDA opt to retain this presumption, then the FDA should provide more clarity regarding the information necessary to demonstrate that the processing supports a definition of minimal manipulation.

## Conclusion

The FDA has created new hurdles and changed the regulatory framework for HCT/Ps. The assumptions and conclusions made in this draft document are scientifically inaccurate. The Coalition believes that a guidance document is not the appropriate mechanism for such drastic changes and recommends that the FDA meet with affected stakeholders and issue a formal regulatory proposal with an appropriate timeframe for notice and comment.

The Coalition appreciates the opportunity to provide our comments. We hope that the FDA will work with stakeholders to craft a more appropriate and well balanced policy. If you need more information or have any questions, please do not hesitate to contact me.

Sincerely,

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