COALITION OF
Wound
Care
Manufacturers

September 27, 2016

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

Re: FDA-2015-D-3581 for "Homologous Use of Human Cells, Tissues, and Cellular and Tissue-Based Products; Draft Guidance for Industry and FDA Staff

Submitted electronically at 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The Coalition of Wound Care Manufacturers ("Coalition") is submitting the following comments in response to the FDA draft guidance document on "***Homologous Use of Human Cells, Tissues, and Cellular and Tissue-Based Products: Draft Guidance for Industry and Food and Drug Administration Staff*** **(December 2015).** The Coalition represents leading manufacturers of wound care products used by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 within this Guidance document. As such we have a particular interest and we offer our specific comments below.

While the Coalition has concerns with and requests clarity on some of the provisions contained in this guidance document, we also agree with some basic principles contained within in this guidance document. Specifically, we agree with the Agency's use of the term "basic function" when referring to the functions of the HCT-Ps. This term is consistent with current regulatory and statutory language and is a more scientifically correct and appropriate term. The Coalition also commends the FDA in recognizing that anatomical location, as well as basic function, determines homologous use and that anatomical location is not the sole determinant of homologous use. Finally, we commend the FDA for its recognition of the unique properties of dermis, which is separate from epidermis in terms of properties and function.

As manufacturers the Coalition agrees that it is appropriate to have a homologous use guidance document as well as a guidance document that addresses minimal manipulation. However, there are too many significant new requirements within the minimal manipulation document which not only conflict with this guidance document, they conflict with current regulatory and statutory language. The Coalition recommended that

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the FDA scrap the minimal manipulation guidance document and instead issue a proposed rule for notice and comment. However, once the notice and comment process is complete and a guidance document is eventually created for minimal manipulation that is consistent with current regulatory/statutory language, the Coalition urges the FDA to ensure these two guidance documents compliment each and NOT be in conflict with one another. Based on the regulatory framework, homologous use is tied to minimal manipulation and therefore language and requirements for these processes must be consistent with specific examples being provided in each guidance document to add additional clarity. Any conflict between minimal manipulation and homologous use must be resolved prior to any guidance moving forward OR any proposed rule being issued on this topic. As such, the Coalition recommends that when the FDA is referring to minimal manipulation or homologous use – that the basic function terminology is utilized – as has been identified in the homologous use guidance document.

In addition to our concern regarding consistency between the two guidance documents as explained above, the Coalition continues to have some concerns with the homologous use guidance document as written and have outlined our concerns below.

Section 4.2

First – the Coalition is extraordinarily concerned about how the narrow definition of homologous use for amnion tissue will impact amnion tissue use for wound care. Section 4.2 states, *"The basic functions of amniotic membrane include serving as a selective barrier for the movement of nutrients between the external and in utero environment and to retain fluid in utero. An amniotic membrane product is used for wound healing of dermal ulcers and defects. This is not homologous use because wound healing of dermal lesions is not a basic function of amniotic membrane."*. Other basic functions of placental membranes include mechanical protection, metabolism, transfer (as noted in the example) and endocrine secretion. The amniotic membrane specifically also is antibacterial and protects from adhesions. In addition to containing the fetus and amniotic fluid, the placental membranes have barrier functions and fulfill paracrine-signaling functions between the maternal and fetal compartments. The membranes also synthesize and metabolize steroids and glucocorticoids locally.

The draft guidance is limiting the benefit of the basic functions of the placental membranes to a literal definition. The basic functions attributed to the membrane during its life in the donor are valuable to promote wound healing beyond that of a simple cover or dressing. Several randomized controlled trials comparing outcomes between those that included amniotic membranes versus those that only had dressings to maintain a moist environment are evidence. In addition, the amnion provides a basement membrane and healthy extracellular matrix (ECM) to replace that which is missing when there is a defect in the skin.

Human skin is composed of dermis, which is predominantly ECM (like amnion) and is covered by basement membrane to which the epithelium is attached (like amnion) when the skin is intact. Indeed, the two structures share the same embryological origins. Application of amnion is a natural human tissue substitute with a matrix that contains structural proteins capable of signaling cells in the recipient to migrate into the structure, attach and begin functioning locally to close (or heal) a wound. As such, the Coalition recommends that the FDA expand the use of amnion in wound healing in their homologous use considerations.

Section 6

Furthermore, we are also concerned about Section 6 of the guidance document on "manufacturer objective intent". The language in the document states, *"A manufacturer's objective intent is determined by the expressions of the manufacturer or its representatives, or may be shown by the circumstances surrounding the distribution of the article. A manufacturer's objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by the manufacturer or its representatives. It may be shown by the circumstances that the HCT/P is, with the knowledge of the manufacturer or its representatives, offered for a purpose for which it is neither labeled nor advertised."* This language conflicts with the current FDA proposed "intended use" regulation. In that proposal, the FDA has stated, "the Agency would not regard a firm as intending an unapproved new use for an approved or cleared medical product based solely on the firm's knowledge that such product was being prescribed or used by doctors for such use.". As such, the Coalition recommends that the FDA delete this entire section or at the very least delete the sentence that reads, "It may be shown by the circumstances that the HCT/P is, with the knowledge of the manufacturer or its representatives, offered for a purpose for which it is neither labeled nor advertised"

Clarification

We also are seeking clarification on a number of issues. The areas in which the Coalition would like clarification include:

- The FDA acknowledged in this document of the need to have claims supported by evidence. However, under the current regulatory framework, there are no Premarket Approvals (PMA) or 510(K) submissions for 361 HCT/P's. So how does the Agency plan to have claims supported for 361 HCT/Ps?
- While the Coalition appreciates that the FDA has attempted to define repair, reconstruction, replacement, or supplementation, we believe that further clarification is necessary for each one of these definitions. We are concerned that the definition of "repair" is limited to the physical or mechanical restoration of tissues in the Guidance and "reconstruction" is limited to "surgical assembling or "re-forming." HCT/P's are biologically active products and the Guidance definition of physical and mechanical activity does not recognize this function.

We also recommend that the FDA expand the definition of repair and reconstruction to include functions previously recognized as potentially homologous uses.

- Since the regulations expressly do not separate the definition of homologous use depending on whether tissue is structural or non-structural, the Coalition recommends that the FDA **delete the "presumption"** that homologous uses of structural tissue "generally" will be structural and homologous uses of nonstructural tissue "generally" will be non-structural. This is not technically correct, as tissue can be structural and nonstructural. One example is the use of split-thickness skin, dermal, and placental tissues and their function as a scaffold and biological modulator. A biological modulator is a material or substance derived from biological sources that influences processes such as wound healing. These tissues act as scaffolds to support cell ingrowth and new ECM (granulation tissue) formation. They have receptors that permit fibroblasts to attach to the scaffold unleashing a cascade of recipient cell activity through release of cytokines and growth factors locally—all as a result of cell attachment to the structural tissues. They have the ability to stimulate angiogenesis, act as chemoattractants for endothelial cells and contain/protect growth factors. This is an example of a tissue having both structural and non-structural characteristics. As such, more clarity is necessary when discussing basic function/functions of both structural and non-structural tissue.
- We would also like to seek clarification that both the homologous use and minimal manipulation documents - which are the subject of these comments - are in fact draft documents. It appears that the FDA is already subjecting manufacturers to the provisions with in these documents – which is completely unacceptable. As such we would appreciate the FDA providing clarification as to whether the provisions in these documents are in fact draft guidance, and if a letter has been provided to a company siting language in the **draft** guidance documents whether the company is required to comply?

CONCLUSION

The Coalition appreciates the opportunity to provide our comments. If you need more information or have any questions, please do not hesitate to contact me.

Sincerely,

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Coalition of Wound Care Manufacturers
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