ALLIANCE OF
WOUND CARE
STAKEHOLDERS
POWER THROUGH COLLECTIVE ADVOCACY

September 27, 2016

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

In Re: Docket No. FDA-2014-D-1696 Comments to the Draft Guidance Document Titled "Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products: Draft Guidance for Industry and Food and Drug Administration Staff" (December 2015)

Submitted electronically at www.regulations.gov

Dear Ms. Kux:

On behalf of the Alliance of Wound Care Stakeholders, I am submitting the following comments in response to the FDA draft guidance document on "***Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products: Draft Guidance for Industry and Food and Drug Administration Staff*** **(December 2015).** The Alliance is a nonprofit multidisciplinary trade association of physician medical specialty societies and clinical associations whose mission is to promote quality care and access to products and services for people with wounds through effective advocacy and educational outreach in the regulatory, legislative, and public arenas. Most of the Alliance clinical members use tissue products in their practices and thus have a vested interest in ensuring patient access to these important products – which may be in jeopardy based on the language contained in the guidance documents.

On September 12, Dr. Paul Kim, Associate Professor in the Department of Plastic Surgery and the Director of Research in the Division of Wound Healing and Hyperbaric Medicine at MedStar Georgetown University Hospital, provided oral testimony on behalf of the Alliance at the FDA's open meeting. During that meeting, a majority of the presenters – whether clinical, patient, industry or other – agreed with our position that the guidance documents are a significant departure from current regulatory language and should be withdrawn. This continues to be our position and our recommendation.

There are two main areas of concern for the Alliance in the minimal manipulation document. 1. The term "main function" introduced in this document conflicts with the current definition of homologous

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use. 2. The change regarding how minimal manipulation is determined and specifically the focus on the "main function" of the tissue in the donor rather than what is written in current law – by the function of the tissue in the recipient. Both of these areas are a significant departure from current regulatory language and therefore would not only be in conflict with current regulation, the added and changed requirements should not be issued in a guidance document but rather in a formal notice and comment period.

The newly created term "main function" in the minimal manipulation guidance document is clinically problematic. The notion that these tissues have a "main function" which determines whether a product is structural or non-structural conflicts with current regulation as well as the draft guidance document on homologous use. The conflict with the homologous use guidance is problematic as it is not possible to separate homologous use from minimal manipulation when considering whether or not a product is regulated as a 361 HCT/P (Human Cells, Tissues, and Cellular and Tissue-Based Products). The homologous use guidance document accurately utilizes the term "basic function/functions" and we recommend that the FDA continue to utilize the term basic function and/or functions.

Furthermore, it is misguided and clinically inaccurate to state that tissue has a "main" function. Tissue products have more than one function and to restrict their use to one function – the "main" function- is scientifically and clinically incorrect. Tissues, even without cells, may have more than structural impact upon application or implantation. For example, amnion contains not only collagen in an extracellular matrix or ECM; it has other proteins and carbohydrates that have biologic functions. Minimal manipulation of the ECM in processing should maintain the ECM biochemical factors such as fibronectin, GAGs, PGs, laminins. There are local biological effects like the organization of cell migration and facilitation of cell attachment that are beyond providing a simple structural support. Cell attachment elicits another cascade of activity related to restoration of healing processes that were absent prior to placement of the donated ECM. Clinicians cannot get this activity with synthetic dressings.

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 the minimal manipulation 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. Despite the regulatory language that the HCT/P performs the same basic function or functions – the key word being functions -- which is plural-- the FDA implies that HCT/Ps have only 1 function – the main function. This is simply not correct. Many HCT/Ps have more than one function, which should be included in these guidance documents.

Many HCT/Ps have more than one function, which should be included in these guidance documents. For example there are different tissue types that would be subject to this guidance (and all should be broken out into specific areas) including but not limited to:

Dermis
Epidermis

Amnion
Chorion

Each of these tissue types has multiple functions – and not simply a main function

For example, the basic functions of placental tissue or amniotic membranes can include – preventing infection, rapid self-restoration, allowing free movement, a protective barrier and a cover. With or without maintenance of the donor cells, many of these basic functions are sustained and observed after placement in the recipient (even after removal of donor cells). By utilizing most of the basic function or functions within the definition of placental tissue a clinician can apply placenta-derived tissues as part of a good wound care treatment for a variety of wound types and severities.

Furthermore, in the FDA guidance document, the main function of skin tissue was defined as "provides a barrier to retain moisture and protect from infection and/or the external environment". There are multiple issues with this statement – first, there are other functions and/inherent characteristics of skin tissue including but not limited to the following:

- Cover
- Structural Support
- Physical Support

The other issue with this statement is that it is not clear if the FDA is referring to dermal or epidermal tissue – each has very different functions. The FDA cannot simply refer to skin tissue as skin. Skin has two major components – the dermis and the epidermis. Each of these components has different basic functions.

The dermis provides strength and elasticity to the skin through extracellular matrix composed of collagen fibrils and elastic fibers along with other ECM biochemicals. The dermis has been extensively used clinically due to its strength and structural composition, donated dermis can provide soft and connective tissue reinforcement or substitution during wound management as well as in the surgical repair of many other defects in the body where its strength and elasticity is beneficial.

The epidermis on the other hand, acts as a watertight barrier to foreign substances from entering the body. This protective barrier helps defend the body against infection and maintains moisture balance in the underlying tissue. Therefore, in the draft document, when the FDA was providing an example of the main function of skin as a protective barrier in the draft document was the Agency stating that the main function of epidermis was to provide a protective barrier or did it inappropriately lump dermis and epidermis tissue together?

If the notion of main function were adopted, then dermis derived allografts would not be used to treat wound care patients yet there are several studies published providing evidence of the clinical benefit of dermis-only allografts when used in the treatment regimen of full thickness chronic wounds.

The Alliance urges the FDA to eliminate the term Main function and instead utilize the term basic function or functions of tissue. If the FDA utilizes two guidance documents – one for minimal manipulation and one for homologous use – they must be consistent and not conflicting. Using main

function in the minimal manipulation guidance document but basic function in the homologous use document is not only confusing – it is contradictory. The FDA must not introduce main function into the equation when describing HCT/P products. It is not only contrary to current regulatory language, it is not scientifically correct and will impact clinicians use of these products.

With respect to he second issue, the FDA 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 are extremely concerned about this departure.

Tissue adapts to its environment. Tissue is often explanted from one area and successfully used in a different area. Just because a tissue may come from a uterus does not mean it must be transplanted into a uterus. Any tissue used must function in the recipient in a manner required by that recipient, regardless of the product origin or source of the material. That said, donated acellular human dermis can be effectively used to reinforce the abdominal wall fascia after hernia repair (and decrease rate of dehiscence compared to no reinforcement). Likewise, dermis may be morselized and injected into soft tissue defects and wrinkles. The tissue in these cases is not reflective of its function in the donor – rather its function in the recipient. The extracellular matrices of tissues are basically the same regardless of where it is placed—the microenvironment into which donated tissue is placed guides its remodeling into functionally useful structures. Historically, several sources of tissue have been used in wound care with success: peritoneum, fascia, pericardium, skin, placental membranes, and blood components at a minimum. The Alliance recommends that the analysis should be based on the effects that the processing has in the tissue's utility for reconstruction, repair or replacement in the recipient. It is not only more accurate it is also what is currently required in the regulations.

Conclusion

The concepts of Minimal Manipulation and Homologous Use are so interrelated that while it is appropriate to have separate guidance documents for each, there must be consistency between the two documents. Each of the guidance documents should provide specific detail in order to give greater clarity and guidance - this does not occur in these particular documents. In fact, many examples that were previously provided have been eliminated. More importantly, there are too many significant new requirements within the minimal manipulation document that not only conflict with the homologous use guidance document, they conflict with current regulatory language. This guidance document should be withdrawn. The FDA should work with stakeholders to develop an appropriate guidance document that is consistent with current regulatory language and actually provides guidance and clarity to existing regulations. The FDA should not conflict with the homologous use guidance document nor should the FDA introduce new requirements or new terminology in the guise of guidance or new ways in which tissue products are and will be regulated.

The Alliance appreciates the opportunity to provide CMS with our comments. If you require additional information or have any questions, please do not hesitate to contact me.

Sincerely,

Marcia Nusgart R. Ph.

Marcia Nusgart, D.Ph.
Executive Director