Alliance of Wound Care Stakeholders' Testimony at FDA Public Hearing
"Draft Guidances Relating to the Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products"
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My name is Paul Kim. I am a wound care/limb salvage podiatrist. I am pleased to be here today representing the Alliance of Wound Care Stakeholders. 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. Several of the professional organizations to which I belong are members of the Alliance. 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.

By way of background, I have been working in wound care and limb salvage for the past 11 years. I am an 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. While I am speaking on behalf of the Alliance, many of my comments are based on my own personal clinical experiences both in research as well as in treating patients with wounds with the types of products that are the subject of this hearing.

My comments today will focus on two of the four guidance documents – Minimal Manipulation and Homologous Use. These two concepts are so interrelated that while it is appropriate to have separate guidance documents for each, there must be consistency between the two documents. Furthermore, while 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 which not only conflict with the homologous use document, they conflict with current regulatory language.

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 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.**

First, I would like to address the newly created term **"main function"** in the minimal manipulation guidance document. 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 structural impact upon application or implantation. For example, amnion contains not only collagen in an extracellular matrix; it has other proteins 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. We can't achieve this with synthetic dressings.

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

Amniotic

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.

If the notion of main function was 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**.

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 different areas of the body. 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. The extracellular matrix 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.

The Alliance does have two specific issues regarding the homologous use guidance document.

First, the Alliance is concerned about how the narrow definition of homologous use for amnion tissue will impact its 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.* There are many basic functions of amniotic tissue as we described earlier and this tissue type should be used for wound healing. The FDA had even stated in the past that amnion may be used for wound healing when cytokines were present—meaning that it was not

decellularized. As such, the Alliance recommends that the FDA continue to permit amnion in their homologous use considerations.

Finally, the Alliance would like to state that regulations expressly do not separate the definition of homologous use depending on whether tissue is structural or non-structural.

On behalf of the Alliance, I thank you for the opportunity to provide you with our testimony. We will be submitting written comments later this month.