February 23, 2015

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


Dear Sir or Madam:

The Advanced Medical Technology Association (“AdvaMed”) is pleased to provide comments on FDA’s draft guidance “Human Cells, Tissues, and Cellular- and Tissue-Based Products from Adipose Tissue: Regulatory Considerations; Draft Guidance for Industry and Food and Drug Administration Staff.”

AdvaMed represents manufacturers of medical devices, diagnostic products, and health information systems that are transforming health care through earlier disease detection, less invasive procedures, and more effective treatment. Our members range from the smallest to the largest medical technology innovators, and many of our members either manufacture or use human cells, tissues, and cellular- and tissue-based products (HCT/Ps) in their products.

AdvaMed appreciates the Agency’s efforts to clarify when adipose tissue can and cannot be regulated as a 361HCT/P. We have administrative/process as well as scientific concerns with the draft guidance, however, that are discussed below.

Administrative/Process Concerns: There are a number of policy or interpretation shifts concerning HCT/Ps introduced in this draft guidance document (enumerated below) that would and should be considered significant enough to warrant Level I guidance status. 1 As such, Good Guidance Practices allow for stakeholder input in the form of workshops and meetings both before and after the issuance of a Level 1 guidance document. 2 As this draft guidance has introduced policy shifts that could have far-reaching impacts on our industry, AdvaMed recommends that FDA seek public stakeholder input prior to finalizing any guidance.

The broad expansion in scope of the definition of “minimal manipulation” by introducing the concept that “[t]he main function of the HCT/P, in the donor, determines which definition of

1 Good Guidance Practices (GGPs) define Level 1 guidances as guidances that “(i) set forth initial interpretations of statutory or regulatory requirements; (ii) set forth changes in interpretation or policy that are of more than a minor nature; (iii) include complex scientific issues; or (iv) cover highly controversial issues” (21 C.F.R. § 10.115(c)).
2 21 C.F.R. § 10.115(g)(1)
minimal manipulation [for structural tissue or cellular/nonstructural HCT/Ps] applies” has the potential for eliminating practically all processing of structural tissue (specifically cell isolation from structural tissue) as more than minimal manipulation. This concept does not appear in regulations and is mentioned only in the “Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products proposed rule.\(^3\)

Notwithstanding the issues with this draft guidance document discussed above and in our specific comments below, we believe that FDA should implement definitions of “minimal manipulation,” “main function,” and the distinction introduced regarding structural and nonstructural tissue through notice and comment rulemaking, and not through guidance. Given that an understanding of what constitutes “minimal manipulation” has been a fundamental aspect of FDA regulatory decision-making regarding HCT/Ps for well over a decade, and, as noted above, the impact of defining the terms has significant consequences, the definition of these terms should prompt notice and comment rulemaking. AdvaMed therefore recommends that FDA withdraw the Minimal Manipulation Draft Guidance and issue an Advanced Notice of Proposed Rule-Making if it chooses to proceed with defining minimal manipulation and main function as it relates to structural and non-structural HCT/Ps as it does in this draft guidance document.

**Scientific Issues:** AdvaMed is concerned with how FDA has defined structural and non-structural tissue in this draft guidance document and the main functions ascribed to the different types of HCT/Ps discussed. For example, the draft guidance does not distinguish between epidermis and dermis, two distinctly different parts of the skin with different functions and therefore, ascribes only epidermal properties to all of skin (“provide a barrier to retain moisture and protect from infection and/or the external environment”). Nor does it acknowledge that HCT/Ps may serve more than one function (with none of them being “main”).

Our specific comments provided in the attachment.

Thank you for the opportunity to submit comments on this draft guidance document.

Respectfully submitted,

/s/

Sharon A. Segal, Ph.D.
Vice President
Technology and Regulatory Affairs

Attachment

\(^3\) FR 26744 at 25649 (May 14, 1998).
## ATTACHMENT
### ADVAMED COMMENTS
"Minimal Manipulation of Human Cells, Tissues, and Cellular- and Tissue-Based Products"

<table>
<thead>
<tr>
<th>Line(s) No.</th>
<th>Change</th>
<th>Reason</th>
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<tbody>
<tr>
<td>General comment</td>
<td>Provide more examples of tissues that meet the minimal manipulation criteria for 361 HCT/Ps throughout the document.</td>
<td>N/A</td>
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<td>Question 7, Example 7-3</td>
<td>Provide clarification for the determination of minimal manipulation if a manufacturer were to use a methodology for cellular removal that did not break down and eliminate structural components.</td>
<td>The example given is helpful in clarifying the thought process regarding minimal manipulation as it relates to breakdown of the relevant structural characteristics of a HCT/P, however, if a process were developed that allowed structural characteristics to remain intact, this example would not address that situation.</td>
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<td>Question 9, Example 9-1</td>
<td>Provide clarification for question 9 as it relates to alteration of the HCT/P’s physical state relating to its utility for reconstruction, repair, or replacement as generally considered more than minimally manipulated. As it pertains to the example, a cartilage slurry for which a manufacturer could demonstrate via <em>in vitro</em> testing that the HCT/P made from cartilage maintains its relevant characteristics (i.e., ability to absorb shock and reduce friction between joints).</td>
<td>Even with an alteration of the physical state of an HCT/P during processing, it may be demonstrated to maintain the relevant characteristics and utility of the tissue. The example pre-supposes that cartilage slurry would alter the ability of the HCT/P to absorb shock and reduce friction, though this contention is debatable.</td>
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<td>Question 12, Example 12-1(b)</td>
<td>Provide guidance regarding minimal manipulation of an HCT/P derived from cord blood that can be shown via <em>in vitro</em> testing to retain the described original characteristics.</td>
<td>The example pre-supposes that a HCT/P derived from cord blood in which culture media and growth factors are used to achieve large numbers of cells would alter the original characteristics of the cells, however, if a process were developed that did not alter these original characteristics, clarification is needed to understand the guidance in regard to minimal manipulation.</td>
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