

February 23, 2015

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

Docket FDA-2014-D-1696-0001

Dear Madams and Sirs:

The American Society of Plastic Surgeons (ASPS) appreciates the opportunity to provide comments on the *Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products: Draft Guidance* [hereafter “draft minimal manipulation guidance”], published on December 23, 2014 by the Food and Drug Administration (FDA or Agency).

ASPS is the largest association of plastic surgeons in the world, representing more than 7,000 members and 94 percent of all American Board of Plastic Surgery board-certified plastic surgeons in the United States. Plastic surgeons provide highly skilled surgical services that improve both the functional capacity and quality of life of patients. These services include the treatment of congenital deformities, burn injuries, traumatic injuries, hand conditions, and cancer. ASPS promotes the highest quality patient care, professional and ethical standards, and supports education, research, and public service activities of plastic surgeons.

ASPS shares the FDA’s commitment to providing patients with access to safe and effective treatments. Additionally, we respect the agency’s tiered, risk-based framework to balance the need to protect patient safety with the need for therapeutic alternatives. It is in all our best interest to be certain that all human cells, tissues, and cellular and tissue-based products (HCT/Ps) are appropriately regulated.

These shared objectives now prompt ASPS to submit these comments to express our concerns about the FDA’s draft minimal manipulation guidance.

For the reasons explained in more detail below, ASPS respectfully requests the FDA to:

- Abandon the concept of main function and instead rely upon the intended use to determine whether a specific Human Cell, Tissue, and Cellular and Tissue-Based Product (HCT/P) is structural or non-structural for the purpose of determining whether it is minimally manipulated. Rather than create a whole new concept with no regulatory basis, we request that the Agency utilize familiar concepts.

- Clarify its stance on the use of acellular dermal matrixes (ADMs) for breast reconstruction to ensure that it qualifies as a 361 HCT/P to maintain this vital option for women post-mastectomy. As written, the FDA's draft minimal manipulation guidance document focuses on HCT/Ps used for the skin, which may inadvertently result in ADMs not being regulated as 361 HCT/Ps.

- I. Abandon the concept of main function and instead rely upon the intended use to determine whether a specific HCT/P is structural or non-structural for the purpose of determining whether it is minimally manipulated.

As outlined in our comments related to the *Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) from Adipose Tissue: Regulatory Considerations; Draft Guidance*¹ (released on December 24, 2014), the ASPS believes that given the non-structural and structural properties of many HCT/Ps (including adipose tissue), the FDA would be better served acknowledging the complex biological characteristics of HCT/Ps. Thus, it seems inappropriate to limit the application of a HCT/P to the main function, and ASPS would argue that the FDA should instead examine intended use. Given that many HCT/Ps exhibit more than one function, this is more biologically accurate.

Consequently, its intended use is a more appropriate paradigm for the determination of whether a HCT/P is considered structural or non-structural, which helps determine what is considered minimal manipulation. This is particularly relevant given that it should be FDA's goal to provide additional clarity regarding the regulation of HCT/Ps and not use the guidance documents to simply re-classify HCT/Ps.

- II. Clarify FDA's stance on the use of acellular dermal matrixes (ADMs) for breast reconstruction to ensure that it qualifies as a 361 HCT/P to maintain this vital option for women post-mastectomy.

Surgeons are increasingly electing to use ADMs to assist with tissue expander or implant-based primary breast reconstruction.^{2,3} Of the approximately 95,000 breast reconstructions performed in the United States in 2013, about 68,000 (roughly 72%) were tissue expander-implant-based breast reconstructions.⁴ Multiple authors have reported favorable outcome studies using ADMs in medical literature, and rapid early expansion has led to improved cosmetic outcomes.^{5,6,7,8}

The introduction of ADMs has provided surgeons with alternative means of obtaining sufficient vascularized soft tissue to cover the implant, thereby alleviating some complications. In addition, the use of ADMs allows for a one stage procedure as opposed to expander based reconstructions that require several inflations in clinic and a second operation to exchange the expander to a silicone implant.⁹ Breuing first reported the use of human acellular dermis in implant-based breast reconstruction in 2005.¹⁰ Not long after, Bindingavele reported acellular dermis-assisted tissue expander-based reconstruction.¹¹

Several authors – including Salzberg,¹² Spear,¹³ and Topol¹⁴ – reported positive outcomes in the following years, citing increased fill volumes and improved aesthetic outcomes. In 2008, Preminger reported the first comparative study that analyzed intraoperative fill volume differences between ADM and non-ADM cohorts.¹⁵ This provided the impetus for several other comparative studies, such as the comparison of ADM technique with submuscular coverage by Sbitany et al.¹⁶

Other positive benefits of the use of ADMs include limiting inflammatory changes believed to play a role in capsular contracture – a common complication of implant-based breast reconstruction¹⁷ – as well as decreased risk of all complications related to radiation.¹⁸

In recognition that breast reconstruction, including reconstruction using ADMs, plays an essential role in both physical and psychological healing following mastectomy, federal law mandates health insurers to pay for breast reconstruction,¹⁹ and states have also enacted separate legislation to further clarify coverage.²⁰ As a result, the vast majority of insurance companies cover the procedure.^{21,22,23,24,25,26}

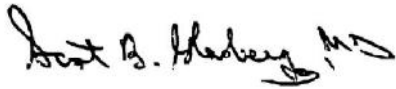
Given the current reliance on the use of ADMs for breast reconstructive surgery, we would like to ensure that, subsequent to implementation of the minimal manipulation guidance, those products are still available to our patients and that the ADMs for breast reconstruction are regulated as 361 HCT/Ps. Thus, we are slightly concerned with what may be an inadvertent descriptor within the draft minimal manipulation guidance.

Specifically, the draft minimal manipulation guidance states that the main function of skin – from which ADMs are derived – is that it “provides a barrier to retain moisture and protect from infection and/or the external environment” (emphasis added). Given that ADMs for breast reconstruction are used internal to the woman’s body, it is unclear if they would fit the FDA’s main function for skin. One potential way of resolving this issue is to simply provide two different HCT/P categories – one for epidermis (for which the currently crafted main function may be appropriate) and one for dermis (which would recognize the connective and supportive functions of dermis).^{27,28} Another alternative, suggested earlier, is to eliminate the concept of main function and then further clarify that the use of ADMs for breast reconstruction is a homologous use. Ultimately, in whatever way the FDA chooses to resolve this issue, we urge the FDA to clarify that ADMs for breast reconstruction are regulated as 361 HCT/Ps.

The ASPS appreciates the opportunity to offer these comments and looks forward to working with the FDA. ASPS has in the past met with representatives of the Center for Biologics Evaluation and Research (CBER) to review current trends in plastic surgery research and development of new therapies, and discuss the regulatory issues involved. **We respectfully request the opportunity to meet with CBER again to further discuss this draft guidance.** In particular, we believe a meeting with CBER's Director, Karen Midthun, would be particularly productive, given the enormous impact this draft guidance will have on plastic surgeons. **In addition, given the potentially broad implications this guidance document may have, we also request that you hold a public meeting on this draft guidance document.**

Should you have any questions about our comments, please contact Catherine French, ASPS Health Policy Manager, at cfrench@plasticsurgery.org or 847.981.5401.

Sincerely,



Scot B. Glasberg, MD
President, American Society of Plastic Surgeons

¹<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm427795.htm>

²Sbitany H, Sandeen SN, Amalfi AN, Davenport MS, Langstein HN. Acellular dermis-assisted prosthetic breast reconstruction versus complete submuscular coverage: a head-to-head comparison of outcomes. *Plast Reconstr Surg.* Dec 2009;124(6):1735-40.

³Spear SL, Parikh PM, Reisin E, Menon NG. Acellular dermis-assisted breast reconstruction. *Aesthetic Plast Surg.* May 2008;32(3):418-25.

⁴American Society of Plastic Surgeons: Reconstructive Breast Surgery Statistics 2013. Available at <http://www.plasticsurgery.org/Documents/news-resources/statistics/2013-statistics/reconstructive-procedures-demographics.pdf>. Accessed 11 September 2015.

⁵Spear SL, Parikh PM, Reisin E, Menon NG. Acellular dermis-assisted breast reconstruction. *Aesthetic Plast Surg.* May 2008;32(3):418-25

⁶Breuing KH, Warren SM. Immediate bilateral breast reconstruction with implants and inferolateral AlloDerm slings. *Ann Plast Surg.* Sep 2005;55(3):232-9.

⁷Salzberg CA. Nonexpansive immediate breast reconstruction using human acellular tissue matrix graft (AlloDerm). *Ann Plast Surg.* Jul 2006;57(1):1-5.

⁸Bindingavele V, Gaon M, Ota KS, Kulber DA, Lee DJ. Use of acellular cadaveric dermis and tissue expansion in postmastectomy breast reconstruction. *J Plast Reconstr Aesthet Surg.* 2007;60(11):1214-8.

⁹Kiernan T, Martin L (2013) Use of Acellular Dermal Matrix is Comparable to Expander Based Breast Reconstructions for Post Operative Physiotherapy Requirements. *Surgery Curr Res* 3:136. doi: 10.4172/2161-1076.1000136. <http://omicsonline.org/use-of-acellular-dermal-matrix-is-comparable-to-expander-based-breast-reconstructions-for-post-operative-physiotherapy-requirements-2161-1076.1000136.php?aid=15706>

¹⁰Breuing KH, Warren SM. Immediate bilateral breast reconstruction with implants and inferolateral AlloDerm slings. *Ann Plast Surg.* Sep 2005;55(3):232-9.

¹¹Bindingavele V, Gaon M, Ota KS, Kulber DA, Lee DJ. Use of acellular cadaveric dermis and tissue expansion in postmastectomy breast reconstruction. *J Plast Reconstr Aesthet Surg.* 2007;60(11):1214-8.

¹²Salzberg CA. Nonexpansive immediate breast reconstruction using human acellular tissue matrix graft (AlloDerm). *Ann Plast Surg.* Jul 2006;57(1):1-5.

¹³Spear SL, Parikh PM, Reisin E, Menon NG. Acellular dermis-assisted breast reconstruction. *Aesthetic Plast Surg.* May 2008;32(3):418-25.

¹⁴Topol BM, Dalton EF, Ponn T, Campbell CJ. Immediate single-stage breast reconstruction using implants and human acellular dermal tissue matrix with adjustment of the lower pole of the breast to reduce unwanted lift. *Ann Plast Surg.* 2008 Nov;61(5):494-9. *Ann Plast Surg.* 2008 Nov;61(5):494-9. doi: 10.1097/SAP.0b013e31816d82d9.

¹⁵Preminger BA, McCarthy CM, Hu QY, Mehrara BJ, Disa JJ. The influence of AlloDerm on expander dynamics and complications in the setting of immediate tissue expander/implant reconstruction: a matched-cohort study. *Ann Plast Surg.* May 2008;60(5):510-3.

¹⁶Sbitany H, Sandeen SN, Amalfi AN, Davenport MS, Langstein HN. Acellular dermis-assisted prosthetic breast reconstruction versus complete submuscular coverage: a head-to-head comparison of outcomes. *Plast Reconstr Surg.* Dec 2009;124(6):1735-40.

¹⁷Leong M, Basu CB, Hicks MJ. Further Evidence that Human Acellular Dermal Matrix Decreases Inflammatory Markers of Capsule Formation in Implant-Based Breast Reconstruction. *Aesthet Surg J.* 2015 Jan;35(1):40-7.

¹⁸Seth AK, Hirsch EM, Fine NA, Kim JY. Utility of acellular dermis-assisted breast reconstruction in the setting of radiation: a comparative analysis. *Plast Reconstr Surg.* 2012 Oct;130(4):750-8.

¹⁹Women's Health and Cancer Rights Act of 1998, PL 105-277.

²⁰<http://www.plasticsurgery.org/reconstructive-procedures/breast-reconstruction/breast-reconstruction-resources/state-laws-on-breast-reconstruction.html>

²¹ "Breast Implants and tissue expanders post mastectomy with or without skin substitutes, approved by the FDA, including but not limited to: Alloderm, Allomax or FlexHD are a covered benefit."

https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesPdf/Tools%20and%20Resources/Policies%20and%20Protocols/Medical%20Policies/Medical%20Policies/BreastReconstruction_CD.pdf

²²Following Medically Necessary removal of all or part of a breast, we cover reconstruction of the breast, surgery and reconstruction of the other breast to produce a symmetrical appearance, and treatment of physical complications, including lymphedemas.

http://info.kaiserpermanente.org/info_assets/child_health_plan/pdfs/membership_agreement_eoc.pdf.

²³Reconstruction of the affected and the contralateral unaffected breast following a medically necessary mastectomy is considered a relatively safe and effective noncosmetic procedure. Accordingly, program payment may be made for breast reconstruction surgery following removal of a breast for any medical reason.

<http://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=64&ncdver=1&bc=AgAAQAAAAAAA&>

²⁴ The use of the following acellular dermal matrices are considered medically necessary for breast reconstruction: Alloderm (LifeCell Corp., Branchburg, NJ), Alloderm-RTU (LifeCell Corp., Branchburg, NJ), FlexHD (Musculoskeletal Transplant Foundation/Ethicon, Inc., Somerville, NJ), DermaMatrix (Musculoskeletal Transplant Foundation/Synthes CMF, West Chester, PA), AlloMax (formerly NeoForm) (Davol, Inc., Warwick, RI), Strattice (LifeCell Corp., Branchburg, NJ) and SurgiMend (TEI Biosciences, Boston, MA).

http://www.aetna.com/cpb/medical/data/100_199/0185.html

²⁵Reconstructive surgery refers to surgical procedures and other techniques, undertaken in the context of breast cancer, to rebuild breast contour and, when necessary, reconstitute the areola and nipple. <https://www.caresource.com/documents/breast-reconstruction-surgery-following-mastectomy/>

²⁶Restoration of a normal breast form through breast reconstruction is performed for patients undergoing mastectomy or lumpectomy. The manner of breast reconstruction is an individualized decision between the patient and their physician.

https://my.cigna.com/teamsite/health/provider/medical/procedural/coverage_positions/medical/mm_0178_coverage_position_criteria_breast_reconstruction_follow_mast_lump.pdf

²⁷The dermis contains tough connective tissue. <http://www.webmd.com/skin-problems-and-treatments/picture-of-the-skin>

²⁸The dermis is the vascular area of connective tissue of skin. Illustrated Dictionary of Podiatry and Foot Science by Jean Mooney © 2009 Elsevier Limited. All rights reserved.