



American Association of Tissue Banks® AATB TPG, LLC

October 5, 2021

Candace Nalls  
Center for Devices and Radiological Health  
Food and Drug Administration  
10903 New Hampshire Avenue  
Bldg. 66, Rm. 5216  
Silver Spring, MD 20993-0002

**In Re: October 20, 2021: General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee Meeting**

Submitted via e-mail to [candace.nalls@fda.hhs.gov](mailto:candace.nalls@fda.hhs.gov)

Dear Madams and Sirs:

The American Association of Tissue Banks (AATB or Association) and the American Association of Tissue Bank's Tissue Policy Group, LLC (AATB TPG) submit these comments related to upcoming General and Plastic Surgery Devices Panel meeting on October 20, 2021 to discuss the premarket approval application (PMA) for the SurgiMend PRS Acellular Bovine Dermal Matrix (SurgiMend PRS ABDM) by Integra LifeSciences Corporation. Specifically, our comments will focus on the key differences between the Integra product and acellular dermal matrixes (ADMs) comprised of human cells, tissues, and cellular and tissue-based products (HCT/Ps) and why those differences should result in a different regulatory stance by the Food and Drug Administration (FDA or Agency), provide information on the history of use of ADMs for breast reconstruction, and re-iterate a request for a public workshop to discuss the appropriate regulation of human ADMs for breast reconstruction procedures.

**I. Interest of AATB**

The American Association of Tissue Banks (AATB) is a professional, non-profit, scientific, and educational organization. AATB is the only national tissue banking organization in the United States, and its membership totals more than 120 accredited tissue banks and over 6,000 individual members. These banks recover tissue from more than 58,000 donors and distribute in excess of 3.3 million allografts for more than 2.5 million tissue transplants performed annually in the US. The overwhelming majority of the human tissue distributed for these transplants comes from AATB-accredited tissue banks.

The AATB's Tissue Policy Group (TPG), LLC (AATB TPG or TPG) includes Chief Executive Officers and senior regulatory personnel from U.S. tissue banks that process donated human tissue. The purpose of the TPG is to drive public policy in furtherance of the adoption of laws and regulations that foster the safety, quality and availability of donated tissue. The TPG's membership is

responsible for the vast majority of tissue available for transplantation within the U.S.

## II. **Human ADMs and Xenograft ADMs are NOT the Same Products**

ADM allografts are derived from donated human skin and are called “human ADMs.” These products typically are used to reinforce damaged or inadequate integumental tissue, and they offer significant clinical advantages over synthetic and xenograft alternatives. In particular, human ADM allografts are incorporated into a patient’s body via revascularization and cellular ingrowth from the surrounding tissues.<sup>1</sup> In contrast, synthetic medical device implants serving a similar function either reside as foreign bodies for the duration of their use or must be made resorbable (i.e., capable of being degraded, metabolized and excreted over time), while bovine xenografts may possess alpha-gal that are known immunomodulatory molecules and can result in an inflammatory response to the tissues.<sup>2</sup>

To further support the use of human ADMs in breast reconstruction, and the distinction between xenografts and synthetic meshes from human ADMs in this procedure, nearly 96% of all materials used to provide support in post-mastectomy breast reconstruction are human ADMs.<sup>3</sup> The table below<sup>4</sup> provides a clearer picture of the difference in these three very distinct materials. All are legally marketed for a general intended use.

Source	Common name	Material Type	Brand Examples (not an exhaustive list)	FDA Branch of Regulation	Percentage when used in implant-based breast reconstruction
Human-Derived	Allograft	Acellular Dermal Matrix (ADM)	FlexHD, AlloDerm, Cortiva, DermACELL	CBER	95.6%
Animal-Derived	Xenograft, Surgical Mesh	Biologic, Extracellular Matrix (NOT always dermis)	Strattice, SurgiMend, Mesobiomatix	CDRH	3.8%
Synthetic	Surgical Mesh	Synthetic, man-made	Vicryl, GalaFlex, TIGR Mesh	CDRH	0.6%

In general, allograft products are regulated by the Center for Biologics Evaluation and Research (CBER) as 361 HCT/Ps. While the Center for Devices and Radiological Health (CDRH) has a long history of regulating a variety of xenograft products, including products like Surgimend, the

<sup>1</sup> Ibrahim AM, Ayeni OA, Hughes KB, et al. Acellular dermal matrices in breast surgery: a comprehensive review. Ann Plast Surg. 2013;70:732–8. doi: 10.1097/SAP.0b013e31824b3d30.

<sup>2</sup> Kuravi KV et al. Allergic response to medical products in patients with alpha-gal syndrome. Allergic response to medical products in patients with alpha-gal syndrome. The Journal of Thoracic and Cardiovascular Surgery, Published: April 08, 2021DOI: <https://doi.org/10.1016/j.jtcvs.2021.03.100>.

<sup>3</sup> Op Cit.

<sup>4</sup> <https://app.smartrak.com/markets/qs/6560> (Smartrak data, 2019).

regulation of xenografts has no direct bearing on HCT/Ps, given that HCT/Ps have a separate regulatory category that is unavailable to xenografts: 361 HCT/Ps. As detailed in attached letters to the Agency dated April 26, 2019 and July 19, 2019 as well as the citizen petition filed on this subject on December 31, 2019 ([FDA-2019-P-6100-0001](#)), **the AATB strongly believes that human ADMs for breast reconstruction are more appropriately regulated by the Agency as 361 HCT/Ps.**

### **III. Long History of Use of Human ADMs for Breast Reconstruction**

Human ADMs were first described for use in breast surgery in 2005.<sup>5</sup> Since this initial report, ADMs have become an increasingly common component of implant-based breast reconstruction procedures to serve as a protective covering.<sup>6</sup> According to the American Society of Plastic Surgeons, of the approximately 101,657 breast reconstruction procedures performed by member surgeons in 2018, about 83,200 (roughly 82%) utilized tissue expanders and/or breast implants. Of these procedures, approximately 74% (61,713) utilized ADMs. Recognizing human ADMs as the proven standard of care, major U.S. payers (e.g., Anthem, CIGNA, Blue Cross Blue Shield, and Aetna) currently regard the use of acellular dermal matrix with breast reconstruction as a clinically supported and clearly reimbursable use, where the tissue assists the surgeons in reconstructing the breast at the time of mastectomy in a process that improves cosmetic outcomes and limits the need for further surgical procedures.<sup>7</sup>

### **IV. Request for a Public Workshop**

As noted in the attached documents, the AATB and the TPG have repeatedly requested that the Agency hold a joint CDRH/CBER public workshop on the use of human ADMs in breast reconstruction with recipients, stakeholders from industry, health care professionals, and other interested parties. A joint CDRH/CBER workshop would be the next best step to address the classification of human ADMs for breast reconstruction. The purpose of this workshop would be to:

- further delineate FDA's regulatory rationale for making any regulatory change to the classification of human ADMs,
- have the appropriate regulatory stakeholders to ascertain next steps (i.e., have representatives from both CDRH and CBER)
- discuss the practicalities of the proposed regulatory framework, especially given that ADMs are utilized in a variety of settings (e.g., with and without devices, with and without breast implants),
- explain any potential safety concerns related to ADMs in breast reconstruction,
- further explore differences in adverse event reporting as it relates to 361 HCT/Ps versus medical devices.

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<sup>5</sup> Breuing KH, Warren SM. Immediate bilateral breast reconstruction with implants and inferolateral AlloDerm slings. Ann Plast Surg. 2005 Sep;55(3):232-9.

<sup>6</sup> Sheina A Macadam, MD MHS and Peter A Lennox, MD. Acellular dermal matrices: Use in reconstructive and aesthetic breast surgery. Can J Plast Surg. 2012 Summer; 20(2): 75-89.

<sup>7</sup> Sbitany, Hani, M.D.; Sandeen, Sven N., M.D.; Amalfi, Ashley N., M.D.; Davenport, Mark S., M.D.; Langstein, Howard N., M.D. Acellular Dermis-Assisted Prosthetic Breast Reconstruction versus Complete Submuscular Coverage: A Head-to-Head Comparison of Outcomes. Plastic and Reconstructive Surgery: December 2009 - Volume 124 - Issue 6 - p 1735-1740; doi: 10.1097/PRS.0b013e3181bf803d

Unfortunately, these key topics were not covered in the September 12-13, 2016 Part 15 hearing related to draft guidances for the regulation of HCT/P. As part of that meeting, one doctor presented with respect to ADMs for breast reconstruction, for approximately three minutes. That presentation only addressed the surgical aspects and did not address the regulatory or practical issues with such a change. During the brief Panel discussion in March 2019, only one manufacturer of human ADM products was able to discuss ADMs amongst a larger set of topics related to breast implants, not all of those who were affected. That manufacturer was able to do so, given that the manufacturer also produces breast implants and the presentation was within the context of informed consent for breast implant, not specific to ADMs. Thus, insufficient time was given to this topic at the 2019 Panel meeting.

Previously, FDA has held these workshops related to other regulatory challenges, including the use of bone. On August 2, 2001, CBER and CDRH co-hosted a public workshop titled *Human Bone Allograft: Manipulation and Homologous Use in Spine and Other Orthopedic Reconstruction and Repair* to solicit information on current practices related to the manipulation and homologous use of human bone allograft in the spine and other orthopedic reconstruction and repair procedures. Many of the comments presented at the meeting indicated that there were misunderstandings about how the criteria set out in Sec. 1271.10 would be applied, and about the meaning of the terms "minimal manipulation" and "homologous use." During this workshop, healthcare professionals, recipients and industry representatives presented the history of the surgical use of allograft bone in the spine. As a result of the meeting, bone used in spine with an objective intent for applications in the spine meet the minimal manipulation and homologous use requirements and are generally considered to be regulated solely as 361 HCT/Ps .

This request is consistent with the regulatory preamble which notes the following: *[W]e recognize that further public discussion of how tissue regulation would be applied to certain categories of human cells, tissues, and cellular and tissue-based products may be warranted due to the complexity or sensitivity of the issues. . . . We intend to provide further opportunities for public discussion of how the regulatory approach should be applied to other HCT/P's. We anticipate that there may be additional needs for discussion through public meetings, public hearings, or guidance as we implement the new regulations.*

Given that the Agency has contemplated a change to the regulatory status of human ADMs for breast reconstruction, ***we request a joint CDRH/CBER public workshop on the regulation of human ADMs used in breast reconstruction*** with stakeholders from industry, health care professionals, recipients and other interested parties as it will be critical to provide appropriate information regarding this potential regulatory shift and forum for discussion.

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We hope that you will find this information useful in your deliberations, and we look forward to future conversations. The AATB and the TPG stand ready and willing to assist the FDA with its deliberations in any way that you deem appropriate.

## *October 20, 2021 Panel Meeting*

*October 5, 2021*

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Respectfully,

*Marc Pearce*

Diana N Beck

Marc Pearce, MBA  
President & CEO  
American Association of Tissue Banks

Diana Buck  
Chair  
American Association of Tissue Banks

Attachments: April 26, 2019 Letter  
July 19, 2019 Letter  
September 17, 2019 Sign-On Letter



April 26, 2019

Center for Devices and Radiological Health  
Food and Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002

**Re: Docket FDA-2019-N-0426-0001, General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee Meeting on March 25 and 26**

To Whom It May Concern:

The American Association of Tissue Banks (AATB or Association) and the American Association of Tissue Bank's Tissue Policy Group, LLC (AATB TPG or TPG) were recently surprised by the comments made by the personnel of the Center for Devices and Radiological Health (CDRH) at the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee Meeting on March 25 and 26, 2019. The AATB and the TPG are concerned with the position taken by the individuals from CDRH that human-derived acellular dermal matrixes (ADMs) used in breast reconstruction procedures is currently being considered a non-homologous use. In addition, the AATB and the TPG were discouraged that no tissue banks were invited to present data or information before the panel and that representatives from the Center for Biologics Evaluation and Research (CBER) were also not included. **The AATB and the TPG strongly believe that human ADMs are appropriately regulated solely as 361 human cells, tissues, and cellular and tissue-based products (HCT/Ps) when promoted under the manufacturer's objective intent for use to augment, reinforce, support, protect, or cover soft tissue weaknesses, including for use in breast reconstruction procedures.** If the Agency disagrees with this regulatory classification, as further detailed below, the AATB and TPG request that the Food and Drug Administration (FDA or Agency) have a CDRH/CBER co-sponsored public workshop on the use of ADMs in breast reconstruction within the next four months.

**I. Statement of Interest**

The American Association of Tissue Banks (AATB) is a professional, non-profit, scientific and educational organization. It is the only national tissue banking organization in the United States, and its membership totals approximately 120 accredited tissue banks and 2,000 individual members. These banks recover tissue from more than 58,000 donors and distribute in excess of 3.3 million allografts for more than 2.5 million tissue transplants performed annually in the U.S. The overwhelming majority of the human tissue distributed for these transplants comes from AATB-accredited tissue banks.

The AATB's Tissue Policy Group (TPG), LLC (AATB TPG or TPG) includes Chief Executive Officers and senior regulatory personnel from U.S. tissue banks that process donated human tissue. The purpose of the TPG is to drive public policy in furtherance of the adoption of laws and regulations that foster the safety, quality and availability of donated tissue. The TPG's membership is responsible for the vast majority of tissue available for transplantation within the U.S.

## **II. Human ADMs for Breast Reconstruction are the Standard of Care**

Recognizing the need to assist individuals with severe burns, skin grafting was one of the first allografts. The use of allograft skin dates back to Reverdin in 1869 describing the use of skin grafting in clinical practice for the first time.<sup>1</sup> George Pollock used his own skin in addition to the patient's own skin to cover a burn in 1871.<sup>2</sup> The first report of successful use of allograft skin to treat a burn was by Girdner in 1881.<sup>3</sup> In 1903, Wentscher reported that allograft skin retained cellular viability after 3-14 days.<sup>4</sup> James Barrett Brown, M.D. (1899-1971), with his work in the early 1930s, revolutionized the concepts of skin grafting.<sup>5,6</sup> His work highlighted the key nature of allografts – that split thickness skin from the mother was completely absorbed within three weeks of being transferred to her severely burned son.<sup>7</sup> Organizations, such as the Ancient Arabic Order of the Nobles of the Mystic Shrine – or Shriners – helped further the use of skin grafts to assist burn care to children for 50 years.<sup>8</sup> As skin grafting became more common to save the life of burn patients, banking of skin paralleled the development of blood banks in the 1930s and gave way to the development of The Navy Tissue Bank in 1949. One of the major contributions of the Navy Tissue Bank was the development of cryopreservation to prolong the shelf life of banked skin to make its use more widely available and retain cellular viability. To further expand the use of donated skin, decellularization technologies were developed and applied to the dermal layer of skin for a variety of intended uses and are the subject of this document.

Human ADMs have been used for many years in various applications, many of which address congenital abnormalities or reconstruction following trauma or disease. These include, but are not limited to, pelvic, abdominal, and chest wall reconstructions;<sup>9</sup> diabetic foot ulcers,<sup>10,11,12</sup> chronic wounds,<sup>13</sup> dural repair,<sup>14</sup> hand

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<sup>1</sup> Reverdin JL. Greffe epidermique, experience faite dans le service de M le docteur Guyon, a l'hopital Necker. Bull Imp Soc Chir Paris. 1869;10:511-5

<sup>2</sup> Pollock GD. Cases of skin grafting and skin transplantation. Trans Clin Soc Lond. 1871;4:37-54

<sup>3</sup> Girdner JH. Skin-grafting with grafts taken from the dead subject. Med Record NY. 1881;20:119-20

<sup>4</sup> Wentscher J. A further contribution about the survivability of human epidermal cells. Dtsch Z Chir. 1903;70:21-44.

<sup>5</sup> Blair VB, Brown JB, Hamm WG. Early Cre of burs. JAMA 1932;98:1355-1359.

<sup>6</sup> Blair VP, Brown JB. The use and uses of split thickness skin grafts of intermediate thickness. Surg Gynocol Obstet. 1928;98:82-97.

<sup>7</sup> Ibid.

<sup>8</sup> Čapek KD, Culnan DM, Desai MH, Herndon DN. Fifty Years of Burn Care at Shriners Hospitals for Children, Galveston. Ann Plast Surg. 2018;80(3 Suppl 2):S90-S94. doi:10.1097/SAP.0000000000001376

<sup>9</sup> Butler CE, Langstein HN, Kronowitz SJ. Pelvic, abdominal, and chest wall reconstruction with AlloDerm in patients at increased risk for mesh-related complications. *Plast Reconstr Surg.* 2005 Oct. 116(5):1263-75; discussion 1276-7.

<sup>10</sup> Guo X, Mu D, Gao F. Efficacy and safety of acellular dermal matrix in diabetic foot ulcer treatment: A systematic review and meta-analysis. *Int J Surg.* 2017 Apr;40:1-7. doi: 10.1016/j.ijsu.2017.02.008. Epub 2017 Feb 14

<sup>11</sup> Cazzell S, Vayser D, Pham H, Walters J, Reyzelman A, Samsell B, Dorsch K, Moore M. A randomized clinical trial of a human acellular dermal matrix demonstrated superior healing rates for chronic diabetic foot ulcers over conventional care and an active acellular dermal matrix comparator. *Wound Repair Regen.* 2017 May;25(3):483-497. doi: 10.1111/wrr.12551. Epub 2017 Jun 12.

<sup>12</sup> Reyzelman AM, Bazarov I. Human acellular dermal wound matrix for treatment of DFU: literature review and analysis. *J Wound Care.* 2015 Mar;24(3):128; 129-34. doi: 10.12968/jowc.2015.24.3.128.

<sup>13</sup> Walters J, Cazzell S, Pham H, Vayser D, Reyzelman A. Healing Rates in a Multicenter Assessment of a Sterile, Room Temperature, Acellular Dermal Matrix Versus Conventional Care Wound Management and an Active Comparator in the Treatment of Full-Thickness Diabetic Foot Ulcers. *Eplasty.* 2016;16:e10. Published 2016 Feb 4.

<sup>14</sup> Chaplin JM, Costantino PD, Wolpo ME, Bederson JB, Griffey ES, Zhang WX. Use of an acellular dermal allograft for dural replacement: an experimental study. *Neurosurgery.* 1999 Aug. 45(2):320-7.

surgery;<sup>15</sup> urethral reconstruction;<sup>16</sup> burn surgery;<sup>17</sup> ENT procedures,<sup>18</sup> venous leg ulcers,<sup>19,20,21</sup> and gingival graft procedures.<sup>22</sup>

During breast reconstruction following mastectomy, the diseased breast tissue is excised and replaced with a tissue expander or breast implant. The mastectomy surgery itself often results in a thin, weakened and inadequate skin envelope that requires support and protection from mechanical stress induced by the implant placed into the reconstructed breast to regain its natural shape and appearance. Human ADMs were first described for use in breast surgery in 2001.<sup>23</sup> Since this initial report, ADMs have become an increasingly common component of implant-based breast reconstruction procedures to serve as a protective covering.<sup>24</sup> Human ADMs have become a vital part of breast reconstruction procedures because they address the tissue deficiencies resulting from mastectomy. The human ADMs provide reinforcement for weakened dermal/skin tissue, supplements thin and overly dissected tissue, and repairs the breast boundaries that were eliminated during the procedure, all with the objective intent of supporting the healing process and returning the patient to normal activities of daily living. Without the ADMs, capsular contracture may occur which can result in limited mobility and use of the arm on the affected side. Human ADMs have been reported to address various issues with previously-used implant-based breast reconstruction techniques, including subcutaneous placement and submuscular placement (both full muscle coverage or FMC and partial muscle coverage or PMC) of the breast implant, and became a cornerstone of immediate breast reconstruction over the last two decades. According to the American Society of Plastic Surgeons, of the approximately 101,657 breast reconstruction procedures performed by member surgeons in 2018, about 83,200 (roughly 82%) utilized tissue expanders and/or breast implants. Of these procedures, approximately 74% (61,713) utilized ADMs.

The introduction of human ADMs within breast reconstruction surgery has provided surgeons with alternative means to augment, reinforce, support, protect, or cover and protect soft tissue weaknesses, thereby alleviating

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<sup>15</sup> Kim JY, Buck DW 2nd, Kloeters O, Eo S, Jones NF. Reconstruction of a recurrent first dorsal web space defect using acellular dermis. *Hand (N Y)*. 2007 Dec; 2(4):240-4.

<sup>16</sup> Kim JY, Bullocks JM, Basu CB, Bienstock A, Link R, Kozovska M. Dermal composite flaps reconstructed from acellular dermis: a novel method of neourethral reconstruction. *Plast Reconstr Surg*. 2005 Jun; 115(7):96e-100e.

<sup>17</sup> Sheridan R, Choucair R, Donelan M, Lydon M, Petras L, Tompkins R. Acellular allograft dermis in burns surgery: 1-year results of a pilot trial. *J Burn Care Rehabil*. 1998 Nov-Dec; 19(6):528-30.

<sup>18</sup> Agir H, Eren GG, Yasar EK. Acellular Dermal Matrix Use in Cleft Palate and Palatal Fistula Repair: A Potential Benefit? *J Craniofac Surg*. 2015 Jul; 26(5):1517-22.

<sup>19</sup> Cazzell S. A Randomized Controlled Trial Comparing a Human Acellular Dermal Matrix Versus Conventional Care for the Treatment of Venous Leg Ulcers. *Wounds*. 2019 Mar; 31(3):68-74. Epub 2019 Jan 31.

<sup>20</sup> Hughes, OB, Rakosi A, Macquhae F, Herskovitz I, Fox JD, Kirsner RS. A Review of Cellular and Acellular Matrix Products: Indications, Techniques, and Outcomes. *Plast Reconstr Surg*. 2016 Sep; 138(3 Suppl):138S-47S. doi: 10.1097/PRS.0000000000002643

<sup>21</sup> Cazzell S. A Randomized Controlled Trial Comparing a Human Acellular Dermal Matrix Versus Conventional Care for the Treatment of Venous Leg Ulcers. *Wounds*. 2019 Mar; 31(3):68-74. Epub 2019 Jan 31.

<sup>22</sup> Aichelmann-Reidy ME, Yukna RA, Evans GH, Nasr HF, Mayer ET. Clinical evaluation of acellular allograft dermis for the treatment of human gingival recession. *J Periodontol*. 2001 Aug; 72(8):998-1005.

<sup>23</sup> Margulies I, Salzberg C. The use of acellular dermal matrix in breast reconstruction: evolution of technique over 2 decades. *Gland Surgery* 2019; 8(1):3-10.

<sup>24</sup> [Sheina A Macadam](#), MD MHS and [Peter A Lennox](#), MD. *Acellular dermal matrices: Use in reconstructive and aesthetic breast surgery*. [Can J Plast Surg](#). 2012 Summer; 20(2): 75-89.

some significant complications. Several authors, including Salzberg<sup>25</sup> and Spear,<sup>26</sup> have reported enhanced outcomes, citing increased fill volumes and improved aesthetic outcomes. According to a recent review article,<sup>27</sup> principal advantages include the potential enhancement of cosmesis in breast reconstruction, amelioration of late or irradiation-induced contracture, improved long-term correction of complications following aesthetic revisionary surgery and cost-savings imparted by the direct-to-implant breast reconstruction model.

Recognizing human ADMs as the proven standard of care, major U.S. payers (e.g. Anthem, CIGNA, Blue Cross Blue Shield, and Aetna) currently regard the use of acellular dermal matrix with breast reconstruction as a clinically supported and clearly reimbursable use, where the tissue assists the surgeons in reconstructing the breast at the time of mastectomy in a process that improves cosmetic outcome and limits the need for further surgical procedures.<sup>28</sup>

While likely not included as part of the manufacturer's objective intent, human ADMs for breast reconstruction may afford additional benefits. A study performed by Leong, Basu, and Hicks investigated whether human ADMs might inhibit the inflammatory and profibrotic signaling, which is characteristic of breast capsule development, and also help to decrease the risk of capsular contracture. Their hypothesis was supported by clinical evidence indicating that the risk of capsular contracture is lower in patients who undergo reconstruction that includes human ADMs.<sup>29</sup> Additionally, Paydar, Wirth, and Mowlds reported that the protection ADMs afford against capsular contracture ultimately saves time and money and anecdotally results in improved patient comfort and satisfaction.<sup>30</sup>

As AATB has noted in previous comments to the docket with respect to regulatory classification, we urge the FDA to provide further clarity regarding common procedures related to breast reconstruction – namely, the use of human ADMs to augment, reinforce, support, protect, or cover soft tissue weaknesses. Unless the FDA clarifies this critical issue, women who choose reconstruction after mastectomy or lumpectomy will have reduced access to the current standard of care to help restore both physical and emotional well-being after a breast cancer diagnosis.

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<sup>25</sup> Salzberg CA. Nonexpansive immediate breast reconstruction using human acellular tissue matrix graft (AlloDerm). *Ann Plast Surg.* 2006 Jul; 57(1):1-5.

<sup>26</sup> Spear SL, Parikh PM, Reisin E, Menon NG. Acellular dermis-assisted breast reconstruction. *Aesthetic Plast Surg.* 2008 May; 32(3):418-25.

<sup>27</sup> <https://emedicine.medscape.com/article/1851090-overview#a1>

<sup>28</sup> Sbitany, Hani, M.D.; Sandeen, Sven N., M.D.; Amalfi, Ashley N., M.D.; Davenport, Mark S., M.D.; Langstein, Howard N., M.D. *Acellular Dermis-Assisted Prosthetic Breast Reconstruction versus Complete Submuscular Coverage: A Head-to-Head Comparison of Outcomes.* Plastic and Reconstructive Surgery: December 2009 - Volume 124 - Issue 6 - p 1735-1740; doi: 10.1097/PRS.0b013e3181bf803d

<sup>29</sup> LEONG, M.; BASU, C. B.; HICKS, M. J. Further evidence that human acellular dermal matrix decreases inflammatory markers of capsule formation in implant-based breast reconstruction. *Aesthetic Surgery Journal*, [s. l.], v. 35, n. 1, p. 40-47, 2015. Disponível em:

<<http://search.ebscohost.com/contentproxy.phoenix.edu/login.aspx?direct=true&db=mdc&AN=25568233&site=eds-live>>. Acesso em: 17 abr. 2019.

<sup>30</sup> Paydar KZ, Wirth GA, Mowlds DS. Prepectoral Breast Reconstruction with Fenestrated Acellular Dermal Matrix. *Plastic and Reconstructive Surgery - Global Open.* 2018;6(4):e1712. doi: 10.1097/GOX.00000000000001712.

**III. Human ADMs are separate and distinct from synthetic surgical meshes and xenografts.**

In reviewing the use of human ADMs use for breast reconstruction, it is important to distinguish this product from certain other FDA-regulated products – namely, synthetic surgical mesh and xenografts (such as porcine dermis). One key distinguishing feature between synthetic surgical meshes and ADMs (both human and xenograft) is ADMs incorporate into the host tissue,<sup>31</sup> while synthetic meshes cannot. To further support the use of human ADMs in breast reconstruction, and the distinction between xenografts and synthetic meshes from human ADMs in this procedure, nearly 96% of all materials used to provide support in post-mastectomy breast reconstruction are human ADMs.<sup>32</sup> The table below provides a clearer picture of the difference in these three very distinct materials.

Source	Common name	Material Type	Brand Examples	FDA Branch of Regulation	Percentage when used in implant-based breast reconstruction
Human-Derived	Allograft	Acellular Dermal Matrix (ADM)	FlexHD, AlloDerm, Cortiva, DermaCell	CBER	95.6%
Animal-Derived	Xenograft, Surgical Mesh	Biologic, Extracellular Matrix (NOT always dermis)	Strattice, SurgiMend,	CDRH	3.8%
Synthetic	Surgical Mesh	Synthetic, man-made	Vicryl, GalaFlex, TIGR Mesh	CDRH	0.6%

According to SmartTrack,<sup>33</sup> more studies examining the benefit of prepectoral placement, which uses a human ADM to create the pocket for the breast implant, come out every day, driving increased use of that technique in breast reconstruction.

**IV. The use of human ADMs in breast reconstruction procedures is a homologous use.**

As part of the FDA's final guidance titled *Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use*, the Agency provided its latest thinking with respect to human ADMs. Specifically, the FDA noted that skin is considered a structural tissue, and it provided other key examples and excerpts related to the question of whether the Agency considers human ADMs for breast reconstruction a 361 HCT/P.

<sup>31</sup> Ibrahim AM, Ayeni OA, Hughes KB, et al. Acellular dermal matrices in breast surgery: a comprehensive review. Ann Plast Surg. 2013;70:732–8. doi: 10.1097/SAP.0b013e31824b3d30.

<sup>32</sup> Op Cit.

<sup>33</sup> <https://app.smartrak.com/markets/qs/6560> (Smartrak data, 2019).

With respect to the question of whether the use of human ADMs for breast reconstruction is a homologous use, the Agency provided the following information in the final guidance:

**18. What does FDA mean by repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues?**

*Repair generally means the physical or mechanical restoration of tissues, including by covering or protecting. For example, FDA generally would consider skin removed from a donor and then transplanted to a recipient in order to cover a burn wound to be a homologous use. Reconstruction generally means surgical reassembling or re-forming. For example, reconstruction generally would include the reestablishment of the physical integrity of a damaged aorta. Replacement generally means substitution of a missing tissue or cell, for example, the replacement of a damaged or diseased cornea with a healthy cornea or the replacement of donor hematopoietic stem/progenitor cells in a recipient with a disorder affecting the hematopoietic system that is inherited, acquired, or the result of myeloablative treatment. Supplementation generally means to add to, or complete. For example, FDA generally would consider the implantation of dermal matrix into the facial wrinkles to supplement a recipient's tissues and the use of bone chips to supplement bony defects to be homologous uses. Repair, reconstruction, replacement, and supplementation are not mutually exclusive functions and an HCT/P could perform more than one of these functions for a given intended use. (emphasis added)*

Thus, the Agency has noted the implantation of [acellular] dermal matrix can be used to supplement the recipient's tissues, as is its basic function during breast reconstruction.

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**20. Does my HCT/P have to be used in the same anatomic location to perform the same basic function or functions?**

*An HCT/P may perform the same basic function or functions even when it is not used in the same anatomic location where it existed in the donor. A transplanted HCT/P could replace missing tissue, or repair, reconstruct, or supplement tissue that is missing or damaged, either when placed in the same or different anatomic location, as long as it performs the same basic function(s) in the recipient as in the donor.*

*Example 20-1: The basic functions of skin include covering, protecting the body from external force, and serving as a water-resistant barrier to pathogens or other damaging agents in the external environment. The dermis is the elastic connective tissue layer of the skin that covers, provides support and protects the body from mechanical stress.*

1. *An acellular dermal product is used for supplemental support, protection, reinforcement, or covering for a tendon. This is homologous use because in both anatomic locations, the dermis provides support and protects the soft tissue structure from mechanical stress.*
2. *An acellular dermal product is used for tendon replacement or repair. This is not homologous use because serving as a connection between muscle and bone is not a basic function of dermis. (emphasis added)*

The FDA acknowledged in its final guidance that ADMs can be used for “supplemental support, protection, and reinforcement.” While the example focuses on a tendon, the process of reinforcing the breast pocket after mastectomy is very similar.

During the *Public Hearing; Request for Comments – Draft Guidances Relating to the Regulation of Human Cells, Tissues or Cellular or Tissue-Based Products* (September 12 and 13, 2016), CBER concluded that fat matrices, which are decellularized and processed in a similar fashion to ADMs, were considered to be homologous use in the breast. This was further exemplified by the final guidance which stated the following: “[a]dipose tissue is used for transplantation into the subcutaneous areas of breast for reconstruction or augmentation procedures. This is homologous use because providing cushioning and support is a basic function of adipose tissue.” This example is analogous to dermal matrices, which also provide cushioning and support for the surrounding tissues in breast reconstruction.

**V. Human ADMs used for breast reconstruction are 361 HCT/Ps.**

The regulatory approaches and processes used for human ADMs have been reasonable and scientifically based and meet the criteria for an HCT/P regulated by FDA solely under section 361 of the Public Health Service Act as defined in 21 C.F.R. Part 1271.

Separate from the question of homologous use, another key factor to ensure that human ADMs for breast reconstruction may be regulated solely as a 361 HCT/P is whether the Agency considers the processing steps to fall within the rubric of minimal manipulation. The key question, given that ADMs are derived from the structural tissue of skin is whether decellularization/acellularization is minimal manipulation. The Agency directly addressed that issue in question #11. As noted below, the Agency affirmatively opined that ADMs are minimally manipulated.

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***11. How does removal of cells from structural tissue affect whether an HCT/P is minimally manipulated?***

*Structural tissues may contain both extracellular matrix and cellular components, and any alteration of these components that relates to the structural tissue’s utility for reconstruction, repair, or replacement generally would be considered more than minimal manipulation. However, separation of structural tissue into components in which the original relevant characteristics relating to the tissue’s utility for reconstruction, repair, or replacement are not altered generally would be considered minimal manipulation. For example, extraction or separation of cells from structural tissue in which the remaining structural tissue’s original relevant characteristics relating to its utility for reconstruction, repair, or replacement remain unchanged generally would be considered minimal manipulation.<sup>15</sup>*

*While some structural tissues may undergo processing that alters the cellular or extracellular matrix components without altering the original relevant characteristics of the tissue, the same processing may alter the original relevant characteristics of a different structural tissue. Therefore, to assess whether a processing step alters the original relevant characteristics of a structural tissue*

*relating to its utility for reconstruction, repair, or replacement, you should consider the effects of the processing on the properties that contribute to the specific tissue's function in the donor, for each type of tissue you manufacture.*

*Example 11-3: The original relevant characteristics of skin relating to its utility to serve as a protective covering generally include its large surface area, keratinized, water-resistant epithelial layer (epidermis), and dense, strong, and flexible connective tissue layer (dermis). A manufacturer processes skin to remove epidermis and freeze-dries and packages the remaining connective tissue, as decellularized dermis. The HCT/P generally is considered minimally manipulated because the processing does not alter the original relevant characteristics of the HCT/P relating to its utility to serve as a protective covering. (emphasis added)*

## **VI. Various studies support the value of human ADMs for breast reconstruction**

Like the Agency, the AATB and the TPG believe that key regulatory decisions should be built upon strong science. Unfortunately, we remain concerned that the FDA is relying too heavily on one study – the Mastectomy Reconstruction Outcomes Consortium (MROC) Study, without fully appreciating its limitations. As discussed during the Panel meeting, the MROC study is now quite dated and did not examine additional, relevant surgical techniques (e.g., pre-pectoral placement of the breast implant which requires the use of human ADM to create the implant pocket). In addition, as previously discussed, MROC pooled the data from porcine and human ADMs, rather than appropriately distinguishing between the two very different ADMs, as porcine tissues may possess alpha-gal that are known immunomodulatory molecules and can result in an inflammatory response to the tissues.<sup>34</sup> Further, as discussed during the panel meeting, plastic surgeons tend to prefer the use of human ADMs as compared to porcine (or even bovine) ADMs. Several authors, including Felix<sup>35</sup> and Kivuls,<sup>36</sup> have highlighted the superior nature of human ADMs to the xenografts for breast reconstruction. Given that the author of the paper explained there were significant differences between ADM types and given the previously cited literature on the topic, the AATB and the TPG assumes that the one outlier is porcine, not human, ADM. Examining only human ADMs would likely result in more favorable outcomes.

Over the last fifteen years, hundreds of articles have been published on this topic demonstrating the value and benefits of human ADMs in breast reconstruction. Several well-controlled and more recent studies than MROC have investigated this topic and have demonstrated several advantages, including shorter time interval to implant

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<sup>34</sup> Vedak P, St John J, Watson A., Garibyan, Mihm MC, Nazarian RM, Levins PC, Cetrulo CL Jr, Schalock P, Kroshinsky D. Delayed type IV hypersensitivity reaction to porcine acellular dermal matrix masquerading as infection resulting in multiple debridements.. Hernia. 2017 Jun;21(3):489-492. doi: 10.1007/s10029-015-1440-z. Epub 2015 Dec 22.

<sup>35</sup>Felix J. Paprottka, Nicco Kreuzdorn, Heiko Sorg, Sören Könneker, Stiliano Bontikous, Ian Robertson, Christopher L. Schlett, Nils-Kristian Dohse, and Detlev Hebebrand. Evaluation of Complication Rates after Breast Surgery Using Acellular Dermal Matrix: Median Follow-Up of Three Years. Plast Surg Int. 2017; 2017: 1283735. Published online 2017 Jun 12. doi: 10.1155/2017/1283735

<sup>36</sup>Kivuls, Juris MD; Taylor, Jason R. MD; Kivuls, Kristine K. Comparison of Human ADM to Porcine ADM in Immediate Breast Reconstruction. Plastic and Reconstructive Surgery: October 2014 - Volume 134 - Issue 4S-1 - p 164. doi: 10.1097/01.prs.0000455549.14835.ba

exchange, possible mitigation of capsular contracture, and greater aesthetic outcomes.<sup>37,38,39</sup> In addition, prepectoral reconstruction techniques are not possible without human ADMs. These techniques have considerable aesthetic and post-operative benefit.<sup>40</sup>

Given the acceptance and clinical benefits to using human ADMs in post-mastectomy breast reconstruction, removing access of human ADMs to surgeons and their breast cancer patients for treatment in breast reconstruction could be catastrophic. The alternative to implant-based breast reconstruction without an ADM is full muscle coverage or partial muscle coverage, which both carry associated limitations compared to ADM-assisted breast reconstruction. In addition, the alternative to implant-based breast reconstruction is autologous reconstruction, which requires a large amount of the patient's own tissue be transferred from one area of the body to create a breast after mastectomy. These procedures are lengthy and expensive. In addition, they have been shown to be associated with higher complication rates.<sup>41</sup>

As 361 HCT/Ps, human ADMs are subject to the significant regulatory and industry requirements set forth in 21 CFR 1271 (including Current Good Tissue Practices, CGTP). Manufacturers of HCT/Ps are required to undergo routine FDA inspection of facilities, equipment, finished and unfinished materials, containers, processes, procedures, labeling, records, files, and controls. FDA's tissue regulation uses a risk-based approach, which has proven fully adequate to ensure safe and appropriate marketing of ADMs for breast reconstruction procedures for more than fifteen years.

**VII. Requested Action: Continue to regulate human ADMs for breast reconstructions procedures solely as a 361 HCT/P**

As previously noted, the AATB and the TPG strongly believe that human ADMs are appropriately regulated solely as 361 HCT/Ps when promoted under the manufacturer's objective intent for use to augment, reinforce, support, protect, or cover soft tissue weaknesses, including for use in breast reconstruction procedures. The AATB and the TPG were discouraged that the recent panel discussion hosted by CDRH did not include key tissue bank or CBER representatives. Further, the agenda and other key documentation focused on "meshes," which are regulated differently and may provide different clinical outcomes than human ADMs. And, as such, many experts on human ADMs did not have the opportunity to provide key witnesses during that discussion. Given that, if the Agency contemplates proceeding with changing the regulatory status of human ADMs used for breast reconstruction, the AATB and the TPG request that the Agency hold a public workshop focused on the use of human ADM in breast reconstruction, similar to what the FDA did for human bone allografts, within the next four months.

On August 2, 2001, CBER and CDRH co-hosted a public workshop titled *Human Bone Allograft: Manipulation and Homologous Use in Spine and Other Orthopedic Reconstruction and Repair* to solicit information on current

<sup>37</sup> [Sobti N, Ji E, Brown RL, Cetrulo CL Jr, Colwell AS, Winograd JM, Austen WG Jr, Liao EC](#). Evaluation of Acellular Dermal Matrix Efficacy in Prosthesis-Based Breast Reconstruction. *Plast Reconstr Surg*. 2018 Mar;141(3):541-549.

<sup>38</sup> [Salzberg CA, Ashikari AY, Berry C, Hunsicker LM](#). Acellular Dermal Matrix-Assisted Direct-to-Implant Breast Reconstruction and Capsular Contracture: A 13-Year Experience. *Plast Reconstr Surg*. 2016 Aug;138(2):329-37.

<sup>39</sup> [Forsberg CG, Kelly DA, Wood BC, Mastrangelo SL, DeFranzo AJ, Thompson JT, David LR, Marks MW](#). Aesthetic outcomes of acellular dermal matrix in tissue expander/implant-based breast reconstruction. *Ann Plast Surg*. 2014;72(6):S116-20.

<sup>40</sup> Sigalove S: Prepectoral Breast Reconstruction and Radiotherapy-a Closer Look. *Gland Surg*. 2019 Feb;8(1):67-74.

<sup>41</sup> [Bennett KG, Qi J, Kim HM, Hamill JB, Pusic AL, Wilkins EG](#). Comparison of 2-Year Complication Rates Among Common Techniques for Postmastectomy Breast Reconstruction. *JAMA Surg*. 2018 Oct 1;153(10):901-908. doi: 10.1001/jamasurg.2018.1687.

April 26, 2019

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practices related to the manipulation and homologous use of human bone allograft in the spine and other orthopedic reconstruction and repair procedures. Many of the comments presented at the meeting indicated that there were misunderstandings about how the criteria set out in Sec. 1271.10 would be applied, and about the meaning of the terms "minimal manipulation" and "homologous use." During this workshop, healthcare professionals, recipients and industry representatives presented the history of the surgical use of allograft bone in the spine. As a result of the meeting, bone used in spine with an objective intent for applications in the spine meet the minimal manipulation and homologous use requirements and are generally considered to be regulated solely as 361 HCT/Ps.

If the Agency opts to change the regulatory status of human ADMs for breast reconstruction, we believe a similar CDRH/CBER co-sponsored public workshop on the regulation of human ADMs used in breast reconstruction with stakeholders from industry, health care professionals, recipients and other interested parties would critical to the appropriate regulation and availability of human ADMs and should occur within the next four months. We would be happy to meet with FDA to discuss this issue as soon as is convenient for the Agency.

Respectfully,



Frank Wilton  
President & CEO  
American Association of Tissue Banks



David M. Smith, MD  
Chair  
Tissue Policy Group

cc: Peter W. Marks, M.D., Ph.D., Director, CBER  
Celia M. Witten, M.D., Ph.D., Deputy Director, CBER



July 19, 2019

Jeffrey Shuren, M.D., J.D.  
Director  
Center for Devices and Radiological Health  
Food and Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002

Dear Dr. Shuren:

The American Association of Tissue Banks (AATB or Association) and the American Association of Tissue Bank's Tissue Policy Group, LLC (AATB TPG or TPG) are writing you once again to **request that the Food and Drug Administration (FDA or Agency) hold a joint Center for Devices and Radiological Health (CDRH)/Center for Biologics Evaluation and Research (CBER) co-sponsored public workshop, or similar public meeting, on the use of human acellular dermal matrixes (ADMs) in breast reconstruction within the next four months**. In addition to requesting this public meeting, the AATB and TPG would like to take this opportunity to provide key background information, provide additional insight regarding the homologous uses of human ADMs (especially with respect to breast reconstruction), discuss appropriate regulatory actions with respect to human ADMs for breast reconstruction, and highlight insufficiencies with the Mastectomy Reconstruction Outcomes Consortium (MROC) study while detailing other key scientific information pertaining to the use of human ADMs for breast reconstruction.

Please refer to our previous letter to the Agency, dated April 26, 2019, in which the AATB and the TPG detailed key information regarding the use of human ADMs for breast reconstruction, including information related to how the use of human ADMs for breast reconstruction is the standard of care; noting that human ADMs are separate and distinct from synthetic surgical meshes and xenografts; providing information regarding the fact that the use of human ADMs in breast reconstruction procedures is a homologous use and, as such, a 361 human cells, tissues, or cellular or tissue-based products (HCT/Ps); detailing various studies support the value of human ADMs for breast reconstruction; and, finally, requesting that the Agency continue to regulate human ADMs for breast reconstruction procedures solely as a 361 HCT/P.

**I. Statement of Interest**

The American Association of Tissue Banks (AATB) is a professional, non-profit, scientific and educational organization. It is the only national tissue banking organization in the United States, and its membership totals approximately 120 accredited tissue banks and 2,000 individual members. These banks recover tissue from more than 58,000 donors and distribute in excess of 3.3 million allografts for more than 2.5 million tissue transplants performed annually in the U.S. The overwhelming majority of the human tissue distributed for these transplants comes from AATB-accredited tissue banks.

The AATB's Tissue Policy Group (TPG), LLC (AATB TPG or TPG) includes Chief Executive Officers and senior regulatory personnel from U.S. tissue banks that process donated human tissue. The purpose of the TPG is to drive public policy in furtherance of the adoption of laws and regulations that foster the safety, quality and

availability of donated tissue. The TPG's membership is responsible for the vast majority of tissue available for transplantation within the U.S.

**II. Key background information**

Human ADMs were first described for use in breast surgery in 2001.<sup>1</sup> Since this initial report, ADMs have become an increasingly common component of implant-based breast reconstruction procedures to serve as a protective covering.<sup>2</sup> According to the American Society of Plastic Surgeons, of the approximately 101,657 breast reconstruction procedures performed by member surgeons in 2018, about 83,200 (roughly 82%) utilized tissue expanders and/or breast implants. Of these procedures, approximately 74% (61,713) utilized ADMs. During the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee Meeting on 26, 2019, CDRH officials stated that ADMs for breast reconstruction was a non-homologous application of the human tissue graft, as such, not regulated solely as a 361 HCT/P.<sup>3</sup> Recognizing human ADMs as the proven standard of care, major U.S. payers (e.g. Anthem, CIGNA, Blue Cross Blue Shield, and Aetna) currently regard the use of acellular dermal matrix with breast reconstruction as a clinically supported and clearly reimbursable use, where the tissue assists the surgeons in reconstructing the breast at the time of mastectomy in a process that improves cosmetic outcomes and limits the need for further surgical procedures.<sup>4</sup> According to a recent review article,<sup>5</sup> principal advantages include the potential enhancement of cosmesis in breast reconstruction, amelioration of late or irradiation-induced contracture, improved long-term correction of complications following aesthetic revisionary surgery and cost-savings imparted by the direct-to-implant breast reconstruction technique.

**III. The Agency erred by not acknowledging some uses of human ADMs for breast reconstruction are homologous.**

Human ADMs are appropriately regulated solely as 361 HCT/Ps under the four-part test provided in 21 CFR §1271.10 and when promoted with an objective intent to augment, reinforce, support, protect, or cover soft tissue weaknesses, including various clinical applications, such as breast reconstruction. We believe these uses and homologous indications properly relate to the basic functions in the recipients that the donated tissues performed in the donor.

**IV. The Agency erred by not appropriately following regulatory procedures for shifting the regulatory status of human ADMs for breast reconstruction**

The AATB and TPG request a joint workshop, or similar public meeting, to address deficiencies in the regulatory process thus far. Namely,

- (1) The FDA notice regarding the Panel meeting focused on "meshes" and such nomenclature seemed to obfuscate the focus on human ADMs;
- (2) Unlike breast implant manufacturers, tissue banks were not afforded the opportunity to provide key data to the FDA during the Panel meeting; and

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<sup>1</sup> Margulies I, Salzberg C. The use of acellular dermal matrix in breast reconstruction: evolution of technique over 2 decades. *Gland Surgery* 2019; 8(1):3-10.

<sup>2</sup> Sheina A Macadam, MD MHS and Peter A Lennox, MD. Acellular dermal matrices: Use in reconstructive and aesthetic breast surgery. *Can J Plast Surg.* 2012 Summer; 20(2): 75-89.

<sup>3</sup> <https://www.fda.gov/media/122962/download>, slide #11.

<sup>4</sup> Sbitany, Hani, M.D.; Sandeen, Sven N., M.D.; Amalfi, Ashley N., M.D.; Davenport, Mark S., M.D.; Langstein, Howard N., M.D. Acellular Dermis-Assisted Prosthetic Breast Reconstruction versus Complete Submuscular Coverage: A Head-to-Head Comparison of Outcomes. *Plastic and Reconstructive Surgery*: December 2009 - Volume 124 - Issue 6 - p 1735-1740; doi: 10.1097/PRS.0b013e3181bf803d

<sup>5</sup> <https://emedicine.medscape.com/article/1851090-overview#a1>

(3) CBER officials were also not involved in the key discussion, despite their current oversight of human ADMs.

The Agency opted to act in a non-transparent manner in changing the regulatory status for human ADMs for breast reconstruction. By not asking the Panel to review whether the regulatory status of human ADMs for breast reconstruction should be changed from a 361 HCT/P to a class III device requiring premarket approval (PMA) but instead focusing on the data requirements of the PMA, the Agency ignored its process for changing the regulatory status of devices. By doing so, the Agency has limited options for rectifying and enforcing the new regulatory status – Untitled Letters, Warning Letters, or newly issued guidance documents.

Given that the Agency has opted to change the regulatory status without using an appropriate, transparent process, it is unlikely that a Warning Letter will be an enforcement option for this key regulatory shift. Therefore, the FDA may opt to either issue Untitled Letters or a guidance document. In reviewing CDRH's guidance document agenda for calendar year 2019,<sup>6</sup> the only possible guidance would be the review of the 1999 final guidance titled *Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh*.

As the AATB and TPG previously noted, in reviewing the use of human ADMs use for breast reconstruction, it is important to distinguish this product from certain other FDA-regulated products – namely, synthetic surgical mesh and xenografts (such as porcine dermis). Though xenografts and synthetic meshes are not explicitly cleared or approved for use in breast reconstruction, there is evidence in the clinical literature that they are used in a small percentage of procedures. One key distinguishing feature between synthetic surgical meshes and ADMs (both human and xenograft) is ADMs incorporate into the host tissue,<sup>7</sup> while synthetic meshes cannot. To further support the use of human ADMs in breast reconstruction, and the distinction between xenografts and synthetic meshes from human ADMs in this procedure, nearly 96% of all materials used to provide support in post-mastectomy breast reconstruction are human ADMs.<sup>8</sup> The table below provides a clearer picture of the difference in these three very distinct materials.

Source	Common name	Material Type	Brand Examples	FDA Branch of Regulation	Percentage when used in implant-based breast reconstruction
Human-Derived	Allograft	Acellular Dermal Matrix (ADM)	FlexHD, AlloDerm, Cortiva, DermaCell	CBER	95.6%
Animal-Derived	Xenograft, Surgical Mesh	Biologic, Extracellular Matrix (NOT always dermis)	Strattice, SurgiMend,	CDRH	3.8%
Synthetic	Surgical Mesh	Synthetic, man-made	Vicryl, GalaFlex, TIGR Mesh	CDRH	0.6%

<sup>6</sup> <https://www.fda.gov/medical-devices/guidance-documents-medical-devices-and-radiation-emitting-products/cdrh-fiscal-year-2019-fy-2019-proposed-guidance-development> (Accessed on July 2, 2019)

<sup>7</sup> Ibrahim AM, Ayeni OA, Hughes KB, et al. Acellular dermal matrices in breast surgery: a comprehensive review. Ann Plast Surg. 2013;70:732–8. doi: 10.1097/SAP.0b013e31824b3d30.

<sup>8</sup> Op Cit.

Therefore, if the Agency decides to act to provide enforcement in this area for certain human ADMs used for breast reconstruction, then the AATB and TPG urge the FDA to develop a separate guidance document for this process. Combining human ADMs with other meshes, as noted earlier, is scientifically inappropriate (given the different characteristics of the grafts) and obfuscates the regulatory process.

If the Agency opts to enforce its new stance using Untitled Letters, then the FDA should only do so cautiously and under specific circumstances. Those certain circumstances include: (1) not publishing the Untitled Letters, given that publication would be seen as a punitive measure; (2) continuing to allow tissue banks to market human ADMs for breast reconstruction as the banks strive to come into compliance with the new regulatory status; (3) hosting a public workshop to allow tissue banks and other key stakeholders to discuss the regulatory shift and obtain answers to key regulatory questions; and (4) provide clear rationale for the change of regulatory status of human ADMs for breast reconstruction, given that the Panel meeting discussion raises more questions than it answers and to help distinguish between the homologous uses which allow human ADMs in breast reconstruction and those outside of that framework.

**V. The Agency erred in relying solely on the MROC study.**

Like the Agency, the AATB and the TPG believe that key regulatory decisions should be built upon strong science. Unfortunately, we remain concerned that the FDA is relying too heavily on one study – the Mastectomy Reconstruction Outcomes Consortium (MROC) Study, without fully appreciating its limitations. As discussed during the Panel meeting, the MROC study is now quite dated and did not examine additional, relevant surgical techniques (e.g., pre-pectoral placement of the breast implant). In addition, MROC pooled the data from porcine and human ADMs, rather than appropriately distinguishing between the two very different ADMs, as porcine tissues may possess alpha-gal that are known immunomodulatory molecules and can result in an inflammatory response to the tissues.<sup>9</sup> Further, as discussed during the panel meeting, plastic surgeons tend to prefer the use of human ADMs as compared to porcine (or even bovine) ADMs. Several authors, including Felix<sup>10</sup> and Kivuls,<sup>11</sup> have highlighted the superior nature of human ADMs to the xenografts for breast reconstruction. Given that the author of the paper explained there were significant differences between ADM types and given the previously cited literature on the topic, the AATB and the TPG assumes that the one outlier is porcine, not human, ADM. Examining only human ADMs would likely result in more favorable outcomes.

Over the last fifteen years, hundreds of articles have been published on this topic demonstrating the value and benefits of human ADMs in breast reconstruction. Several well-controlled and more recent studies than MROC have investigated this topic and have demonstrated several advantages, including shorter time interval to implant

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<sup>9</sup> Vedak P, St John J, Watson A., Garibyan L, Mihm MC, Nazarian RM, Levins PC, Cetrulo CL Jr, Schalock P, Kroshinsky D. Delayed type IV hypersensitivity reaction to porcine acellular dermal matrix masquerading as infection resulting in multiple debridements.. Hernia. 2017 Jun;21(3):489-492. doi: 10.1007/s10029-015-1440-z. Epub 2015 Dec 22.

<sup>10</sup>Felix J. Paprottka, Nicco Kreuzdorn, Heiko Sorg, Sören Könneker, Stiliano Bontikous, Ian Robertson, Christopher L. Schlett, Nils-Kristian Dohse, and Detlev Hebebrand. Evaluation of Complication Rates after Breast Surgery Using Acellular Dermal Matrix: Median Follow-Up of Three Years. Plast Surg Int. 2017; 2017: 1283735. Published online 2017 Jun 12. doi: 10.1155/2017/1283735

<sup>11</sup>Kivuls, Juris MD; Taylor, Jason R. MD; Kivuls, Kristine K. Comparison of Human ADM to Porcine ADM in Immediate Breast Reconstruction. Plastic and Reconstructive Surgery: October 2014 - Volume 134 - Issue 4S-1 - p 164. doi: 10.1097/01.prs.0000455549.14835.ba

exchange, possible mitigation of capsular contracture, and greater aesthetic outcomes.<sup>12,13,14</sup> In addition, prepectoral reconstruction techniques are not possible without human ADMs. These techniques have considerable aesthetic and post-operative benefit.<sup>15</sup>

Finally, the AATB and TPG remain concerned that the Agency has erroneously opted to include human ADMs within the discussion of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL). Human ADMs have been utilized for abdominal wall repair and breast reconstruction for decades without any reports of ALCL. Further, we are unaware of any data or expert opinion which would support the hypothesis that human ADMs could be in any way responsible for ALCL.

**VI. Requested Action: Host a public workshop**

As previously noted, the **AATB and the TPG strongly believe that human ADMs are appropriately regulated solely as 361 HCT/Ps when promoted under the manufacturer's objective intent for use to augment, reinforce, support, protect, or cover soft tissue weaknesses, including for use in breast reconstruction procedures.** The AATB and the TPG were discouraged that the recent panel discussion hosted by CDRH did not include key tissue bank or CBER representatives. Further, the agenda and other key documentation focused on "meshes," which are regulated differently and may provide different clinical outcomes than human ADMs. And, as such, many experts on human ADMs did not have the opportunity to provide key witnesses during that discussion. Given that, if the Agency contemplates proceeding with changing the regulatory status of human ADMs used for breast reconstruction, the AATB and the TPG request that the Agency hold a public workshop, or similar public meeting, focused on the use of human ADM in breast reconstruction, similar to what the FDA did for human bone allografts, within the next four months.

On August 2, 2001, CBER and CDRH co-hosted a public workshop titled *Human Bone Allograft: Manipulation and Homologous Use in Spine and Other Orthopedic Reconstruction and Repair* to solicit information on current practices related to the manipulation and homologous use of human bone allograft in the spine and other orthopedic reconstruction and repair procedures. Many of the comments presented at the meeting indicated that there were misunderstandings about how the criteria set out in Sec. 1271.10 would be applied, and about the meaning of the terms "minimal manipulation" and "homologous use." During this workshop, healthcare professionals, recipients and industry representatives presented the history of the surgical use of allograft bone in the spine. As a result of the meeting, bone used in spine with an objective intent for applications in the spine meet the minimal manipulation and homologous use requirements and are generally considered to be regulated solely as 361 HCT/Ps.

Given that the Agency has opted to change the regulatory status of human ADMs for breast reconstruction, we believe a similar CDRH/CBER co-sponsored public workshop on the regulation of human ADMs used in breast reconstruction with stakeholders from industry, health care professionals, recipients and other interested parties would critical to provide appropriate information regarding this key regulatory shift and should occur within the

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<sup>12</sup> [Sobti N, Ji E, Brown RL, Cetrulo CL Jr, Colwell AS, Winograd JM, Austen WG Jr, Liao EC](#). Evaluation of Acellular Dermal Matrix Efficacy in Prosthesis-Based Breast Reconstruction. *Plast Reconstr Surg.* 2018 Mar;141(3):541-549.

<sup>13</sup> [Salzberg CA, Ashikari AY, Berry C, Hunsicker LM](#). Acellular Dermal Matrix-Assisted Direct-to-Implant Breast Reconstruction and Capsular Contracture: A 13-Year Experience. *Plast Reconstr Surg.* 2016 Aug;138(2):329-37.

<sup>14</sup> [Forsberg CG, Kelly DA, Wood BC, Mastrangelo SL, DeFranzo AJ, Thompson JT, David LR, Marks MW](#). Aesthetic outcomes of acellular dermal matrix in tissue expander/implant-based breast reconstruction. *Ann Plast Surg.* 2014;72(6):S116-20.

<sup>15</sup> Sigalove S: Prepectoral Breast Reconstruction and Radiotherapy-a Closer Look. *Gland Surg.* 2019 Feb;8(1):67-74.

*ADMs and breast reconstruction*

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next four months. We would be happy to meet with FDA to discuss this issue as soon as is convenient for the Agency.

Respectfully,

*Louis E Barnes III*

Louis E. Barnes, III  
Chairman  
American Association of Tissue Banks

*David M. Smith*

David M. Smith, MD  
Chair  
Tissue Policy Group

Cc: Binita Ashar, M.D.; Peter Marks, M.D., Ph.D.

September 17, 2019

Jeffrey Shuren, M.D., J.D.  
Director  
Center for Devices and Radiological Health (CDRH)  
Food and Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002

Peter Marks, M.D., Ph.D.  
Director  
Center for Biologics Evaluation and Research (CBER)  
Food and Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002

Dear Dr. Shuren and Dr. Marks:

The undersigned organizations, representing patient advocacy groups, surgeons, and tissue banks, request that the Food and Drug Administration (FDA or Agency) hold a joint CDRH/CBER public workshop on the use of human ADMs in breast reconstruction with recipients, stakeholders from industry, health care professionals, and other interested parties.

Human acellular dermal matrixes (ADMs) were first described for use in breast surgery in 2001.<sup>1</sup> Since this initial report, ADMs have become an increasingly common component of implant-based breast reconstruction procedures.<sup>2</sup> According to the American Society of Plastic Surgeons, of the approximately 101,657 breast reconstruction procedures performed by member surgeons in 2018, about 83,200 (roughly 82%) utilized tissue expanders and/or breast implants. Of these procedures, approximately 74% (61,713) utilized ADMs.

During the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee Meeting on March 25 and 26, 2019, FDA officials seemed to indicate that ADMs for breast reconstruction would soon be regulated as class III medical devices.<sup>3</sup> Prior to the Panel meeting, licensed tissue banks marketed human ADMs for breast reconstruction as 361 HCT/Ps. Therefore, this potential policy shift could result in loss of access to these ADMs for breast reconstruction.

To avoid any disruption in patient access to key components of reconstructive surgery, we look forward to working with the Agency to plan such a public workshop, prior to implementation of any regulatory change by the Agency.

Sincerely,

American Association of Tissue Banks  
American Society of Breast Surgeons  
American Society of Plastic Surgeons  
Living Beyond Breast Cancer  
The American College of Surgeons Commission on Cancer  
Tiger Lily Foundation

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<sup>1</sup> Margulies I, Salzberg C. The use of acellular dermal matrix in breast reconstruction: evolution of technique over 2 decades. *Gland Surgery* 2019; 8(1):3-10.

<sup>2</sup> Sheina A Macadam, MD MHS and Peter A Lennox, MD. Acellular dermal matrices: Use in reconstructive and aesthetic breast surgery. *Can J Plast Surg.* 2012 Summer; 20(2): 75–89.

<sup>3</sup> <https://www.fda.gov/media/122962/download>, slide #11.