



American Association of Tissue Banks®

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BY ELECTRONIC DELIVERY

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

CITIZEN PETITION

The American Association of Tissue Banks (AATB or the Association) respectfully submits this citizen petition (Petition) under the Federal Food, Drug, and Cosmetic Act of 1938, as amended (FDCA), the Public Health Service Act of 1944, as amended (PHSA), and 21 C.F.R. § 10.30. The AATB requests that the Commissioner of Food and Drugs (Commissioner) take the two actions described below with respect to human-derived acellular dermal matrix (human ADM) allografts intended for use in post-mastectomy breast reconstruction surgery.

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. The overwhelming majority of the human tissue distributed for these transplants comes from AATB-accredited tissue banks.

The Association was founded in 1976 by a group of doctors and scientists who in 1949 had started our nation's first tissue bank, the U.S. Navy Tissue Bank. Recognizing the increasing use of human tissue for transplant, the founders saw the need for a national organization to develop standards, promote ethics, and increase human tissue donations. Since its beginning, the AATB has been dedicated to improving and saving lives by promoting the safety, quality, and availability of donated human tissue. To fulfill that mission, the AATB publishes standards and accredits tissue banks. The Association also regularly interacts with regulatory agencies, like FDA, and conducts educational meetings.

Acellular dermal matrix (ADM) allografts are derived from donated human skin and are called "human ADM allografts." These products typically are used to reinforce damaged or inadequate integumental tissue, which is tissue that covers or encloses an

organism or one of its parts. Human ADM allografts offer significant clinical advantages over synthetic alternatives. In particular, human ADM allografts are incorporated into a patient's body via revascularization and cellular ingrowth from the surrounding tissues. 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). AATB members distribute almost all of the human ADM allografts used in the United States, and the Association therefore has a powerful interest in ensuring that FDA properly classifies these products for regulatory purposes to maintain continued patient access.

Given the benefits human ADM allografts provide, it is hardly surprising that these products are used in a wide range of clinical applications. Perhaps none of these applications is more important than to assist with post-mastectomy breast reconstruction in women who have received treatment for breast cancer. During a typical mastectomy, surgeons remove breast tissue in order to excise cancerous masses from the body but—to the maximum extent possible—leave the overlying dermal layer and epidermis of the breast intact so that it later can be used to hold and protect a reconstructed breast (if the patient opts to undergo post-mastectomy reconstruction, as the overwhelming majority of female breast cancer patients do). In most cases, some damage or denuding of the patient's dermis is an unintended-but-inevitable byproduct of this surgery.

Human ADM allografts play a vital role in helping clinicians repair the damage to the dermis caused by a mastectomy. The surgeon implants a human dermis allograft under the epidermis of the breast to repair, reinforce, replace, reconstruct, or supplement the remaining native dermis. Within a short period after the surgery, the recipient begins to incorporate the human ADM allograft as living tissue with revascularization and cellular ingrowth. The human ADM allograft performs the same integumental functions that the patient's native dermis would perform if it had not been damaged (namely, to hold, cushion, and protect the underlying anatomy from exposure and likely damage, and support the overlying skin).

This use of human ADM allografts has been so successful that throughout the United States it has become the standard of care, as pointed out in recent comments to a Center for Devices and Radiological (CDRH) Advisory Committee Meeting by the American Society of Plastic Surgeons (ASPS), representing 97% of board-certified Plastic Surgeons in the United States. These clinical surgeons have performed hundreds of thousands of breast reconstructions using human ADM allografts for close to two decades. Many thousands of women treated in this manner have had excellent results and a return to normality to a degree not formerly possible. In the past few years, improvements in

surgical techniques and breast implant devices, combined with use of human ADM allografts, have led to striking results in post-mastectomy breast reconstructions.

Despite this success, the Agency has recently taken a classification position that threatens access to human ADM allografts for this application. For the past two decades, FDA has treated human ADM allografts as “361 human cellular and tissue-based products” or “361 HCT/Ps.” All HCT/Ps must comply with 21 C.F.R. Part 1271 (Part 1271), which is aimed at ensuring that donated human skin is screened, processed, labeled, and distributed in a manner that prevents the transmission of disease. Most HCT/Ps are regulated exclusively under section 361 of the PHSA and Part 1271 and, therefore, are not subject to the premarket review, approval and/or clearance requirements that apply to medical devices and biological products. The approach applied by FDA is risk-based and based on the premise that the “comprehensive” regulatory framework for 361 HCT/Ps provides “adequate protection of public health, both from the risks of transmission of communicable disease and from the risks of therapies that may be dangerous” without premarket review.¹

Tissue products qualify for classification as 361 HCT/Ps if the tissue is: (i) minimally manipulated; (ii) intended for homologous use (i.e., serves the same basic functions in the recipient as in the donor); (iii) not combined during manufacture with an excluded article such as a medical device, drug or biologic product; and (iv) acts locally and not via metabolic or systemic action. For many years, tissue processors have marketed human ADM allografts commonly used in post-mastectomy breast reconstruction as 361 HCT/Ps, exempt from the additional review, clearance, and approval requirements to which medical devices and/or biological products typically are subject.

In March 2019, however, representatives of CDRH announced at a public forum that FDA has “determined” that the use of “[h]uman-derived ADMs used for breast reconstruction procedures is considered a non-homologous use and therefore does not meet the criteria for regulation solely under 21 C.F.R. Part 1271,” and further suggested that allografts intended for such uses should be classified as Class III medical devices that would require approval of a premarket application (PMA) prior to marketing.² CDRH subsequently sent “It Has Come to Our Attention” letters to several processors of human ADM allografts that are marketed for use in connection with breast reconstruction,

¹ Proposed Approach to Regulation of Cellular and Tissue Based Products, Docket No. 97N-0068 (Feb. 28, 1997) (Proposed Approach), at 27.

² See Transcript, CDRH, Medical Devices Advisory Committee, General and Plastic Surgery Devices Panel, at 277 (Mar. 26, 2019), *available at* <https://www.fda.gov/media/123746/download>; *id.* at 292.

asserting that these products appear to be medical devices under section 201(h) of the FDCA and may be marketed in potential violation of the FDCA.

As explained in the Statement of Grounds below, CDRH's position is contrary to law. Human ADM allografts meet all the requirements for classification as 361 HCT/Ps when recommended by the manufacturer's statement of objective intent for use to reinforce, repair, replace, reconstruct, or supplement dermis that has been damaged or denuded during a mastectomy. In particular, this intended use meets the "homologous use" requirement. This allograft dermis is placed in a location where the patient's own dermis otherwise would be present if it had not been damaged or denuded and is intended to function as dermis—indeed, it is incorporated into the body as living dermis over time. As discussed more fully in the Statement of Grounds, this intended use is homologous according to FDA's regulatory definition. Accordingly, since CDRH does not dispute that the other requirements for 361 classification are typically met, there is not a lawful basis to classify these allografts as Class III medical devices.

The actions requested below are urgent. The use of human ADM allografts in oncological post-mastectomy breast reconstruction has become the standard of care across the country. These crucial allografts are safe and benefit many cancer patients. The regulatory uncertainty CDRH has created is unnecessary and counter-productive. CDRH's approach, if formalized, threatens to interfere with patient access, potentially denying this aspect of medical care to thousands of women who need it. Already, due largely to the Agency's actions creating the impression that the products are "unapproved," women receiving health coverage through the Oregon Medicaid program are being denied access to human ADM allografts for breast reconstruction procedures.³ We ask that the Commissioner grant the actions requested in the Petition as soon as possible.

ACTIONS REQUESTED

The AATB respectfully requests that the Food and Drug Administration (FDA or the Agency) take the following two actions:

³ ASPS, Advocacy News, "Oregon: Cover Acellular Dermal Matrix," <https://www.plasticsurgery.org/for-medical-professionals/advocacy/advocacy-news/oregon-cover-acellular-dermal-matrix>; Value-based Benefits Subcommittee Recommendations Summary For Presentation to: Health Evidence Review Commission on August 8, 2019, <https://www.oregon.gov/oha/HPA/DSI-HERC/MeetingDocuments/VbBS-Minutes-8-8-2019.pdf>.

- (1) Confirm in response to this Petition that human ADM allografts that otherwise meet the requirement for regulation solely under Section 361 of the PHSA shall not be considered non-homologous or otherwise ineligible for classification as “361 HCT/Ps” solely because they are labeled and/or advertised for use in post-mastectomy breast reconstruction.
- (2) Revise the Final Guidance, Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use (2017) to present human ADM allografts for post-mastectomy breast reconstruction as an example of a homologous use.

STATEMENT OF GROUNDS

I. REGULATION OF HCT/Ps UNDER SECTION 361 OF THE PHSA

Section 361 of the PHSA authorizes FDA to make and enforce regulations “necessary to prevent the introduction, transmission, or spread of communicable diseases” from foreign countries into the United States or between states. 42 U.S.C. § 264(a). In 1997, FDA proposed a new regulatory framework for HCT/Ps. Proposed Approach to Regulation of Cellular and Tissue-Based Products, Docket No. 97N-0068 (Feb. 28, 1997) (Proposed Approach).⁴ *See also* Proposed Approach to Regulation of Cellular and Tissue-Based Products, 62 Fed. Reg. 9721, 9722 (Mar. 4, 1997). The framework specified criteria for regulation and provided for harmonized review of applications across Centers, while subjecting these products to “only the degree of government oversight necessary to protect the public health” in order to permit maximum “flexibility and innovation without an application review process.” Proposed Approach at 6. As part of this risk-based approach, FDA identified various “factors” that affected its level of public health and regulatory concerns associated with HCT/Ps, including “minimal manipulation,” “homologous use,” combination with “non-cell/non-tissue components,” and “metabolic function.” *Id.* at 15-20.

To implement the proposed approach, FDA issued regulations through notice-and-comment rulemaking.⁵ These regulations define HCT/Ps as “articles

⁴ Available at <https://www.fda.gov/media/70704/download>.

⁵ See Proposed Rule, Establishment Registration and Listing for Manufacturers of Human

(cont.)

containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.” 21 C.F.R. § 1271.3(d). Examples include skin, bone, ligaments, tendons, fascia, cartilage, cornea, dura mater, heart valve, hematopoietic stem/progenitor cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive tissue. *See id.* *See also* FDA Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/P's) Product List, <https://tinyurl.com/rwcftpa> (last visited Nov. 19, 2019).⁶

FDA also set forth regulatory requirements with which HCT/P processors must comply, including: establishment registration and product listing (subpart B); donor screening and testing (subpart C); current Good Tissue Practices (cGTPs) (subpart D); labeling (subparts D and E); adverse-event reporting (subparts D and E); and inspection and enforcement (subpart F). For example, establishments must screen and test all tissue donors for all relevant communicable diseases or agents, using qualified, FDA licensed screening tests. *See* 21 C.F.R. § 1271.85; *id.* § 1271.80(c). Establishments must also comply with cGTPs, which govern the methods, facilities, and controls used in the manufacture and distribution of HCT/Ps to prevent the introduction, transmission, or spread of communicable diseases. *Id.* § 1271.150(a). CBER enforces the cGTP requirements for 361 HCT/P establishments.

Cellular and Tissue-Based Products, 63 Fed. Reg. 26744 (May 14, 1998); Final Rule, Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing, 66 Fed. Reg. 5447 (Jan. 19, 2001); Proposed Rule, Suitability Determination for Donors of Human Cellular and Tissue-Based Products, 64 Fed. Reg. 52696 (Sept. 30, 1999); Final Rule, Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products, 69 Fed. Reg. 29786 (May 25, 2004); Proposed Rule, Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products, 66 Fed. Reg. 1508 (Jan. 8, 2001); Current Good Tissue Practice for Human Cell, Tissue, and Cellular and Tissue-Based Product Establishments; Inspection and Enforcement; Final Rule, 69 Fed. Reg. 68612 (Nov. 24, 2004).

⁶ The following are excluded from regulation as HCT/Ps: vascularized human organs for transplantation; whole blood or blood components or derivative products already regulated as biologics under 21 C.F.R. Parts 607 and 207; secreted or extracted human products except semen (e.g., milk collagen, and cell factors); minimally manipulated bone marrow for homologous use (and not combined with another article except for water, crystalloids, or a sterilizing, preserving, or storage agent that does not raise new clinical safety concerns with respect to the HCT/P); ancillary products used in the manufacture of an HCT/P; cells, tissues and organs derived from animals other than humans; and in vitro diagnostic products. 21 C.F.R. § 1271.3(d).

The regulations specify that HCT/Ps which meet certain criteria are governed exclusively by Part 1271—even if such HCT/Ps also meet the FDCA’s definition of a “drug” or “device” or the PHSA § 351’s definition of a “biological product.” Such 361 HCT/Ps fall under the lead center jurisdiction of CBER. To the extent that an HCT/P does not meet the criteria for regulation as a 361 HCT/P, it will be regulated under both Part 1271 and FDA’s traditional premarket and postmarket regulation of medical devices and drugs under the FDCA or biological products under the PHSA § 351.⁷

An HCT/P qualifies as a 361 HCT/P if it meets all of the following four criteria:

- (1) The HCT/P is minimally manipulated;
- (2) The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer’s objective intent;
- (3) The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and
- (4) Either: (i) The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or (ii) the HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and: (a) Is for autologous use; (b) Is for allogeneic use in a first-degree or second-degree blood relative; or (c) Is for reproductive use.

Id. § 1271.10(a). These criteria mirror the risk-based factors set out by FDA in the Proposed Approach.

FDA’s interpretation of these criteria has been set out in the preambles to its various HCT/P final rules comprising Part 1271. Further, CBER has issued draft and final guidance documents over the years that reflect its interpretation of these criteria or

⁷ Other exceptions, not relevant to here, are set out at 21 C.F.R. § 1271.15.

application in particular cases. *E.g.*, Guidance, Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) Small Entity Compliance Guide (Aug. 2007); Draft Guidance, Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (Dec. 2014); Draft Guidance, Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) from Adipose Tissue: Regulatory Considerations (Dec. 2014); Draft Guidance, Homologous Use of Human Cells, Tissues, and Cellular and Tissue-Based Products (Oct. 2015). Most recently, in 2017, CBER consolidated and revised its guidance on the first two criteria into a single final guidance document. *See* Guidance, Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use (corrected Dec. 2017) (2017 Guidance).⁸

II. HUMAN ADM ALLOGRAFTS

One of the first uses of allografts, i.e., grafts sourced from a donor, was split thickness skin comprised of the epidermis and a thin layer of dermis developed to assist individuals with severe burns. The use of skin allografting in clinical practice was first described in 1869,⁹ and in the early 1930s, skin grafting was revolutionized by Dr. James Barrett Brown, whose work highlighted a key aspect of allografts: that split thickness skin from a donor could be completely incorporated within weeks of transfer to the recipient.¹⁰ The use of skin grafts was furthered by organizations such as Shriners Hospitals, which used grafts to assist burn care to children for 50 years.¹¹ As skin grafting became more common to save the lives of burn patients, so did the banking of human cadaveric skin. This led to the development of the Navy Tissue Bank in 1949, which developed crucial techniques like cryopreservation, freeze-drying, and irradiation sterilization of tissue that expanded the safe use of allografts and made them more widely available.¹²

⁸ Available at <https://www.fda.gov/media/124138/download>.

⁹ J.L. Reverdin, M.D., Greffe Epidermique–Experience Faite Dans Le Service De M. Le Docteur Guyon, à l’Hôpital Necker, 10 Bull. Imp. Soc. Chir. Paris 511–15 (1869) (Attachment A).

¹⁰ V.P. Blair, M.D. et al., The Early Care of Burns and the Repair of Their Defects., 98 JAMA 1355-59 (1932) (Attachment B); V.P. Blair, M.D. & J.B. Brown, M.D., The Use and Uses of Large Split Skin Grafts of Intermediate Thickness, 49 Surgery, Gynecology, & Obstetrics 82-97 (1929) (reprinted in 42 Plastic & Reconstructive Surgery 65-75 (1968) (Attachment C)).

¹¹ K.D. Čapek, M.D. et al., Fifty Years of Burn Care at Shriners Hospitals for Children, Galveston, 80(3 Suppl 2) Annals of Plastic Surgery S90–S94 (2018) (Attachment D).

¹² D.M. Strong, The US Navy Tissue Bank: 50 Years On the Cutting Edge, 1 Cell & Tissue

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To further expand the use of donated skin, decellularization technologies were developed. Decellularization removes the donor's native cells and genetic material that could lead to an immunologic response or rejection by the recipient, while maintaining the structural, biochemical and biomechanical aspects of the tissue (such as the extracellular matrix, growth factors, proteoglycans and vascular channels).¹³ Typically, the epidermis is removed with a highly concentrated salt solution and the resultant decellularized dermis is disinfected with chemical agents. It may be cut into various sizes and shapes. It may also be terminally sterilized, freeze-dried, and/or mechanically meshed (i.e., fenestrated) before placement into final packaging for use in transplant. This process yields an intact ADM that retains its biomechanical integrity, and that can be repopulated by the recipient's own cells and revascularized following implantation, thereby facilitating integration of the tissue into the recipient and avoiding graft rejection.

ADM allografts have been used for decades in various applications. Many human ADM allografts on the market are indicated for the reinforcement of damaged or inadequate integumental tissue.¹⁴ These ADM allografts are used to repair, reinforce, replace, reconstruct or supplement dermis in clinical procedures to address congenital abnormalities or soft tissue reconstruction following disease or trauma, such as abdominal,

Banking 9–16 (2000) (Attachment E).

¹³ See A. Gilpin & Y. Yang, Decellularization Strategies for Regenerative Medicine: From Processing Techniques to Applications, BioMed Res. Int'l (2017) (Attachment F).

¹⁴ See, e.g., Stryker® Sterile Decellularized Dermis - Instructions for Use ("Decellularized dermis serves as a scaffold which is suitable for the reinforcement of damaged or inadequate integumental tissue at the surgical site."); SimpliDerm™ Hydrated Acellular Dermal Matrix – Instructions for Use ("SimpliDerm™ is to be used for the repair or replacement of damaged or insufficient integumental tissue or for other homologous uses of human integument. SimpliDerm™ is to be used for the replacement of damaged or insufficient integumental tissue or for the repair, reinforcement, or supplemental support of soft tissue defects."). The IFUs are included in Attachment G.

and chest wall reconstructions;¹⁵ diabetic foot ulcers;¹⁶ chronic wounds;¹⁷ hand surgery;¹⁸; burn surgery;¹⁹ tendon covering;²⁰ venous leg ulcers;²¹ gingival graft procedures;²² and—as described in greater detail below—breast reconstruction. Typically, the processing of the tissue is the same regardless of the intended use. The tissue sizes and shapes may be tailored for ease or convenience in specific clinical applications.

Among the various clinical uses, human ADM allografts have been used for post-mastectomy breast reconstruction for almost twenty years.²³ In 2018, the American

¹⁵ C.E. Butler, M.D. et al., Pelvic, Abdominal, and Chest Wall Reconstruction with AlloDerm in Patients at Increased Risk for Mesh-Related Complications, 116(5) Plastic & Reconstructive Surgery 1263, 1276-77 (2005) (Attachment H).

¹⁶ X. Guo et al., Efficacy and Safety of Acellular Dermal Matrix in Diabetic Foot Ulcer Treatment: A Systematic Review and Meta-Analysis, 40 Int'l J. Surgery 1-7 (2017) (Attachment I); S. Cazzell et al., 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, 25(3) Wound Repair & Regeneration 483-497 (2017) (Attachment J); A.M. Reyzelman & I. Bazarov, Human Acellular Dermal Wound Matrix for Treatment of DFU: Literature Review and Analysis, 24(3) J. Wound Care 128, 129-34 (2015) (Attachment K).

¹⁷ J. Walters et al., 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, 16:e10 Eplasty (2016) (Attachment L).

¹⁸ J.Y.S. Kim et al., Reconstruction of a Recurrent First Dorsal Web Space Defect Using Acellular Dermis, 2 Hand 240-244 (2007) (Attachment M).

¹⁹ R. Sheridan, M.D. et al., Acellular Allodermis in Burns Surgery: 1-Year Results of a Pilot Trial, 19(6) J. Burn Care & Rehabilitation 528-30 (1998) (Attachment N).

²⁰ W. Cole et al., Achilles Tendon Augmented Repair Using Human Acellular Dermal Matrix: A Case Series, 57(6) J. Foot & Ankle Surgery 1225-1229 (2018) (Attachment O).

²¹ S. Cazzell, A Randomized Controlled Trial Comparing a Human Acellular Dermal Matrix Versus Conventional Care for the Treatment of Venous Leg Ulcers, 31(3) Wounds 68-74 (2019) (Attachment P).

²² M.E. Aichelmann-Reidy et al., Clinical Evaluation of Acellular Allograft Dermis For the Treatment of Human Gingival Recession, 72(8) J. Periodontol. 998-1005 (2001) (Attachment Q).

²³ I.G. Margulies, M.D. & C.A. Salzberg, M.D., 8(1) The Use of Acellular Dermal Matrix in Breast Reconstruction: Evolution of Techniques Over 2 Decades, Gland Surgery 3-10

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Society of Plastic Surgeons (ASPS) reported that, of 101,657 breast reconstruction procedures performed by member surgeons, about 83,200 (roughly 82%) utilized tissue expanders and/or breast implants and, of these procedures, approximately 74% (61,713) utilized ADM allografts. *See* ASPS, 2018 Plastic Surgery Statistics Report.²⁴ Although ADMs are available on the market as human-derived, synthetic, or animal-derived sources (i.e., xenografts), the vast majority used in post-mastectomy breast reconstruction are human ADM allografts.²⁵ These latter allografts alone are the subject of the Petition.²⁶

III. USE IN BREAST RECONSTRUCTION

As noted, human ADM allografts are typically indicated for use in the repair, replacement, reinforcement, or supplementation of damaged or inadequate integumental tissue (e.g., skin).²⁷ Within this broad intended use, manufacturers in some cases call out or recommend various specific clinical applications, including post-mastectomy breast reconstruction. In the latter, the skin tissue of the breast, especially the dermis, may be damaged or denuded during the primary mastectomy surgery and may need repair, replacement, reinforcement, and/or supplementation.

The figure below shows a normal breast anatomy (Fig. 1). Mastectomy surgery is usually aimed at removing the breast tissue (shown in pink) containing the cancerous mass(es).

(2019) (Attachment R).

²⁴ Available at

<https://www.plasticsurgery.org/documents/News/Statistics/2018/reconstructive-breast-procedures-age-2018.pdf>.

²⁵ SmartTRAK data from Q418/FY18 (Attachment S).

²⁶ Neither synthetic meshes nor xenografts are classified as HCT/Ps because they are not human-derived, and, accordingly, are not subject to the regulatory analysis set forth in the Petition.

²⁷ The indications for the allograft are provided in the product label and package insert (i.e., labeling). Pursuant to AATB's *Standards for Tissue Banking* (14th Edition), "[a]ll labeling claims shall be clear, accurate, substantiated, and not misleading" and the labeling must contain "known contraindications (if any) to the use of the tissue; warnings and list of known possible significant adverse reactions; a statement that adverse outcomes potentially attributable to the tissue must be reported promptly to the tissue supplier; presence of known sensitizing agents (if any); a statement that indicates that the tissue may transmit infectious agents," among other items.

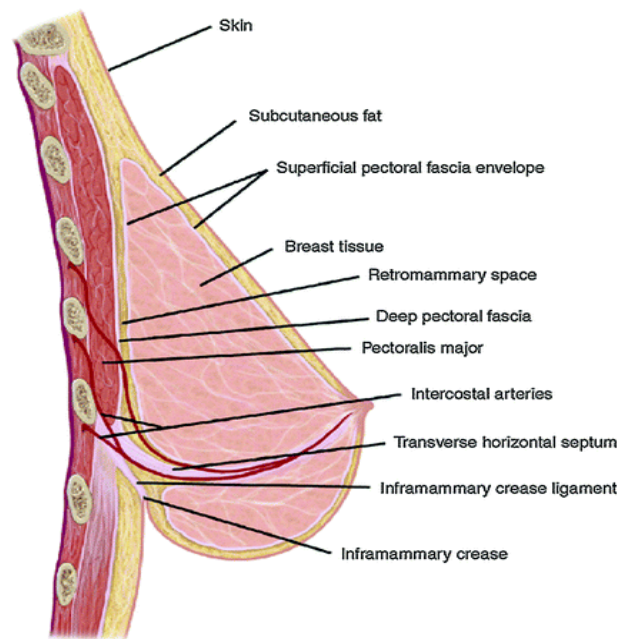


Figure 1. Normal anatomy of the breast²⁸

The breast integument (skin) is shown in greater detail in the figure below (Fig. 2). During a mastectomy, the skin typically is not removed, but is left at the original site and commonly is referred to as a “mastectomy flap.” An implant (or tissue expander, later substituted with an implant) replaces the breast tissue, and the mastectomy flap then is returned to its normal position as integumentary tissue.

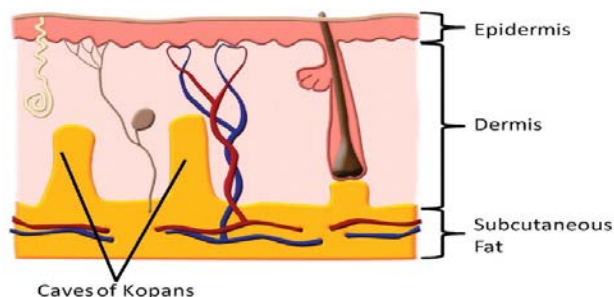


Figure 2. Normal anatomy of breast integument²⁹

²⁸ Drawing excerpted from P.M. Prendergast, *Anatomy of the Breast*. In: *Cosmetic Surgery* M.A. Shiffman & A. Di Giuseppe (eds) (2013).

²⁹ Drawings excerpted from S. Kalli et al., *Lesions of the Skin and Superficial Tissue at Breast MR Imaging*, 30(7) *RadioGraphics* 1891, 1892 (2010).

Even if a surgeon's intention is to preserve the patient's entire native dermis during these procedures, the surgical techniques used to cut or cauterize breast tissue almost invariably damage or denude the dermis to some extent. That is particularly so if a surgeon uses a wide margin to ensure that all potentially cancerous tissue is removed.

A damaged or denuded dermis can create a host of problems. For one thing, it cannot adequately support the epidermis, and because the dermis otherwise supplies connective tissue and a rich blood supply, its damage may allow the epidermis to stretch excessively, weaken, and potentially become non-viable and necrotic (at least in spots) due to lack of a blood supply. Accordingly, in order to reinforce, replace and/or supplement the damaged or denuded dermis, a human ADM allograft is placed immediately under the mastectomy flap—in the location of the dermal layer underneath the epidermis. Once placed, the human ADM allograft provides a “scaffold” on which the patient's native cells can repopulate and revascularize the allograft tissue, which is thereby incorporated into the host mastectomy flap tissue. As part of that process, there is little or no integration of the ADM with the tissue expander or breast implant.

IV. CLASSIFICATION AS 361 HCT/Ps

Firms that distribute human ADM allografts for breast reconstruction, including many companies within the AATB's membership, have done so for nearly two decades based upon FDA's longstanding acceptance of their position that these products qualify for regulatory treatment as 361 HCT/Ps. These processors have assessed their human ADM allografts for use in breast reconstruction under the HCT/P criteria and have uniformly and consistently determined that use of their products to repair, reinforce, replace, reconstruct or supplement dermis in for breast reconstruction procedures meets the four criteria for classification as 361 HCT/Ps.

Notwithstanding this history, CDRH recently indicated that the use of human ADM allografts for breast reconstruction constitutes a “non-homologous” use. Therefore, according to CDRH, these allografts do not qualify for classification as 361 HCT/Ps. CDRH announced this position during its General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee Meeting on March 25-26, 2019 (the Panel).³⁰ CDRH officials further suggested that allografts promoted for this purpose should be classified as Class III medical devices, requiring a PMA and subjecting these products to

³⁰ See Transcript, *supra* n. 2, at 277, 292.

additional post-market requirements.³¹ CDRH thereafter sent “It Has Come to Our Attention” letters to several processors of human ADM allografts promoted for use in breast reconstruction. CDRH asserted that such products allegedly are medical devices within the meaning of FDCA section 201(h). The letters did not explain how CDRH concluded these allografts do not qualify as 361 HCT/Ps.

CDRH’s assertions are not predicated on a proper HCT/P classification analysis. Human ADM allografts promoted for use in breast reconstruction applications are objectively intended to be used to repair, replace, reinforce or supplement damaged dermis or reconstruct dermis in the patient—the same function that the dermis performed in the donor—because they are limited in intended use to repair, replacement, reinforcement and/or supplementation of soft tissue per their labeling and advertising. The intended use is virtually the textbook definition of homologous use.

A. Use of Human ADM Allografts for Breast Reconstruction is a Homologous Use

The long-standing HCT/P regulations define “homologous use” as “the repair, reconstruction, replacement, or supplementation of a recipient’s cells or tissues with an HCT/P that *performs the same basic function or functions* in the recipient as in the donor.” 21 C.F.R. § 1271.3(c) (emphasis added). Consistent with the Agency’s intention to provide HCT/P manufacturers with maximum regulatory “flexibility” and to promote clinical “innovation without an application review process,” *see* Proposed Approach at 6, the preamble to FDA’s HCT/P regulations made clear that this functional standard should be construed expansively (and that exceptions are intended to be rare): “We intend to interpret ‘nonhomologous’ *narrowly*” where examples of uses that would be considered nonhomologous include “[t]he use of cartilage in the bladder.” 66 Fed. Reg at 5457 (emphasis added); *see id.* (“For example, promotion of an HCT/P for an unproven therapeutic use, such as curing cancer, would clearly make it inappropriate to regulate the HCT/P solely under section 361 of the PHS Act.”).

The Agency also emphasized that the “use of a structural tissue may be homologous *even when it does not occur in the same location as it occurred in the donor.*” *Id.* at 5458 (emphasis added). What matters, then, is not the location of the source of HCT/P, but how it functions when implanted in the recipient—a standard that almost invariably is satisfied when an HCT/P is placed in the *same* location in which it otherwise is present in the recipient (such as a split thickness skin graft on a skin burn wound, or as relevant here, a dermis graft in damaged or denuded dermis).

³¹ *See id.*

1. Repair / Reconstruction / Replacement / Supplementation

A homologous use assessment is based upon a manufacturer's "objective intent," as reflected by the product's labeling and advertising. 21 C.F.R. § 1271.10(a)(2). To come within the regulatory definition of "homologous use," HCT/Ps therefore must be intended for use in the "repair, reconstruction, replacement or supplementation" of a recipient's tissues. *Id.* § 1271.3(c). The 2017 Guidance defines these terms as follows:

"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."

2017 Guidance at 16 (boldface and paragraphing added).

As explained above, human ADM allografts are typically labeled for the repair, reinforcement, replacement, or supplementation of damaged or inadequate integumental tissue. On its face, this labeling shows that the dermis allograft is intended to repair,

reconstruct, replace, and/or supplement integumental tissue in a like-for-like exchange (i.e., homologous use).³²

Additionally, some processors also recommend human ADM allografts more specifically for use in connection with “breast reconstruction” procedures, but neither the labeling of these products nor the advertising for these products promote them for *any* possible use in breast reconstruction [for instance, to replace the breast tissue (i.e., adipose and glands) removed during the mastectomy portion of the procedure]. Instead, the product’s use remains constrained by the labeled homologous indication to repair, reinforce, replace, or supplement integumental tissue (dermis) only. The identification of “breast reconstruction” procedures simply suggests a clinical context in which integumental tissue repair frequently is necessary (and for which human ADM allografts are uniquely well-suited). Per this use, the allograft dermis is intended to repair, replace, reconstruct, and/or supplement dermis that has been damaged or denuded during a mastectomy. Accordingly, the first part of the definition of homologous use is met.³³

2. *Same basic function or functions in the recipient as in the donor*

Human ADM allografts used in post-mastectomy breast reconstruction also satisfy the second part of the “homologous use” standard: Such allografts perform “the same basic function” in the recipient as in the donor (and indeed do so in the same location and for the same purposes). The term “basic function” seeks to assess what an HCT/P “does from a biological/physiological point of view, or is capable of doing when in its native state.” 2017 Guidance at 16. FDA describes the basic functions of dermis in its native state as follows: “The dermis is the elastic connective tissue layer of the skin that covers, provides support and protects the body from mechanical stress.” *Id.* at 20. Accordingly,

³² The ordinary meaning of “reinforce” is to strengthen or increase by addition, *see* Merriam-Webster.com, <https://tinyurl.com/qo7l7xy>; therefore, “reinforcement” falls under FDA’s interpretation of “supplementation.” An ADM used for “reinforcement” is also an example from FDA of homologous use, *see* 2017 Guidance at 20, making clear that use in reinforcement falls within the regulatory terms of “repair, reconstruction, replacement or supplementation.”

³³ They may also be labeled to be used for other homologous uses, such as wound covering, which are not the subject of the Petition. To the extent new information comes to our attention indicating that FDA intends on classifying as medical devices human ADMs intended for use in clinical applications other than breast reconstruction, we reserve the right to supplement the Petition or file a separate petition.

the critical basic functions of dermis as elastic connective tissue are to provide coverage, support and protection.³⁴

That is precisely what human ADM allografts do in the breast reconstruction context. Used in accordance with their labeling, these HCT/Ps are intended to repair, replace, reconstruct, and/or supplement dermis that has been damaged or denuded during surgery, and (once implanted) they help renew the dermal layer in order to cover an underlying structure (the breast implant), provide support to the overlying epidermal tissue, and protect the underlying anatomy against mechanical stress. Each of these basic functions (covering, supporting, protecting) are performed in both the donor and recipient, which meets the second requirement for homologous use.

Although FDA's definition of homologous use does not require that tissue be used in the same anatomical location in the recipient as in the donor, in this case it is in fact so used. It is placed underneath the epidermis where dermis ordinarily resides, to perform the functions of dermis as elastic connective tissue, and thereby even more strongly demonstrates that the allograft is intended for homologous use. It is difficult to imagine how allograft dermis intended to be placed in the same location where dermis naturally resides would not be intended to perform the same functions in the recipient as in the donor.

The fact that the allograft covers a breast implant, rather than breast tissue, does not alter the regulatory conclusion. Regardless of whether the underlying structure is breast tissue or a breast implant, or a combination of the two, the human ADM allograft is dermis functioning as dermis. That is, the allograft dermis is elastic connective tissue placed in the location where dermis ordinarily occurs, and it offers the same type of functions as elastic connective tissue ordinarily provides (coverage, support, and protection). Furthermore, dermis in the donor provides, among other things, coverage of *various* structures throughout the body (e.g., bone, muscle, and other soft tissue). In the recipient, the dermis is performing this same function even when covering a breast implant rather than breast tissue; the homologous use criterion does not require the same structure to be covered in the donor and recipient. Accordingly, because the human ADM allograft is performing the same integumental functions in the recipient as in the donor, this intended use is homologous.

³⁴ See T. M. Brown & K. Krishnamurthy, Histology, Dermis, StatPearls (describing the functions of dermis as providing strength, flexibility, and support to the epidermis and deeper anatomical structures), <https://www.ncbi.nlm.nih.gov/books/NBK535346/> (last visited Dec. 4, 2019).

3. *The Tissue Reference Group's 2013 Recommendation*

The foregoing regulatory analysis is dispositive of the question of homologous use. In anticipation of potential objections, we note that in 2013, FDA's Tissue Reference Group (TRG) posted an informal recommendation on its website, which stated: "[t]he use of a human dermis product in breast reconstruction procedures where the dermis is used to form an extension of the submuscular pocket for placement of a breast implant or tissue expander constitutes nonhomologous use and therefore is not a 361 HCT/P."³⁵

The TRG recommendation is no longer on FDA's website. Per a Federal Register notice on November 17, 2017,³⁶ the Agency announced that, "although the TRG will continue to provide recommendations, the TRG annual reports will no longer be posted on FDA's Web site. We note that [the 2017 Guidance] is intended to help clarify the minimal manipulation and homologous use criteria in § 1271.10(a)(1) and (2), and thus addresses many of the questions that had been posed to the TRG." The final guidance did not specifically address the use of human ADM allografts to repair or supplement damaged or denuded dermis. Further, the TRG recommendations are based on specific facts provided by an individual sponsor and FDA has noted that "it may not be appropriate to generalize broadly from the updates."³⁷ To the best of our knowledge, in the past six years since the TRG recommendation was posted, FDA has never regulated any particular human ADM allograft product as a medical device.

It is not clear even now if CDRH is relying on this withdrawn recommendation, because CDRH has not provided any rationale for its position. Even considering the TRG's recommendation at face value, so far as we are aware, no manufacturer has indicated or promoted a human ADM allograft for use in "extending a submuscular pocket" and any such use readily could be disclaimed from labeling or promotion if the Agency deems that necessary.

Equally important, a proper homologous use assessment must focus on the function the dermis is performing in the recipient as compared to the donor. Although FDA characterizes the allograft as being "used to form an extension of the submuscular

³⁵ The TRG provides informal jurisdiction recommendations to sponsors and the Centers as to a sponsor's specific product. No information was provided on the website about the product.

³⁶ 82 Fed. Reg. 54290, 54292 (Nov. 17, 2017).

³⁷ Archived version of the Tissue Reference Group website from March 2017, *available at* <https://tinyurl.com/tez4akn>.

pocket,” the allograft is nonetheless implanted in the same location where dermis ordinarily occurs and is performing the basic functions of dermis. The location of the allograft in two common surgical approaches is shown in Fig. 3, below. On the left is the “sub-pectoral” approach.³⁸ That is the one that could be said to create a submuscular pocket. On the right is the “pre-pectoral” approach.³⁹ It does not create a submuscular pocket.

In *both* cases, the allograft is placed where the dermis ordinarily resides under the epidermis. There may be a difference in location along the plane of the dermis, but in both cases the allograft dermis is placed so as to repair, replace, reconstruct, and/or supplement a patient’s native dermis. Therefore, even though the TRG’s recommendation refers to the allograft as “form[ing] an extension of the submuscular pocket,” in reality, in all cases the human ADM allograft is used to repair, replace, reconstruct, or supplement an inadequate dermal layer. It is an elastic connective tissue layer placed underneath the epidermis in the recipient, which is where such dermis would be located in the donor as well. Because it is placed in its usual anatomical location, it is self-evidently intended to perform the same functions in the recipient as in the donor (coverage, support, protection). Such use of an HCT/P allograft cannot reasonably be characterized as anything but homologous.

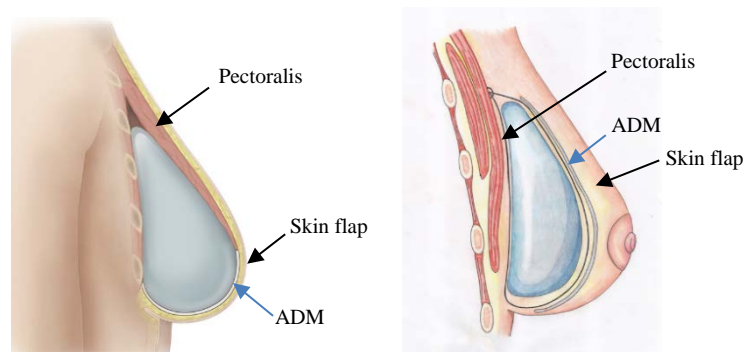


Figure 3: Illustrative placement of human ADM allograft in the dermal layer in the sub-pectoral approach (left) and pre-pectoral approach (right)

³⁸ Margulies, *supra* n. 23 (describing sub-pectoral technique).

³⁹ *Id.* (describing pre-pectoral technique).

B. Human ADM Allografts for Breast Reconstruction Meet the Remaining Criteria for Regulation as a 361 HCT/P

Human ADM allografts also meet the remaining criteria for 361 HCT/Ps because they are minimally manipulated; their manufacture does not involve combination with excluded articles; and they do not have a systemic effect and are not dependent on the metabolic activity of living cells for their primary function. The following discussion addresses these remaining prongs.

1. Minimal Manipulation

For almost 20 years, FDA has considered the manufacturing of human ADM allografts to be minimal manipulation. For structural tissues, such as dermis,⁴⁰ the Agency's regulations define "minimal manipulation" as "processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement." 21 C.F.R. § 1271.3(f)(1). The preamble to the final rule on establishment registration and listing expressly anticipates the processing steps used by manufacturers to make human ADM allograft for breast reconstruction described above – specifically, cell removal, shaping and cutting, disinfection and sterilization, and lyophilization. *See* 66 Fed. Reg. 5447, 5457 (Jan. 19, 2001). Furthermore, the 2017 Guidance reinforces that standard human ADM allograft processing meets the definition of minimal manipulation:

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.

2017 Guidance at 11-12. Therefore, it is indisputable that human ADM allografts meet the criterion for minimal manipulation when processed by the usual means, consistent with the guidance's example.

⁴⁰ FDA stated in the 2017 Guidance that skin is an example of a structural tissue (as opposed to a cellular/nonstructural tissue). 2017 Guidance at 7-8. "Tissues that physically support or serve as a barrier or conduit, or connect, cover, or cushion in the donor are generally considered structural tissues." *Id.* at 7.

2. *Combination with Excluded Article*

An HCT/P meets this criterion if “[t]he manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P.” 21 C.F.R. § 1271.10(a)(3). FDA defines “manufacture” as used in this regulation to include “any or all steps in the recovery, processing, storage, labeling, packaging, or distribution of any human cell or tissue, and the screening or testing of the cell or tissue donor.” *Id.* §1271.3(e). Examples provided by FDA during its rulemaking of agents that would generally be acceptable include cryoprotectants, chemicals used for sterilization, and storage solutions. 66 Fed. Reg. at 5459.

Human ADM allografts are not typically manufactured in combination with another article except for permitted articles like preservatives, sterilizing – including disinfecting – agents, and crystalloids. Accordingly, human ADM allografts meet this criterion.

3. *Systemic Effect and Metabolic Activity*

An article meets this criterion if it “does not have a systemic effect” and is “not dependent upon the metabolic activity of living cells for its primary function.” 21 C.F.R. § 1271.10(a)(4)(ii)(a). The effect of human ADM allografts is local, and they do not have a systemic effect. Further, human ADM allografts are decellularized, meaning that they do not contain living cells and therefore cannot depend on cellular activity for their primary function of cushioning, protecting and reinforcing. As such, human ADM allografts readily meet this regulatory criterion.

C. FDA Cannot Consider Factors Outside Its HCT/P Regulations to Assess Whether Human ADM Allografts Are 361 HCT/Ps

Because human ADM allografts meet all of the criteria for classification as a 361 HCT/P, they are not subject to regulation as medical devices or biological products. The result is fully in accord with FDA’s underlying policy and rulemaking. As FDA recognized in the Proposed Approach, the “comprehensive” framework for 361 HCT/Ps provides “adequate protection of public health, both from the risks of transmission of communicable disease and from the risks of therapies that may be dangerous,” and therefore such HCT/Ps should be developed “with as little regulatory burden as

possible.”⁴¹ Only if an HCT/P fails to meet all four criteria for classification as 361 HCT/P can such a product be subject to additional regulation as a drug, device, or biological product. *See* 66 Fed. Reg. at 5456 (“Our ability to regulate an HCT/P as a drug, device, and/or biological product derives from the [FD&C] act and section 351 of the PHS Act, authorities that are distinct from our authority to issue regulations to prevent the transmission of communicable disease under section 361 of the PHS Act. If an HCT/P does not meet the criteria in § 1271.10 for regulation solely under section 361 of the PHS Act . . . the HCT/P will be regulated under the [FD&C] act and/or the PHS Act and applicable regulations.”).

Nonetheless, CDRH appears to have relied on information outside of the regulatory framework when deciding to classify human ADM allografts as Class III medical devices. At the 2019 Panel where CDRH announced that these products should be regulated as medical devices if recommended for breast reconstruction, Professor Edwin Wilkins, M.D., University of Michigan, presented to FDA on outcomes from the Mastectomy Reconstruction Outcomes Consortium (MROC) study. The MROC study aimed to compare long-term outcomes for commonly used options for breast reconstruction and evaluate complications and patient-reported outcomes. As presented, based on the study authors’ assessment, use of human ADM allografts in immediate expander/implant reconstruction was associated with a marginally higher complication rate, but had no significant effects on patient-reported outcomes, compared with non-human ADM allograft cases.⁴²

There were significant limitations to the MROC study. For example, as noted by Dr. Wilkins, it was not a randomized clinical trial; there may have been selection bias and confounding variables not controlled for; and the analyses did not evaluate immediate reconstructions or use of pre-pectoral implants/expanders.⁴³ Most importantly for the present analysis, the MROC study was not pre-specified to and did not distinguish between outcomes for synthetic mesh, animal-derived grafts, and human ADM allografts, and even though there were various types of ADM used, they were “not of sufficient numbers to analyze.”⁴⁴ Further, the MROC study was not powered to examine the issues surrounding the use of human ADM allografts; it relied upon an observational (not

⁴¹ Proposed Approach, at 27.

⁴² Edwin G. Wilkins, M.D., Acellular Dermal Matrix in Immediate Implant-Based Breast Reconstruction Findings from the Mastectomy Reconstruction Outcomes Consortium (MROC) Study, *available at* <https://www.fda.gov/media/123029/download>.

⁴³ *Id.*

⁴⁴ Transcript, *supra* n. 2, at 293.

randomized) study design, which complicates the assignment of causality, and it focused on a heterogenous population that was not well-controlled, further clouding the assignment of causality.

Despite these manifest limitations, CDRH reached its conclusions about human ADMs from these data. In response to a discussion with Dr. Wilkins on the various types of ADMs used in the MROC study, a CDRH representative noted that FDA was not going to distinguish between the source of the ADM in terms of how much weight to give the MROC study: “So, for the Panel’s purposes, we were considering whether it’s animal derived, human derived, or synthetic to be comparable and to understand what the level of evidence is regardless of its source. You could go back and try to say oh, okay, this one category should be treated differently than another, *but the Agency is not doing that.*”⁴⁵

These statements suggest FDA’s reliance on the MROC study to support its classification of human ADM allografts as medical devices. Further, the Panel discussion strongly suggests that FDA may have conflated different types of meshes and human ADM allografts, even though the former are not derived from humans, and relied on this mixed data set to advocate a medical device classification for human ADM allografts. This approach fails to comport with FDA’s regulation defining 361 HCT/Ps. As discussed above, FDA must assess the regulatory status of human ADM allografts under the appropriate HCT/P framework, which is a *different regulatory framework* from either synthetic surgical meshes or xenograft-based surgical meshes. For example, FDA failed to supply a “homologous use” analysis with respect to the human ADM allografts, but simply asserted as a conclusion that use in breast reconstruction would be non-homologous.

Finally, CDRH’s reliance on the MROC study is troubling not only because the study cannot account for outcomes specific to human ADMs (because this end point was not pre-specified nor statistically powered), but because CDRH appears to have overlooked the large volume of publicly available data and literature demonstrating that human ADM allografts can be used safely and reliably in breast reconstructions.⁴⁶ CDRH’s reliance on factors outside of the HCT/P framework, including the MROC study, for its classification decision is a hallmark of decision-making that the courts have deemed arbitrary and capricious. *See Motor Vehicle Mfrs. Ass’n of U.S. v. State Farm Mut. Auto.*

⁴⁵ *Id.* at 292-293 (emphasis added).

⁴⁶ *See* Primer: Use of Human Acellular Dermal Matrices (ADMs) in Breast Reconstruction (ADM Primer), at 3-6, attached to Letter from Diana Buck and David M. Smith, M.D., AATB, to CDRH and CBER, dated Nov. 5, 2019 (Attachment T). Articles referenced in footnotes 23 to 53 of the ADM Primer are included in Attachment U.

Ins. Co., 463 U.S. 29, 43 (1983) (agency action is arbitrary and capricious and must be set aside “if the agency has relied on factors which Congress has not intended it to consider”); *Defenders of Wildlife v. Babbitt*, 958 F. Supp. 670, 682 (D.D.C. 1997) (agency’s decision was arbitrary and capricious because, among other things, it was based on faulty factual premises, contained factual errors, and made unsupported statements that were contradicted by evidence).

V. THE REQUESTED ACTIONS ARE NECESSARY

Human ADM allografts labeled for use to repair, reinforce, replace, reconstruct, or supplement integumental tissue and promoted for use in post-mastectomy breast reconstruction should be classified as 361 HCT/Ps. Recognizing that CBER is primarily responsible for assessing HCT/P regulatory status under Part 1271, the AATB previously requested input from CBER and CDRH jointly as to why human ADMs intended for use in breast reconstruction are to be considered nonhomologous and classified as medical devices,⁴⁷ but the Agency has declined to publicly clarify the basis for its position or to hold a public meeting allowing tissue banks and other stakeholders to further discuss the use of human ADM allografts in breast reconstruction surgeries.⁴⁸ Nonetheless, CDRH appears to have moved ahead with its position that these products are Class III medical devices requiring a PMA approval, even as it conspicuously has declined to explain how this position complies with the 361 HCT/P eligibility criteria in 21 C.F.R.

⁴⁷ See, e.g. Comment from American Association of Tissue Banks and AATB Tissue Policy Group, Docket FDA-2019-N-0426-0378 (Apr. 26, 2019), *available at* <https://www.regulations.gov/document?D=FDA-2019-N-0426-0378>.

⁴⁸ See Letter from J. Shuren, M.D., J.D. and P. Marks, M.D., Ph.D., to D. Buck, M.Ed., MBA, CTBS and D. M. Smith, M.D. (Dec. 6, 2019) (Attachment V). This letter also refers to ADM as a type of “mesh,” again conflating HCT/P ADMs with meshes derived from non-human sources, and assumes from the start that human ADM allografts are medical devices by referencing the Q Submission Program, which is only for medical devices and administered by CDRH. Moreover, FDA’s classification appears predicated on a desire for more data of a specific type; however, this is not a factor within the HCT/P framework. To the extent that FDA requires more data, the AATB has cited numerous literature references to FDA, *see* ADM Primer, and nothing forecloses FDA from inviting industry to provide those data in a meeting or workshop. During the March panel meeting, the FDA opted not to invite industry to provide perspective on this topic. But FDA cannot ignore the existing HCT/P framework.

§ 1271.10(a) or, specifically, why use of human ADM allografts in post-mastectomy breast reconstruction is non-homologous.

Individual companies have an option to seek a confidential Request for Designation (RFD) from FDA regarding the classification of their particular human ADM allograft. This approach is likely to result in inconsistency and expense, with little clarity offered across the board to physicians, patients, or industry. Human ADM allografts for breast reconstruction meet the 361 HCT/P criteria so there is little benefit to case-by-case decisions over a class-wide approach to updating the 2017 Guidance to include human ADM allografts for use in post-mastectomy breast reconstruction as an example of homologous use.

Accordingly, we ask that FDA take the actions requested in the Petition. It is critical that FDA promptly confirm the 361 HCT/P regulatory status of human ADM allografts to ensure that women with breast cancer have continued access to these allografts.

ENVIRONMENTAL IMPACT

The actions requested in this petition are subject to categorical exclusions under 21 C.F.R. §§ 25.30(h) and 25.31.

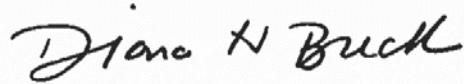
ECONOMIC IMPACT

Upon request by the Commissioner, Petitioner will submit economic impact information under 21 C.F.R. § 10.30(b).

CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this Petition includes all information and views on which the Petition relies, and that it includes representative data and information known to the Petitioner which are unfavorable to the Petition.

Respectfully submitted,

A handwritten signature in black ink that reads "Diana H Buck". The signature is written in a cursive style with a small dot above the 'i' in Diana.

Diana Buck, M.Ed., MBA, CTBS
Chair, American Association of Tissue Banks
Board of Governors

Attachments