August 25, 2022

Marc Pierce
American Association of Tissue Banks
8200 Greensboro Drive, Suite 320
McLean, VA 22102

Re: Docket No. FDA-2019-P-6100

Dear Mr. Pierce:

This letter responds to the Citizen Petition (Petition) dated December 30, 2019, which you filed with the Food and Drug Administration (FDA, the Agency, we) on behalf of the American Association of Tissue Banks. In your Petition, you request that the Commissioner of FDA take two actions with respect to human-derived acellular dermal matrix (human ADM) allografts intended for use in post-mastectomy breast reconstruction surgery. Specifically, you requested FDA to:

(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"; and

(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."[1]

FDA has reviewed and considered the information submitted in your Petition, including the supporting data provided in the docket. For the reasons explained below, your Petition is granted in part and denied in part. Specifically, we grant Request No. 1[2] and deny Request No. 2.

I. BACKGROUND

A. Human ADM Allograft Use in Post-mastectomy Breast Reconstruction

Human ADM allografts are human cells, tissues, and cellular and tissue-based products (HCT/Ps) derived from donated human skin. The dermis is the elastic connective tissue layer of

[1] Petition at 5.
[2] We grant Request No. 1, because as discussed below, use in breast reconstruction could include both nonhomologous and homologous applications of ADM, and products labeled and/or advertised for use in the context of postmastectomy reconstruction could fall into either category (nonhomologous or homologous), depending upon the specific intended use.

the skin that covers, provides support and protects the body from mechanical stress. To obtain the human ADM allografts, manufacturers may, for example, process skin to remove epidermis and freeze dry and package the remaining connective tissue. In general, ADMs vary significantly in their source, processing, level of sterility, biomechanical properties, thickness, final product state, and preparation methods prior to clinical application.

Over the past several years, the use of ADM products, including FDA cleared human-derived ADM, has increased. While such products are sometimes used in implant-based breast reconstruction, the FDA has not cleared or approved any ADM product for use in breast reconstruction.[3]

B. Statutory and Regulatory Background

Human cells, tissues, and cellular and tissue-based products (HCT/Ps) are defined in Title 21 Code of Federal Regulations (CFR) 1271.3(d) as articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. Because of the unique nature of HCT/Ps, FDA proposed and in 2005 implemented a tiered, risk-based approach to the regulation of HCT/Ps. Although FDA is authorized to apply the requirements in the Federal Food, Drug, and Cosmetic Act (FD&C Act) and the Public Health Service Act (PHS Act) to those products that meet the definition of drug, biologic, or device, under this tiered, risk-based approach, those HCT/Ps that meet specific criteria or fall within detailed exceptions do not require premarket review and approval. In developing the tiered, risk-based approach the Agency focused on public health and regulatory concerns, including how transmission of communicable disease can be prevented; what processing controls are necessary to prevent contamination that could result in an unsafe or ineffective product, and to preserve integrity and function so that the products will work as they are intended; and how clinical safety and effectiveness can be assured. The tiered, risk-based approach is contained in a set of regulations commonly referred to as the "tissue rules," issued by FDA through notice and comment rulemaking, under the communicable disease authority of section 361 of the PHS Act (42 U.S.C. 264). These regulations explain the types of HCT/Ps that do not require premarket approval; and the registration, manufacturing, and reporting steps that must be taken to prevent the introduction, transmission, and spread of communicable disease by these HCT/Ps. These regulations can be found in 21 CFR part 1271.

In 21 CFR 1271.10, the regulations identify the criteria for regulation solely under section 361 of the PHS Act and 21 CFR part 1271. An HCT/P is regulated solely under section 361 of the PHS Act and 21 CFR part 1271 if it meets all of the following criteria (21 CFR 1271.10(a)):

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;

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[3] *See* Acellular Dermal Matrix (ADM) Products Used in Implant-Based Breast Reconstruction Differ in Complication Rates: FDA Safety Communication available at https://www.fda.gov/medical-devices/safety-communications/acellular-dermal-matrix-adm-products-used-implant-based-breast-reconstruction-differ-complication.

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.

If an HCT/P does not meet the criteria set out in 21 CFR 1271.10(a), and the establishment that manufactures the HCT/P does not qualify for any of the exceptions in 21 CFR 1271.15, the HCT/P will be regulated as a drug, device, and/or biological product under the FD&C Act, and/or section 351 of the PHS Act (42 U.S.C. 262), and applicable regulations, including 21 CFR part 1271, and premarket review will be required.

If sponsors have questions about whether their products qualify for regulation solely under section 361 of the PHS Act and 21 CFR part 1271, FDA has multiple resources for seeking feedback at various stages of product development. One option is to submit a Request for Designation (RFD) to receive a formal, binding determination for the sponsor's product with respect to (1) the regulatory identity or classification of a human medical product as a drug, device, biological product, or combination product, including whether the product may be regulated solely under section 361 of the PHS Act and part 1271; and/or (2) assignment to the appropriate Agency Center (e.g., the Center for Devices and Radiological Health (CDRH); Center for Biologics Evaluation and Research (CBER); or Center for Drug Evaluation and Research (CDER)). The RFD process is codified in 21 CFR part 3, and FDA has published a guidance document that provides information about the requirements and processes for such submissions.[4] Another, less formal option is the Pre-Request for Designation (Pre-RFD) process, which provides non-binding feedback regarding the classification and/or assignment of the product. The outcome of the pre-RFD process is that sponsors receive a preliminary jurisdictional assessment, which is not binding, and throughout the process sponsors may interact with the Agency to obtain feedback. FDA has published guidance that describes this structured process with clear recommendations for sponsors wishing to submit Pre-RFDs.[5] A third option is to seek a non-binding recommendation from the Tissue Reference Group (TRG). The TRG, which is composed of representatives from CBER, CDRH and FDA's Office of Chief Counsel (OCC), is a resource for sponsors seeking guidance on whether a specific product meets the criteria in 1271.10(a) for regulation solely under section 361 of the PHS Act and 21 CFR part 1271.[6] The TRG is composed of representatives from CBER and CDRH, and the TRG provides recommendations that are then forwarded to the sponsor. These recommendations are based on

[4] *See* https://www.fda.gov/combination-products/rfd-process.
[5] *See* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/how-prepare-pre-request-designation-pre-rfd.
[6] *See* https://www.fda.gov/vaccines-blood-biologics/tissue-tissue-products/tissue-reference-group.

the information known at the time and are fact specific (e.g., product composition, intended use, mode of action, method of manufacture). Together, these options provide multiple pathways for sponsors to receive timely and effective feedback on the appropriate classification and/or assignment for their products, and sponsors can choose whether they wish to receive a binding determination or whether they prefer more informal feedback. These options also help to avoid sponsors developing and marketing their product when they are uncertain about the appropriate classification of their product. FDA has multiple programs specifically designed to resolve such uncertainty. And FDA has made those programs more accessible by issuing guidance and posting information about them on the Agency's website.

C. Homologous Use

Section 1271.10(a)(2) (21 CFR 1271.10(a)(2)) provides that one of the criteria for an HCT/P to be regulated solely under section 361 of the PHS Act and the regulations in part 1271 is that the "HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent." As defined in 21 CFR 1271.3(c), homologous use means 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.

In applying the homologous use criterion, FDA will determine what the intended use of the HCT/P is, as reflected by the labeling, advertising, and other indications of a manufacturer's objective intent, and will then apply the homologous use definition. A manufacturer's objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by the manufacturer or its representatives. It may be shown by surrounding circumstances under which an HCT/P is offered for a purpose for which it is neither labeled nor advertised.

FDA promulgated the homologous use criterion as part of a public rulemaking. This criterion reflects the Agency's conclusion that there would be increased safety and effectiveness concerns for HCT/Ps that are intended for a nonhomologous use, because there is less basis on which to predict the product's behavior, whereas HCT/Ps for homologous use can reasonably be expected to function appropriately (assuming all of the other criteria are also met).[7] FDA's public rulemaking process provided interested persons with the opportunity to comment on this proposed criterion and the underlying rationale through both a public meeting[8] and written comments to the rulemaking docket. In the final rule promulgating the homologous use criterion, FDA explained the Agency's consideration of these comments and also responded to comments seeking clarification.[9] As an example of a homologous use of dermis, FDA stated that the use of dermis as a replacement for dura mater would be considered homologous.[10]

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[7] "Proposed Approach to Regulation of Cellular and Tissue-Based Products," 62 FR 9721 (March 4, 1997) (proposed rule).
[8] *See* 62 FR 9721, March 4, 1997.
[9] *See* "Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing," Final Rule, 66 FR 5447 (January 19, 2001).
[10] Id. at 5458.

Subsequent to the rulemaking, FDA received many inquiries from manufacturers about whether their HCT/Ps meet the homologous use criterion. FDA again initiated a public process to provide stakeholders with the opportunity to offer comments and seek clarification. FDA published a draft and then final guidance[11] that provides examples of different types of HCT/Ps and addresses how the regulations in 21 CFR 1271.10(a)(1) and (2) apply to them, and also sets forth general principles that can be applied to HCT/Ps not specifically addressed in the guidance. The guidance includes examples for when dermis may perform the same basic function or functions in the donor as the recipient. For example, Example 20-1 in the guidance describes the dermis as the elastic connective tissue layer of the skin that covers, provides support and protects the body from mechanical stress.[12] The guidance states that an acellular dermal product used for supplemental support, protection, reinforcement, or covering for a tendon is a homologous use because in both anatomic locations, the dermis provides support and protects the soft tissue structure from mechanical stress.[13] The guidance also states that an acellular dermal product used for tendon replacement or repair is not homologous use because serving as a connection between muscle and bone is not a basic function of dermis.[14]

Although neither the preambles nor the guidance documents described above directly addressed the use of human ADM in post-mastectomy breast reconstruction, FDA has engaged the public on this use through multiple channels. Literature reports on the use of ADM in breast reconstruction were first published in the early 2000s.[15,16] In 2012, the TRG published a short description on the FDA website providing an informal assessment that the 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.[17] In 2019, CDRH held a public advisory committee meeting of the General and Plastic Surgery Devices Panel of the Medical Devices

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[11] This guidance is entitled, "Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use" (MM/HU Guidance), *available at* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/regulatory-considerations-human-cells-tissues-and-cellular-and-tissue-based-products-minimal. It supersedes a guidance of the same title dated November 2017 and corrected December 2017. The November 2017 version of the guidance finalized the document entitled "Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps); Draft Guidance for Industry and Food Administration Staff" dated December 2014, and "Homologous Use of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps); Draft Guidance for Industry and FDA Staff" dated October 2015. It also finalized certain material related to adipose tissue that was included in draft guidance entitled "Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) from Adipose Tissue: Regulatory Considerations; Draft Guidance for Industry" dated December 2014 (Adipose Draft Guidance).

[12] MM/HU Guidance at 20.

[13] Id. at 21.

[14] Id. at 22.

[15] Breuing KH, Warren SM. "Immediate bilateral breast reconstruction with implants and inferolateral AlloDerm slings." Ann Plast Surg. 2005 Sep; 55(3):232-239;

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

[17] The archived version of this website is available at, https://wayback.archive-it.org/7993/20170111014754/http://www.fda.gov/BiologicsBloodVaccines/TissueTissueProducts/RegulationofTissues/ucm152857.htm.

Advisory Committee to discuss and make recommendations regarding the benefits and risks of breast implants indicated for breast augmentation and reconstruction.[18]

In 2021, FDA sent an untitled letter to one company stating that the company was marketing an ADM product as a pocket for placement of a breast implant during breast reconstruction without required premarket approval, and stated that the use of a human dermis product in breast reconstruction procedures where the dermis is used in the recipient to form an extension of the submuscular pocket for placement of a breast implant constitutes a nonhomologous use. FDA has also sent "It Has Come To Our Attention Letters" seeking additional information from several other firms. Notably, all of these letters were to individual manufacturers about specific products based on information available to the Agency regarding those particular products. They did not constitute an Agency policy that all uses of human ADM in breast reconstruction surgery are homologous or nonhomologous. Nor did they constitute a change from any previously-issued policy.

D. Safety Concerns

FDA's promulgation of the homologous use criterion reflects our conclusion that there would be increased safety and effectiveness concerns for HCT/Ps that are intended for a nonhomologous use, because there is less basis on which to predict the product's behavior, whereas HCT/Ps for homologous use can reasonably be expected to function appropriately assuming all of the other 21 CFR 1271.10(a) criteria are also met.

Separate from our evaluation of the homologous use criterion in relation to ADM for use in postmastectomy breast reconstruction, we note that safety risks regarding the use of ADM in breast reconstruction have become apparent over time.[19] The Mastectomy Reconstruction Outcomes Consortium (MROC) Study evaluated 1297 patients from 2012 to 2015 that underwent post mastectomy breast reconstruction. When published in 2017 the authors reported use of ADM in immediate expander/implant reconstruction was associated with higher overall complication rates two-year post operation, but had no significant effects on patient-reported outcomes (BREAST-Q Physical Well-being or Numerical Pain Rating Scale), compared with

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[18] https://www.fda.gov/advisory-committees/advisory-committee-calendar/march-25-26-2019-general-and-plastic-surgery-devices-panel-medical-devices-advisory-committee. The meeting included discussion of ADM in breast reconstruction surgery, and the transcript reflects a statement by an FDA speaker that human-derived ADMs used for breast reconstruction procedures is considered nonhomologous. Transcript, CDRH, Medical Devices Advisory Committee, General and Plastic Surgery Devices Panel (Mar. 26, 2019), *available at* https://www.fda.gov/media/123746/download at 277. However, the FDA speaker's accompanying written presentation refers only to use in the recipient to form an extension of the submuscular pocket for placement of a breast implant being nonhomologous. *See* https://www.fda.gov/media/122962/download at 11. Use of ADM to form a submuscular pocket is just one use of ADM in breast reconstruction surgery, so the speaker's statement should not be understood to constitute an Agency policy that all uses of ADM in breast reconstruction surgeries are nonhomologous. Furthermore, FDA's good guidance practice regulations make clear that FDA staff cannot establish Agency policies through informal communications such as public speaking engagements. *See* 21 CFR 10.115(e) (providing that the Agency may only use guidance documents, not other means of communication, to communicate new or different regulatory expectations to a broad public audience). Speeches are excluded from the definition of guidance documents. 21 CFR 10.115(b)(3).

[19] *See* "Safety Risks of Acellular Dermal Matrix in Breast Reconstruction" CDRH Memo to the Record. Dated August 11, 2022.

non-ADM cases. Authors reported a higher rate for major complications for the ADM group compared to non-ADM group. Complications requiring rehospitalizations or reoperations were designated by authors as "major."[20] FDA conducted its own analysis of the MROC dataset, and found that certain commonly used ADMs were associated with higher complication rates compared to the control arm where no ADM was used. FDA's analysis thus confirmed that the use of ADM in the types of breast reconstruction surgery studied is associated with a higher complication rate. In 2021, FDA issued a safety communication to inform patients and health care providers that certain ADM products used in implant-based breast reconstruction may have a higher chance for complications or problems.[21]

Throughout this regulatory and scientific process, FDA has not issued any determinations that all uses of human ADM in post-mastectomy breast reconstruction are homologous, or that all such uses are nonhomologous. Rather, as specific products have presented themselves over time, FDA has addressed those particular products based on a careful evaluation of the specific facts and circumstances involved. The Agency has provided clarity in guidance regarding how homologous use is defined, including how it is defined for skin.

II. DISCUSSION

A. Request that FDA "confirm" that human ADM allografts that otherwise meet the requirement for regulation solely under Section 361 of the PHS Act shall not be considered nonhomologous or otherwise ineligible for classification as "361 HCT/Ps" solely because they are labeled and/or advertised for use in "post-mastectomy breast reconstruction."

The Petition requests that FDA "confirm" that human ADM allografts that otherwise meet the requirement for regulation solely under Section 361 of the PHS Act shall not be considered nonhomologous or otherwise ineligible for classification as "361 HCT/Ps" solely because they are labeled and/or advertised for use in "post-mastectomy breast reconstruction." We generally consider an HCT/P to be for homologous use when it is used to repair, reconstruct, replace, or supplement:

- Recipient cells or tissues that are identical (e.g., skin for skin) to the donor cells or tissues, and perform one or more of the same basic functions in the recipient as the cells or tissues performed in the donor; or
- Recipient cells or tissues that may not be identical to the donor's cells or tissues, but that perform one or more of the same basic functions in the recipient as the cells or tissues performed in the donor.[22]

For the purpose of applying the HCT/P regulatory framework, the same basic function or functions of HCT/Ps are considered to be those basic functions the HCT/P performs in the body of the donor, which, when transplanted, implanted, infused, or transferred, the HCT/P would be

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[20] Sorkin, M., et al. "Acellular Dermal Matrix in Immediate Expander/Implant Breast Reconstruction: A Multicenter Assessment of Risks and Benefits." Plast Reconstr Surg. 2017 Dec; 140(6): 1091-1100

[21] *See* https://www.fda.gov/medical-devices/safety-communications/acellular-dermal-matrix-adm-products-used-implant-based-breast-reconstruction-differ-complication.

[22] "Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products" 63 FR 26744 at 26748-26749 (May 14, 1998). (Tissue Registration and Listing; Proposed Rule)

expected to perform in the recipient. While it is not necessary for the HCT/P in the recipient to perform all of the basic functions it performed in the donor in order to meet the definition of homologous use, to meet the definition of homologous use, any of the basic functions that the HCT/P is expected to perform in the recipient must be a basic function that the HCT/P performed in the donor.

FDA has identified the basic functions of skin as covering, protecting the body from external force, and serving as a water-resistant barrier to pathogens or other damaging agents in the external environment (see the MM/HU Guidance).

Although your Petition states that "human ADM allografts are typically labeled for the repair, reinforcement, replacement, or supplementation of damaged or inadequate integumental tissue," FDA is aware that human ADM allografts may be used for multiple functions in post-mastectomy breast reconstruction. Examples of such functions include managing a potential skin defect created from harvesting tissue for use in autologous tissue reconstruction and formation of an extension of the submuscular pocket for placement of a breast implant or tissue expander in breast reconstruction procedures. These examples are within the scope of your Petition because they involve use of human ADM allografts in post-mastectomy breast reconstruction.

Some uses of ADM in post-mastectomy breast reconstruction may be homologous. One example of a homologous use could include managing a potential skin defect created from harvesting tissue for use in autologous tissue reconstruction. This use may be considered homologous if the human ADM allograft is used to cover the skin wound, because covering is consistent with the basic function of skin (as described above). Human ADM allograft intended for homologous use may be regulated solely under section 361 of the PHS Act and 21 CFR part 1271 provided the HCTP meets all of the other criteria specified in 21 CFR 1271.10(a)).

In contrast, other potential uses of human ADM allograft encompassed in post-mastectomy breast reconstruction may be considered nonhomologous. For example, a nonhomologous use could include the use of a human dermis product to form an extension of the submuscular pocket for placement of a breast implant or tissue expander in breast reconstruction procedures. This use may be considered nonhomologous because the use for breast reconstruction after mastectomy where the product is used to extend the muscle to form a muscle pocket for placement of a breast implant or tissue expander and functions to prevent expander or implant extrusion and to constrain the expander or implant in the correct position is not consistent with the basic function of skin. Human ADM allograft intended for nonhomologous use do not meet all the criteria set out in 21 CFR 1271.10(a), and in such cases, the HCT/P will be regulated as a drug or device under the FD&C Act, and/or a biological product under section 351 of the PHS

Act (42 U.S.C. 262), and applicable regulations, including 21 CFR part 1271, and premarket review will be required.[23]

Therefore, we acknowledge that certain uses of human ADM allograft in post-mastectomy breast reconstruction could be considered homologous, and human ADM intended for homologous use may be regulated solely under section 361 of the PHS Act and the regulations in part 1271 provided the HCT/P meets all of the other criteria specified in 21 CFR 1271.10(a)). At the same time, certain uses of human ADM allograft in post-mastectomy breast reconstruction would *not* be considered homologous. Where such ADMs are intended for nonhomologous use, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent, the ADMs would not be eligible to be regulated solely under section 361 of the PHS Act and part 1271.

We provide this background as the context for how we are addressing your citizen petition requests. Your petition asks that we "confirm" that human ADM allografts shall not be considered nonhomologous "solely" because they are labeled and/or advertised for use in post-mastectomy breast reconstruction. We do not view use in post-mastectomy breast reconstruction, in and of itself, as determinative of whether a use is homologous, because certain uses in the context of breast reconstruction surgery could be homologous and certain uses could be nonhomologous. As described above, some uses of ADM in breast reconstruction fall on either side of the homologous vs. nonhomologous line. In determining whether a particular product is intended for homologous use, we would look at evidence of how the product is intended to be used in post-mastectomy breast reconstruction. Specifically to make a jurisdictional determination, we would consider evidence relevant to the manufacturer's objective intent, including statements and circumstances surrounding the distribution of the product and the design or composition of the article. See 21 CFR 1271.10(a)(2) (providing that whether the intended use of a product is homologous is "reflected by the labeling, advertising, or other indications of the manufacturer's objective intent"); see also Regulations Regarding "Intended Uses," 86 FR 41383, 41386 (Aug. 2, 2021) (describing types of evidence that may be relevant to determining the manufacturer's objective intent). Products labeled and/or advertised for use in the context of postmastectomy reconstruction, would not automatically be considered nonhomologous or homologous simply because they are labeled and/or advertised for use in breast reconstruction, but rather would be evaluated based on their specific claims and other indications of the manufacturer's objective intent.

If sponsors have questions about the appropriate classification of their product, including whether a particular intended use is homologous or nonhomologous, they may contact us with any questions. As described above, the Agency provides multiple options for sponsors to seek

[23] As our discussion makes clear, labeling "for use in post-mastectomy breast reconstruction" may not be determinative of the question of whether the use is homologous or nonhomologous. The homologous/nonhomologous use determination would be based on a product-specific evaluation by the appropriate product office, for example, taking into consideration data submitted to FDA as part of a marketing application. In considering your petition request regarding the phrase "for use in post-mastectomy breast reconstruction," we are only considering the phrase's relevance to whether a use may be considered homologous or nonhomologous. We also note that to the extent that a particular human ADM allograft is regulated as a device under the FD&C Act, and applicable regulations, including 21 CFR part 1271, its classification is outside the scope of the requests in this Petition.

our feedback and help resolve any regulatory uncertainty. FDA's programs for resolving classification questions ensure timely and thorough reviews focused on the specific characteristics of individual products, and are designed to evaluate questions such as which uses are homologous.

B. Request that FDA revise the final guidance, "Regulatory Consideration for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use" to present human ADM allografts for post-mastectomy breast reconstruction as an example of a homologous use.

The Petition requests that FDA revise the final MM and HU Guidance. Specifically, the Petition requests that FDA revise this guidance "to present human ADM allografts for post-mastectomy breast reconstruction as an example of a homologous use."[24] As described above, in 2015 the Agency issued draft guidance regarding this topic and received input from stakeholders. Additionally, FDA held a public hearing in 2016 to hear further comments from stakeholders. During finalization of this guidance in 2017, FDA carefully considered all comments received on the draft guidance and at the public hearing. Accordingly, the Agency has already provided a robust process for public participation in the guidance development and has already invested considerable time and resources in drafting and finalizing the guidance document. Our views about the homologous use criterion have not changed since we issued the guidance, and as outlined above, the guidance already sets forth general principles that are applicable to assessing whether particular uses of dermis are homologous. For all these reasons, we do not agree with your request that we reopen the guidance document at this time.

As an additional matter, even if we were to reopen the guidance development process, we do not agree with your suggestion for how we might do so. You request that FDA update the guidance to "present human ADM allografts for post-mastectomy breast reconstruction as an example of a homologous use." But as the discussion above makes clear, whether a human ADM will be used in post-mastectomy breast reconstruction is not determinative as to whether a particular use is homologous. Some uses of human ADM in breast reconstruction are homologous, and some are not.

Finally, with respect to those uses that may be homologous, FDA does not at this time see a need to revise its guidance document, because FDA may communicate to individual sponsors about their products. While guidance documents allow the Agency to articulate its interpretation of or policy on a regulatory matter (21 CFR § 10.115(b)), FDA also provides advice to individual manufacturers based on their specific products, and it may be more helpful for manufacturers to seek our feedback through the options (RFD, pre-RFD, TRG) discussed above. To date, FDA has not received many pre-RFD, RFD, or TRG requests or submissions related to ADM for breast reconstruction. If there is any regulatory uncertainty, FDA encourages sponsors to seek our feedback through one of these options. Accordingly, we decline to revise the guidance as requested in the petition, and we deny your request that we do so. However, FDA remains committed to reviewing the evolving science of these products.

[24] Petition at 5.

If the Agency becomes aware of new information that would justify updating the guidance document, FDA may do so in the future.

III. CONCLUSION

For the reasons described above, the Agency GRANTS Request No. 1 and DENIES Request No. 2 in the Citizen Petition.

We appreciate your concerns and appreciate you contacting us concerning this matter.

Sincerely,

Peter W. Marks -S
Digitally signed by Peter W. Marks -S
Date: 2022.08.25 13:15:38 -04'00'

Peter Marks, MD, PhD
Director
Center for Biologics Evaluation and Research

Jeffrey E. Shuren -S
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Jeffrey Shuren, MD, JD
Director
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cc: Dockets Management Staff