American Association of Tissue Banks® AATB TPG, LLC

April 7, 2021

Janet Woodcock, MD
Acting Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

In Re: FDA Safety Communication on March 31, 2021 titled *Acellular Dermal Matrix (ADM) Products Used in Implant-Based Breast Reconstruction Differ in Complication Rates*

Submitted electronically at Janet.Woodcock@fda.hhs.gov

Dear Dr. Woodcock:

The American Association of Tissue Banks (AATB or Association) and the American Association of Tissue Bank's Tissue Policy Group, LLC (AATB TPG) submit these comments related to a safety communication on March 31, 2021 by the Food and Drug Administration (FDA or Agency) titled *Acellular Dermal Matrix (ADM) Products Used in Implant-Based Breast Reconstruction Differ in Complication Rates.* In reviewing the communication, not only are we concerned that the information presented lacks scientific rigor by not including a comprehensive evaluation of all ADM data, while also not detailing the full limitations of the dataset FDA reviewed, but we also caution that the information presented does a disservice to women – those who are considering, or who have undergone, breast reconstructive surgery, especially given that ADMs for implant-based breast reconstruction has become the standard of care. Especially in light of the new Administration's focus on maintaining scientific integrity, we are disappointed in this communication, as further detailed below.

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

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

With respect to the scientific issues, we note multiple problems with the communication and the single analysis performed by the Agency, including a misleading title, focus on a single unpublished analysis, a lack of key information (including data tables and the statistical analysis and criteria employed), limited focus on certain surgical types while also (by default) comparing two different surgical techniques, lack of patient-reported outcomes (PROs), and failure to acknowledge other published studies that show disparate results. Simply put, the analysis performed by the Agency lacked the necessary scientific rigor (i.e., lacks comprehensive data inclusion and is limited to only certain surgical procedures) to be shared publicly, and, as such, **we request the FDA update the communication with additional clarifications, as noted below.**

Misleading title. The title of the communication -- *Acellular Dermal Matrix (ADM) Products Used in Implant-Based Breast Reconstruction Differ in Complication Rates*, which suggests that there is a definitive difference between ADM products, is not consistent with the actual text in which the FDA acknowledges four times that certain ADMs "may have" a higher risk profile. Therefore, the Agency should ensure that the key information shared with the public is accurately represented and consistent in messaging. Given that, ***we request, at a minimum, the title be edited to acknowledge uncertainty in whether certain ADMs may have different complication rates.***

Single, unpublished analysis and lack of data tables and other key information. The Agency acknowledges in its communication that it performed its own analysis of the data collected as part of the Mastectomy Reconstruction Outcomes Consortium (MROC). Based on the references provided, it seems as if this analysis is from 2012-2015, with a two year follow up. Unfortunately, based on the FDA's summary of its own analysis (i.e., "suggests that two ADMs . . . . may have a higher risk profile than others."), the FDA failed to provide key data tables, p-values, confidence intervals, definitions of complications, major complications and other key analytical parameters or other necessary information, which would be required for a peer-reviewed publication and allow the reader to critically review the data and analysis against the conclusions. In addition, it is unclear how relevant the data is, given advances in surgical techniques. Therefore, it is unclear why the Agency would share certain potential conclusions with the public without providing additional context, especially given the lack of peer review. Therefore, **at a minimum, *we request the FDA provide clear data tables, statistical approach, parameter definitions and other key information in an updated communication.***

Limited surgical techniques involved. The Agency notes that its analysis was limited to "immediate, two-stage, under-the-muscle, implant-based reconstruction with up to two-year follow-up" comparing to a "control group which did not receive ADM and groups receiving one of the four ADM brands." Thus, by its very nature, the FDA's analysis did not include pre-pectoral placement of ADMs for breast reconstruction, given that this technique is not "under-the-muscle".[1] Further, to create the "no ADM" versus "ADM" cohorts, the analysis would have likely relied on two different surgical techniques – (1) partial muscle coverage or sub-pectoral placement with ADM and (2) full muscle coverage without ADM. Therefore, in acknowledging the confounding factors and limited application, the Agency failed to make clear that the analysis not only focused on ADM use but, by default, the two cohorts also differed in surgical technique, which can influence the overall

[1] For more information on the pre-pectoral surgical technique and its benefits and current use, see here.

findings. Thus, ***we request, that, at a minimum, the FDA clarify in the communication that surgical techniques also vary with the use or non-use of ADMs and further note that the analysis does not take into consideration pre-pectoral placement of the breast implant.***

Lack of PROs. During the March 2019 Panel discussion, FDA officials highlighted the value of PROs, and yet, the Agency's analysis failed to include such information, even though references 1 and 2 (related to peer-reviewed analysis of the MROC data) heavily report on PROs and thus the data were clearly available for the Agency's analysis. Given that the Agency has deemed that their communication need not include PROs, we look forward to further discussing the value of PROs, when they are available, in additional research, especially in light of a sister agency's draft report[2] on this topic which notes that "[r]egarding ADMs, their use does not appear to impact patient-reported clinical outcomes."

Failure to include additional studies. In providing support for its analysis, the Agency opted to reference six previously published studies that support its analysis, but unfortunately the Agency failed to include additional studies that demonstrate results that did not support the Agency's position and are thus favorable to the safety and effectiveness of ADMs.

The Agency's approach runs afoul of guidance titled *Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims*, that requires industry to "evaluate the **totality** of scientific evidence" (emphasis added). Examining the totality of the evidence is also a requirement of FDA submissions; industry is expected to include all studies, regardless of the outcome, to provide a balanced perspective on the product's performance in the submission for FDA to evaluate.

In selecting the six studies, the Agency failed on at least two levels. First, it did not provide a comprehensive analysis of the literature. And, it did not ensure that the referenced studies were the most relevant and up-to-date information. With respect to the literature analysis, the Agency also failed to be transparent by not supplying the search terms used and the rules for inclusion and exclusion of articles included in its communication that resulted in only six being chosen, given that there were 319 returns in PUBMED when searching, "ADM and breast reconstruction" -- 16 in 2021

[2] The AATB and TPG note that the draft report also states the following:
Use versus nonuse of human ADMs during IBR: The results are inconsistent regarding whether ADM use impacts physical well-being, psychosocial well-being, satisfaction with breast aesthetics, pain, or risks of wound dehiscence or capsular contracture. ADM use probably increases the risk of implant failure/loss or need for explant surgery (summary adjOR 1.28, 95% CI 0.97 to 1.70; 6 studies) (Moderate SoE) and may increase the risk of infections not explicitly related to the implants or ADM (summary adjOR 1.56, 95% CI 0.96 to 2.53; 7 studies) (Low SoE). However, ADM use and nonuse groups probably experience comparable risks of seroma (summary adjOR 1.52, 95% CI 0.62 to 3.71; 4 studies) (Moderate SoE) and unplanned repeat surgeries for revision (Moderate SoE). ADM use and nonuse groups may experience comparable risks of necrosis (summary adjOR 0.89, 95% CI 0.63 to 1.25; 4 studies) (Low SoE).
While this information, on its face, may seem to support the FDA's other conclusions, the sister agency (Agency for Healthcare Resarch and Quality or AHRQ) provided additional context related to its analysis – namely, the odds ratios and confidence intervals as well as a measure of the standard of evidence. Not only does the AATB and the TPG appreciate that scientific rigor, but we would also note that AHRQ determined that there was a low or moderate standard of evidence for those statements. Further, given that the 95% confidence intervals for the odds ratio crossed one, the values are not considered statistically significant. Finally, AHRQ provided an opportunity for full review of the data, including public comment, before finalizing the document. That transparency of key research information is important.

thus far; 80, 2020 (as of April 1, 2021); and 78, 2019. Thus, from PUBMED, there were at least 172 articles to analyze just over two years, and unfortunately the FDA only chose to cite six.

In addition, the Agency also failed to follow its own guidance titled *Meta-Analyses of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biological Products Guidance for Industry*, that states, "[c]hanges over time in the practice of medicine may affect the usefulness of some trials for contributing data to a meta-analysis. Older trials may no longer be relevant, if medical practice has changed such that current practices are able to prevent or reduce the occurrence of the safety outcome under investigation." Thus, in performing literature searches for FDA submissions, industry is typically held to the standard that references be less than 5-years old, unless they are foundational. Foundational articles must be supported with current literature. The FDA bibliography contains four articles (refereces 3-6) that are more than 5 years old (without any current literature to support them), while references 1 and 2 collect data from 2012-2015; and thus, do not adequately represent the evolution of surgical techniques and the current state of ADM safety and effectiveness in breast reconstruction. Thus, the Agency failed in its communication to follow its own guidance to ensure that the literature cited is the most relevant and up-to-date.

In light of these limitations, please note additional studies, contrary to the communication's findings, which should have been included in the Agency's analysis:

Brooke S, Mesa J, Uluer M, Michelotti B, Moyer K, Neves RI, Mackay D, Potochny J. Complications in tissue expander breast reconstruction: a comparison of AlloDerm, DermaMatrix, and FlexHD acellular inferior pole dermal slings. Ann Plast Surg. 2012 Oct;69(4):347-9. doi: 10.1097/SAP.0b013e31824b3d97. PMID:22868313. https://pubmed.ncbi.nlm.nih.gov/22868313/

Seth AK, Persing S, Connor CM, Davila A, Hirsch E, Fine NA, Kim JY. A comparative analysis of cryopreserved versus prehydrated human acellular dermal matrices in tissue expander breast reconstruction. Ann Plast Surg. 2013 Jun;70(6):632-5. doi: 10.1097/SAP.0b013e318250f0b4. PMID: 23429218. https://pubmed.ncbi.nlm.nih.gov/23429218/

Palaia DA, Arthur KS, Cahan AC, Rosenberg MH. Incidence of Seromas and Infections Using Fenestrated versus Nonfenestrated Acellular Dermal Matrix in Breast Reconstructions. Plast Reconstr Surg Glob Open. 2015 Dec 9;3(11):e569.doi: 10.1097/GOX.0000000000000559. PMID: 26893994; PMCID: PMC4727721.https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4727721/

Schnarrs RH, Carman CM, Tobin C, Chase SA, Rossmeier KA. Complication Rates With Human Acellular Dermal Matrices: Retrospective Review of 211 Consecutive Breast Reconstructions. Plast Reconstr Surg Glob Open. 2016 Nov 21;4(11):e1118.doi: 10.1097/GOX.0000000000001118. PMID: 27975023; PMCID: PMC5142489. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5142489/

Lee KT, Mun GH. A Meta-analysis of Studies Comparing Outcomes of Diverse Acellular Dermal Matrices for Implant-Based Breast Reconstruction. Ann Plast Surg. 2017 Jul;79(1):115-123. doi:10.1097/SAP.0000000000001085. PMID: 28509698.https://pubmed.ncbi.nlm.nih.gov/28509698/

Chang, E. I. & Liu, J. Prospective unbiased experience with three acellular dermal matrices in breast reconstruction. Journal of surgical oncology 116, 365-370, doi:10.1002/jso.24656 (2017). https://pubmed.ncbi.nlm.nih.gov/28444764/

Sobti N, Liao EC. Surgeon-Controlled Study and Meta-Analysis Comparing FlexHD and AlloDerm in Immediate Breast Reconstruction Outcomes. Plast Reconstr Surg. 2016 Nov;138(5):959-967. doi: 10.1097/PRS.0000000000002616. PMID: 27782982. https://pubmed.ncbi.nlm.nih.gov/27782982/

Therefore, on balance, the current evidence is not strong enough to suggest a significant difference between ADMs. And, with that, it is unclear why such a communication was warranted. In light of this lack of key data, ***we request, at a minimum, that the aforementioned studies (and resultant conclusions) be added to the communication.***

Given the aforementioned limitations, the information presented by the Agency provides a disservice to the public and especially to the women who have received and are receiving breast reconstruction with ADMs, given that the information (as acknowledged by the Agency) is not definitive, does not require immediate action, seems solely designed to promote its perspective conclusions, does not promote true informed consent, and fails to acknowledge the standard of care.

Not definitive. As the Agency acknowledges multiple times within the communication, the data related to whether ADMs may vary in safey is not definitive. As such, it is unclear why the FDA felt as if the information would be beneficial for women receiving post-mastectomy implant-based reconstruction and their health care providers. This is further confounded by the fact that the communication notes that it is possible to perform implant-based reconstruction without ADMs, but it fails to note that this requires a different surgical technique and its limitations and complications lead to the use of ADMs to overcome these challenges. And, as such, the overall end result of the procedure may vary, based on the surgical technique and not the ADM itself.

No immediate action. The information acknowledges that the "FDA does not recommend reoperation or removal of implanted ADM as a preventive measure." Rather, it seems solely to be designed to create unnecessary worry among women who have received or are receiving breast reconstructive procedures.

Fails to enhance informed consent. For all of the reasons outlined above, the recent FDA information fails to enhance informed consent. As previously indicated in our comments to the draft guidance document titled *Breast Implants - Certain Labeling Recommendations to Improve Patient Communication*, the AATB and the TPG support additional informed consent related both to the overall labeling for breast implants as well as communication related to other medical products,

including ADMs, which may be used in conjuction with breast implants. The final guidance notes the following, which is better than the communication because it acknowledges that the ADM use is tied to the surgical approach and ensures that the full context is provided:

> "My physician has discussed the potential use of other implanted products during my breast implant surgery. My physician has also discussed the risks and benefits of using these implanted products and their planned surgical approach."

Therefore, for any future communication with the public and the medical community, we hope that the Agency follows its guidance document and provides a more balanced approach related to informed consent for women receiving these procedures.

Standard of care. That balanced approach is particularly important, given the current use of human ADMs for breast implant-based reconstruction. Human ADMs were first described for use in breast surgery in 2001.[3] Since that time, the vast majority of breast-implant-based reconstructions utilize human ADMs. According to the American Society of Plastic Surgeons, of the approximately 101,657 breast reconstruction procedures performed by member surgeons in 2018, about 83,200 (roughly 82%) utilized tissue expanders or breast implants. Of these procedures, approximately 74% (61,713) utilized ADMs. Recognizing human ADMs as the proven standard of care, major U.S. payers (e.g. Anthem, CIGNA, Blue Cross Blue Shield, and Aetna) currently regard the use of acellular dermal matrix with breast reconstruction as a clinically supported and clearly reimbursable use, where the tissue assists the surgeons in reconstructing the breast at the time of mastectomy in a process that improves cosmetic outcome and limits the need for further surgical procedures.[4] For more information regarding the history of its use, please see our attached ADM primer.

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We hope that you will find this information useful in your deliberations, and we look forward to future conversations, as part of the upcoming Panel meeting on the topic or as a separate discussion, if the Agency would find that helpful. As previously noted, we are discouraged, especially with this Administration's mandate, that the scientific integrity of the data analysis was not maintained in this communication, and, as such, the communication did a disservice to the American public and especially to women who have received or are receiving reconstructive surgery, especially given that ADMs for implant-based breast reconstruction has become the standard of care. As such, we recommend that the FDA appropriately update your communication to include relevant, scientific information. The AATB and the TPG stand ready and willing to assist the FDA with its deliberations in any way that you deem appropriate.

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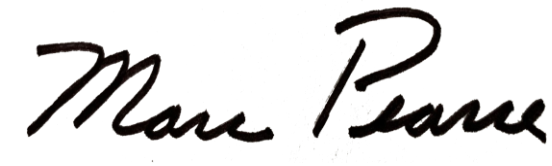
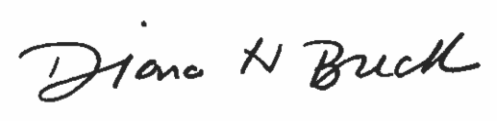
[3] Margulies I, Salzberg C. The use of acellular dermal matrix in breast reconstruction: evolution of technique over 2 decades. Gland Surgery 2019; 8(1):3-10.

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

Respectfully,





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Attachment: ADM primer