American Association of Tissue Banks® AATB TPG, LLC

September 6, 2022

Peter Marks, MD, PhD
Director
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

In Re: Lessons Learned from Recent Tissue Bank Submissions to the Tissue Reference Group

Submitted electronically via Peter.Marks@fda.hhs.gov

Dear Dr. Marks:

The American Association of Tissue Banks (AATB or Association) and the American Association of Tissue Bank's Tissue Policy Group, LLC (AATB TPG or TPG) submit these comments related to data regarding and lessons learned from recent tissue bank submissions to the Tissue Reference Group (TRG) in response to various payer and other entity requests for documentation of "proof" of 361 status, along with the history of such requests.

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

The AATB 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 policy in furtherance of the adoption of laws, regulations, and standards 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.

Recent History of Requests for Documentation of 361 Status

In the past several years, tissue banks have been asked by payers and other regulators (including the Defense Health Agency, Centers for Medicare and Medicaid Services, and the State of New York) to provide "proof" of 361 status for their allografts. Given that the Food and Drug Administration

(FDA or Agency) may not be aware of these requests, we first wanted to provide information regarding those requests.

Defense Health Agency

In November 2020, several tissue banks were individually contacted by the Defense Health Agency (DHA) Patient Safety Analysis Center, with a request for additional documentation from the FDA regarding all tissue products the tissue bank distributed to the DHA.[1] In light of various concerns with this new policy, in December 2020, the AATB sent a letter to the DHA, noting that the request to submit a Request for Designation (RFD)or TRG submission for all tissue products: (1) is contrary to the regulations detailed by the FDA, (2) will likely put an undue burden on the FDA, and (3) may result in loss of key health care resources for the military. In addition, the AATB sent an e-mail to Dr. Marks in December 2020, highlighting concerns and asking for a further conversation. On behalf of Dr. Marks, Ms. Maloney responded in January 2021, asking that the discussion occur as part of the FDA-AATB liaison meeting in May 2021. Later in January 2021, LTC Alexander Shilman, PharmD, BCPS, FISMP with the DHA responded to the AATB letter, noting communication with the FDA to ensure that it was not an undue burden while confirming that the requirement would still stand.[2]

During the May 2021 FDA-AATB liaison meeting, an AATB representative discussed the various requests from payers and others for documentation of 361 status, described the TPG's approach to the requests (including developing and sharing key templates for TRIP/TRG requests), and detailed ongoing concerns with the requests for documentation (e.g., additional burden on tissue banks and the FDA for paperwork that is not required by the FDA regulations and a lack of clarity whether additional payers or other organizations will make such requests). AATB requested that the FDA and AATB work together to streamline the requirements of the submissions to reduce the burden on tissue banks and the FDA. While there was a good discussion about the various submission processes, no further action occurred on the request. As such, tissue banks continued to submit documentation on certain products to comply with the DHA requirement, until May 2022, when the DHA notified individual tissue banks that the requirements had changed and the FDA documentation stating the regulatory status of the allograft was no longer required.[3]

New York State

In October 2020, the New York State Department of Health began sending letters to individual tissue banks noting that they would only receive provisional licenses until they received "documentation of FDA approval for such use, or documentation of a recommendation or designation by FDA that the tissue or cells is/are regulated solely under section 361 of the Public Health Service Act." In a follow-up conversation with Dr. Matthew Kohn and others in October 2020, they clarified that the key tissue products of concern were amnion (unless it was in sheet form) and umbilical cord tissue (unless it was used as a conduit). In January 2022, New York State Tissue Resource Program issued a policy reiterating concerns with these two product categories, noting the following:

> "Furthermore, the Department will not approve a license for the distribution or transplantation of umbilical cord tissue without documentation that:
>
> - FDA has approved its use;
> - An IND is in effect to test the umbilical product in clinical trials;

- FDA has determined or recommended that the product is regulated solely under section 361; or
- FDA amends its guidance or regulations.

Additionally, amniotic membrane products in formats other than a sheet of tissue may not be distributed or transplanted in NYS without the same documentation from FDA."

Since that policy announcement, New York State has clearly made it a priority to inspect tissue banks to ascertain whether this policy is being followed.

Centers for Medicare and Medicaid Services

Starting in January 2020, the Center for Medicare and Medicaid Services (CMS) started requiring certain FDA documentation[4] to support an application for an HCPCS code for "skin substitutes."[5] In addition, as part of the 2023 calendar year proposed rules for the (1) Medicare Physician Fee Schedule (PFS) and (2) the Hospital Outpatient Prospective Payment System (HOPPS) and Ambulatory Surgical Center (ASC) Payment System, CMS proposed that, by January 1, 2024, all "361" skin substitutes would be required to submit a TRG letter from the FDA to retain payment codes. Per the Current Procedural Terminology definition, skin substitutes include non-autologous skin (i.e., dermal or epidermal, cellular and acellular) grafts (e.g., homograft, allograft), non-human skin substitute grafts (i.e., xenograft), and biological products that form a sheet scaffolding for skin growth.[6] As a result, tissue banks have been complying with such requests.

Data Analysis of Tissue Bank Submissions to the TRG

As indicated in the attached tables [Table 1 related to requests submitted before March 31, 2021 to the TRG Rapid Inquiry Program or TRIPS; Table 2 related to requests subsequently submitted to the TRG], due to requirements from payers and others, several tissue banks within the TPG have opted to request TRIPS/TRG recommendations for products in which the tissue bank fully expected the Agency to determine that such products were, indeed, "361 HCT/Ps". As a result, a large number of submissions have occurred, and, as the chart indicates, ultimately, the FDA also agreed with the initial tissue bank assessment that the products were "361 HCT/Ps".

Average Length of Time Before Receiving Final TRG Recommendation

Per SOPP 8004 "[t]he TRG generally responds in writing to the inquirer within 60 days of receipt by the Executive Secretary of an inquiry that contains sufficient detail for evaluation." As noted in the attached tables, as expected, the average number of days before receiving a final determination from the TRG/TRIPS varied by the program utilized. Under TRIPS, the response was quicker (average of 47 days, with a range of 14 to 125 days) compared to the TRG response times (average of 140.7 days, with a range of 26 to 344 days.

Number and Types of Questions Asked by the TRG

Not surprisingly, if there were more questions asked of the tissue bank, then the time until receipt of the FDA determination was longer, given that the Agency needed additional information before considering the application complete. In reviewing the questions received by tissue banks and the

information on the Agency website related to TRG submissions,[1] it may be beneficial for the FDA to review this information and update to include:

- Submission of relevant instructions for use (IFUs),
- A table that provides information related to (1) common names, (2) proprietary names included as part of the Human Cell and Tissue Establishment Registration (HCTERS), and (3) relevant sizing.

Tissue Types

The most prevalent tissue type falling into this dataset included bone (N=17), and it has the most varied response time (average of 125 days, with a range of 14 to 344 days). See Table 3 for more information related to submissions by tissue type, compiled data for any tissue type in which there were four or more submissions by at least two tissue banks.

Fascia lata

In addition to the general data analysis, we also felt it would be helpful to highlight the Agency's varied approach for determining the homologous use of fascia lata.[2] As Table 3 indicates, there were five different submissions from tissue banks related to fascia lata. Two tissue banks received a TRIPS determination stating that allograft fascia lata "used for repair, reinforcement or supplemental support of soft tissue defects" was a 361 HCT/P, while yet another tissue bank was asked to resubmit the TRIPS response to the TRG and focus solely on utilizing fascia lata to support fascia lata, not all soft tissue defects. While tissue banks understand that the TRG determinations are not binding on the Agency, it would be beneficial if all of those determinations were at least consistent.

Other Lessons Learned

In examining the average review time of various tissue bank submissions, several tissue banks have noted that, in hindsight, they would have submitted fewer tissue types in each submission, maintained more consistent language through the submission (e.g., if the homologous use related to support, then maintaining such language through the document), and taken advantage of the

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[1] To facilitate review of your inquiry by the TRG, you may want to include the following:

- Your name and contact information, and if applicable, the name and contact information of the party you represent
- Manufacturer of product
- The way the product is to be used
- Source of the product
- A clear, step by step, description of how the product is processed from the time of recovery to the point of use

https://www.fda.gov/vaccines-blood-biologics/tissue-tissue-products/tissue-reference-group

[2] As part of the final guidance titled *Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use*, Example 17-2 focuses on the homologous use of pericardium. As the FDA acknowledged in Example 10-3, the homologous use of fascia lata is to cover muscle and aid in movement. While pericardium covers the heart, Example 17-2 notes that a homologous use for pericardium would be to cover dura mater defects. Thus, it is unclear why the FDA limited the homologous use of fascia lata to only covering fascia lata and not other soft tissue defects.

Example 17-2: Pericardium is intended to be used as a wound covering for dura mater defects. This is homologous use because the pericardium is intended to serve as a covering in the recipient, which is one of the basic functions it performs in the donor.

TRIPS program (given the speedier responses).

Opportunity for Education

The goal of this letter is to provide a particular perspective of several tissue banks' experience with the TRG process and to, hopefully, share some lessons learned through the process. The AATB and the TPG stand ready to assist the FDA with any additional information about the TRG process or tissue banking in general.

Summary of Recommendations for the FDA

As previously noted, this learning experience resulted in key recommendations for both the Agency and tissue banks. With respect to the FDA, we recommend that the FDA:

- Update the TRG submission process to explicitly mention the inclusion of
    - Instructions for use (IFUs),
    - A table that provides information related to
        - common names,
        - proprietary names included as part of the Human Cell and Tissue Establishment Registration (HCTERS), and
        - relevant sizing.
- Provide more consistency in the TRG recommendations, especially in light of fascia lata, and
- Utilize the AATB more for educational opportunities.

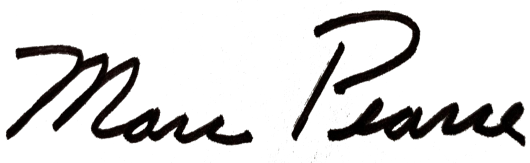
Summary of Recommendations for tissue banks

With respect to tissue banks, we advise our member banks to

- Submit fewer tissue types in each TRG application;
- Use language consistently within the TRG process; and
- When submitting to the TRG, include:
    - Relevant instructions for use (IFUs),
    - A table that provides information related to (1) common names, (2) proprietary names included as part of the Human Cell and Tissue Establishment Registration (HCTERS), and (3) relevant sizing.

We hope that you will find this information useful in your deliberations and as you continue to review and improve the TRG process. The AATB and the TPG stand ready and willing to assist the FDA in any way that you deem appropriate.

Respectfully,



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

Joe Yaccarino
Chair
Tissue Policy Group

Attachment: Tables

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[1] Dear Manufacturer,

The Defense Health Agency (DHA) is reaching out to you as a manufacturer of biological product(s) used in the Military Health System. We would like to verify that the specific product(s) listed below meet(s) the U.S. Food and Drug Administration's (FDA) regulatory requirements. We request that you provide specific legal authority under which the product(s) in question is/are marketed, and one or more of the following documents for the specific product(s) currently marketed and sold to the Military Health System.

Specific Product(s) List: [Redacted]

Document List (any or all that are applicable):
(i) A written response from the Tissue Reference Group (TRG), (ii) the TRG rapid inquiry program (TRIP), (iii) the Office of Combination Products (OCP) in either a response to a Request for Designation (RFD) or pre-RFD, (iv) other written communication from FDA indicating that your product is legally on the market under an approved biologics license application (BLA), premarket approval application (PMA), or (v) FDA device clearance (510k).

We understand that registration in the electronic Human Cell and Tissue Establishment Registration System (eHCTERS) is not an FDA product classification recommendation or determination. It is also not a reflection of compliance and inclusion of this document will not be sufficient proof to satisfy our internal verification process. Your prompt response to the requested documents will facilitate verification process and quicker product authorization in Military Health System.

Sincerely,

DHA Patient Safety

The TRG is the 'Tissue Reference Group'. Information on how to request a recommendation from the TRG can be found at: https://www.fda.gov/vaccines-blood-biologics/tissue-tissue-products/tissue-reference-group

The TRIP is the 'TRG rapid inquiry program'. This is a temporary program that expires March 31, 2020. Information on how to make inquires to this program can be found at: https://www.fda.gov/vaccines-blood-biologics/trg-rapid-inquiry-program-trip

The pre-RFD and RFD process are administered by FDA's Office of Combination Products. The Request for Designation (RFD) process is a formal determination, the pre-RFD is an informal inquiry. For information on the two processes and requirements for submission see: https://www.fda.gov/combination-products/rfd-process
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Patient Safety Analysis Center
Patient Safety Program, Clinical Support Division
Defense Health Agency
7700 Arlington Boulevard
Falls Church, VA

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[2] Thank you for the letter, we appreciate the interest and the input from you and your organization.

I would like to help clarify the Defense Health Agency (DHA) policy regarding Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps).

We have been, and continue to be, in close contact with officials at the Food and Drug Administration (FDA)'s Center for Biologics Evaluation and Research (CBER). While the FDA requires that HCT/Ps meet the requirements in Section 361 of the Public Health and Safety (PHS) Act, there is no specific process for providers or health systems to ensure that the manufacturer is actually meeting this legal requirement. We are aware of examples where they clearly do not. The work we are doing with officials at FDA's CBER is to establish a simple process for manufacturers to quickly receive confirmation that they are meeting the legal intent.

Also, these FDA CBER officials have assured us that this process that they recommended is not causing them any undue burden. I'd ask that if you hear something differently when you speak with individuals at CBER, please let us know.

We are acutely aware that this process has some risks associated with it. But we also are aware that not doing this type of verification, to ensure these products meet federal legal requirements, may also cause harm to our patients. We believe our policy adequately considers both.

Again, thank you for your communication, and we look forward to continue working with you. Please let us know if you have any questions.

LTC Alexander Shilman, PharmD, BCPS, FISMP
Medication and Health IT Safety Officer
DHA Patient Safety Program and MEDCOM QS
JBSA-Ft. Sam Houston, TX 78234
Contact on MSTeams: alexander.s.shilman.mil@cvr.mil

[3] Recently, the DHA has revised the requirements for HCTP tissue based products. We no longer require prior approval through the Centers of Biologics from manufacturers.

DHA will allow our surgeons to use their clinical judgement with a few stipulations.

- All products must be registered as HCTPs with the FDA
- Manufacturers must not have an FDA warning letter with no closeout letter.
- Products must be marketed legally. If you have a product that is an HCTP, but injectable, then the requirement for a 351 must be met with the FDA.

Please let me know if you have any further questions.
Brenda

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[4] After review of FDA's guidance, it does not appear to CMS that [insert name of product] is suitable for registration as an HCT/P. CMS refers the applicant to the FDA's Tissue Reference Group or the Office of Combination Products to obtain written feedback regarding how the product is

appropriately regulated. After obtaining the FDA's written feedback, the applicant is welcome to submit a complete HCPCS code application in a subsequent coding cycle.
Information for submitting questions to the TRG is located at:
https://www.fda.gov/vaccines-blood-biologics/tissue-tissue-products/tissue-reference-group

[5] See https://www.cms.gov/files/document/2020-hcpcs-application-summary-quarter-1-2020-drugs-and-biologicals-updated-04142020.pdf for information related to CMS' information from January 2020.

[6] See https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleId=57680&ver=7.

Table 1. TRIP Submissions (before March 31, 2021)

Tissue Bank	Inquiry #	Product Covered	Submission and Response Dates	# of days before receiving final TRG recommendation[1]	# of Questions before receiving final TRG recommendation	Questions Received	361 HCT/P?
A	1	Tendon/ Ligament	1/26/21– 2/12/21	17	0	n/a	Yes
	2	Fascia Lata	3/10/21 – 5/26/21	77	0	n/a	Yes
	3	Amniotic membrane	3/22/21 – 6/4/21	74	0	n/a	Yes
B	1	Amniotic membrane with chorion	12/22/20 –1/5/21	14	Unknown		Yes
	2	Amniotic membrane dual layer	2/12/21 – 4/7/21	54	Unknown		Yes
	3	Amniotic membrane	2/12/21 – 4/7/21	54	Unknown		Yes
	4	Cryoskin	3/23/21 – 4/7/21	15	Unknown		Yes
	5	Bone particulate and microparticulate	3/30/21 – 8/1/21	124	Unknown		Unable to determine[2]
	6	Umbilical cord and amniotic membrane cryopreserved	3/31/21 – 8/3/21	125	Unknown		Yes
	7	Dermal matrix	3/31/21 – 5/17/21	47	Unknown		Yes
	8	Fascia lata	3/31/21 – 5/17/21	47	Unknown		Unable to determine[2]
	9	Tendon	3/31/21 – 5/17/21	40	Unknown		Unable to determine[2]
	10	Bone fibers	3/31/21 – 5/17/21	47	Unknown		Yes
C	1	Demineralized particulate bone with mineralized particulate; Corticocancellous	4/9/2020 –4/23/2020	14	1	Please confirm whether, for any of these four products, human cells or tissue from two or more donors are pooled (placed in physical contact or mixed in a single receptacle) during manufacturing.	Yes
	2	Demineralized particulate bone	4/9/2020 – 4/23/2020	14	1	See above.	Yes
	3	Mineralized particulate bone	4/9/2020 – 4/23/2020	14	1	See above.	Yes
	4	Cryopreserved pulmonary artery patches	4/27/2020 – 6/11/2020	45	1	See above.	Yes
	5	Cryopreserved aortic and pulmonary heart valves	4/27/2020 – 6/11/2020	45	0	n/a	Yes
	6	Fascia lata	4/27/2020 – 6/11/2020	45	2	(1) Please describe how Fascia Lata may be used as a "Supplemental covering for soft tissue repairs, such as the rotator cuff, ACL and PCL." (2) Components of detergent solution	Yes
	7	Pericardium	4/27/2020 – 6/11/2020	45	1	Components of detergent solution	Yes
	8	Meniscus	5/1/2020 – 6/11/2020	41	0	n/a	Yes
	9	Ligaments	5/1/2020- 6/11/2020	41	0	n/a	Yes
	10	Tendons	5/1/2020 – 6/11/2020	41	0	n/a	Yes
				47 (14-125)			

[1] Utilized the following website to obtain this information: https://www.timeanddate.com/date/duration.html.

[2] Tissue bank opted to subsequently submit a TRG inquiry.

Table 2. TRG Submissions (after March 31, 2021)

Tissue Bank	Inquiry #	Product Covered	Submission and Response Dates	# of days before receiving final TRG recommendation[1]	# of Questions before receiving final TRG recommendation	Questions Received	361 HCT/P?
A	4	Mineralized bone[3]	3/10/21 – 7/22/21	134	0	n/a	Yes
	5	Bone and cartilage[3]	3/15/21 – 10/7/21	211	2	(1) Whether certain products (providing proprietary names) are included within the submission (2) Whether a certain product type should be included within the submission	Yes
	6	Demineralized bone[3]	3/19/21 – 1/21/22	308	1	Questions related to the hydration solution	Yes
	7	Skin/dermis[3]	3/15/21 – 1/21/22	312	4	(1) Question related to antimicrobial solution and disinfection and sizing information (2) Soaking in ethanol solution and request for IFUs (3) Time that the ADMs soaked in ethanol had been on the market (4) For the "A" in ADM, does it stand for allograft or acellular?	Yes
B	11	Cartilage in saline	4/9/21 – 5/19/21	26	Unknown		Yes
	12	Frozen bone, freeze-dried bone and sheets	4/19/21 – 5/19/21	30	Unknown		Yes
	13	Demineralized cortical strips	5/4/21 – 6/8/21	35	Unknown		Yes
	14	Tendon	5/28/21 – 8/9/21	73	Unknown		Yes
	15	Fascia lata	6/25/21 – 9/3/21	97	Unknown		Yes
	16	Bone particulate	9/3/21 – 12/22/21	110	Unknown		Yes
C	11	Demineralized fiber bone	1/6/22 – 4/22/22	106	1	Confirming composition	Yes
	12	Demineralized fiber strip	1/6/22 – 4/22/22	106	0		Yes
	13	Placental membrane	6/9/22 – 8/2/22	54	0		Yes
D	1	Demineralized bone	7/20/21-6/7/22	322	6	(1) List of product(s), specifically by name, under each proprietary name included in the submission (2) Clarify which products were "Demineralized Bone" or "Demineralized Bone Matrix (Not Combined with Any Other Component." Also, for each of the specific product names in the previous response, they requested that we associate the common name (chips, cubes, crushed, etc.) in another column on the table. (3) Clarification on spelling of one proprietary name, inclusion of other proprietary names, and questions on common names. (4) IFUs for select products (5) More IFUs (6) Additional clarification on proprietary and common names	Yes

[3] Note: This request was initially submitted to TRIPS, but given that a response had not been received by March 31, 2021, it was referred to the TRG.

Tissue Bank	Inquiry #	Product Covered	Submission and Response Dates	# of days before receiving final TRG recommendation[1]	# of Questions before receiving final TRG recommendation	Questions Received	361 HCT/P?
	2	Fascia	7/20/21-12/7/21	149	1	Request for size ranges and associated proprietary names	Yes
	3	Mineralized bone	7/20/21-6/29/22	344	3	(1) Correlation of proprietary and common names (2) Additional common name clarification (3) Additional proprietary name clarification	Yes
	4	OA-Cartilage	7/20/21-12/7/21	149	0		Yes
	5	Skin	7/20/21-12/7/21	149	0		Yes
	6	Tendon/ ligament	3/30/21-6/19/21	81	0		Yes
E	1	Tendons/ ligament	2/2/2022-4/22/2022	79	0	n/a	Yes
	2	Mineralized bone	3/9/2022-6/29/2022	112	0	n/a	Yes
	3	Demineralized bone	3/11/2022-6/29/2022	110	0	n/a	Yes
				140.7 (26-344)			

Table 3. Analysis by Tissue Type

Tissue Type	# of Submissions	Average Response Time (in days)	Range (in days)
Bone	17	125.9	14 - 344
Tendon/Ligament	7	53.1	17-81
Fascia lata	5	83.0	45-149
Amniotic membrane	6	62.5	14-125
Skin	4	130.8	15-312