



American Association of Tissue Banks® AATB TPG, LLC

October 5, 2021

Judith McMeekin, Pharm.D.
Associate Commissioner for Regulatory Affairs
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

In Re: Special Consideration for HCT/Ps receiving a BLA

Submitted via e-mail to Judith.McMeekin@fda.hhs.gov

Dear Dr. McMeekin:

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 requesting special consideration by the Food and Drug Administration (FDA or Agency) for human cells, tissues, and cellular and tissue-based products (HCT/Ps) that may require a Biologics License Application (BLA).

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

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

As discussed during the AATB-FDA liaison meeting with the Center for Biologics Evaluation and Research (CBER) in May 2021, the AATB and the TPG seek additional clarity regarding how the Agency intends to impose certain regulatory requirements for HCT/Ps that may require a BLA and continue to seek special consideration. While we still believe a joint working group to include representatives from both CBER and the Center for Devices and Radiological Health (CDRH), at a minimum, to better define the risk continuum between a 361 HCT/P and a BLA would be beneficial, in the interim, we have copied the respective heads of those centers on this letter to provide some potential areas of discussion and initial recommendations. Given the need for cross-center dialogue and the focus on special consideration, we are addressing these comments to the Office of

Regulatory Affairs. Specifically, we want to highlight six key areas for future collaboration: pooling, retention samples, sterility testing, potency testing, identify, and required clinical studies.

Pooling. We recognize the limitation detailed under 21 CFR 1271.220(b), which states that “[h]uman cells or tissue from two or more donors must not be pooled (placed in physical contact or mixed in a single receptacle) during manufacturing.” We understand the concerns that resulted in the implementation of this regulation, however, in certain cases, the benefit of patient access to pooled product may outweigh the risk of pooling. Regulations currently allow for an exemption or alternative granted by the Director of CBER. Considering advancements in donor screening and testing processes, traceability controls, and digital records, risks associated with pooling may be minimized to safe thresholds in certain cases. Additionally, industry wide bioburden controls have been shown effective in reducing bacterial transmission. Furthermore, many products are terminally sterilized providing a level of viral inactivation for increased risk reduction. While we recognize FDA’s resource constraints, especially during the current pandemic, we ask that ***FDA develop a guidance or frequently asked questions (FAQs) related to the FDA’s expectations for pooling risk/benefit analyses and a risk management framework for HCT/Ps requiring a BLA.*** We can confirm that tissue banks would be interested in contributing to this effort if the FDA wishes to engage industry in this activity.

Retention samples. Currently, with pooling restrictions, section 351 and 361 HCT/Ps are produced in single donor lots. This results in a limited amount of product available from each lot for release testing, retains, and patient use. With the additional requirements for release testing and retains for Section 351 products, the amount of product available for patient access can be significantly reduced, and in some cases, would not be feasible in terms of product production. We are aware of CBER suggesting options, such as using process by-products to meet testing and retain requirements, but this may not be acceptable in many cases. With pooled product, lots sizes would be larger and more product from each lot would be available for release testing, retains, and distribution for patient access. Without the option of pooling, for some 351 HCT/Ps, the amount of product required for testing and retains can be prohibitive, reducing the amount of product available for patients to an unacceptable level. ***We recommend FDA establish a framework for pooling that allows processors to meet standard testing and retains requirements with sufficient additional product available for patient use.***

Sterility testing. The AATB and the TPG are heartened by the flexibility provided under 21 CFR 610.12(h)(2) that states: *A manufacturer is not required to comply with the sterility test requirements if the Director of the Center for Biologics Evaluation and Research or the Director of the Center for Drug Evaluation and Research, as appropriate, determines that data submitted in the biologics license application or supplement adequately establish that the route of administration, **the method of preparation, or any other aspect of the product** precludes or does not necessitate a sterility test to assure the safety, purity, and potency of the product.* (emphasis added) In light of that flexibility, ***we urge the FDA to clarify that any HCT/P that has been terminally sterilized to a validated Sterility Assurance Level (SAL) of 10⁻⁶ in conformity with ISO 11137 Parts 1 & 2 “Radiation Sterilization of Healthcare Products” would not require sterility testing on individual lots.*** We recommend this clarification based upon current consensus standards, the mathematical limitation of sterility testing of a terminally sterilized product, potential for inaccurate results due to cross-

contamination, and greater harmonization of requirements across Centers within the FDA.

Consensus standards. Our recommendation is consistent with FDA [consensus standards](#) (namely, recognition numbers 14-528 and 14-409), and as such, validations conducted in accordance with these recognized standards and the ongoing dose verifications are sufficient to meet the requirement of safety with respect to microbial contamination. Further, as defined in the [consensus standards](#) developed by the International Standards Organization (ISO), “sterilization is a process used in manufacturing for which the results and effectiveness cannot be fully verified by subsequent inspection and testing of the product.”

Mathematical limitation. The regulatory requirement to label a product sterile is based upon a validated SAL, not one-off testing or testing of small sample numbers. Performing endpoint sterility testing is not a valid test because the product has been validated, after sterilization, to have the probability of one viable microorganism in 1,000,000 products. As such, it is neither reasonable to test over 1,000,000 products nor is it reasonable to test a small number of products and consider that to be representative of an entire manufacturing lot to demonstrate sterility. The FDA’s final [guidance](#) titled *Sterile Drug Products Produced by Aseptic Processing —Current Good Manufacturing Practice* states in section XI.B that “sterility tests are limited in their ability to detect contamination because of the small sample size typically used . . . the USP<71> sterility test sampling plan only enables the detection of contamination in a lot in which 10% of the units are contaminated . . . in a 10,000-unit lot with a 0.1% contamination level, sterility tested 20 units, there is a 98% chance that the batch would pass.” As applied to terminal sterilization, where there is a 10^{-6} SAL (or a one-in-a-million chance of a surviving microorganism), it is mathematically apparent that any USP <71> sterility test would be useless in detecting a nonsterile unit.

Inaccurate results due to cross-contamination. One of the problems associated with sterility testing is contamination of the test by nonproduct related microorganisms that could originate from the environment, the person performing the culture or the person performing the microbiological tests. The process of performing sterility testing requires removal of the product from the package and aseptically transferring the allograft into a culture medium. USP <1211> describes a typical contamination rate for sterility testing of 0.1%, or 1 per 1,000 samples. This level is likely to increase as the size, complexity, and manipulation of test articles increase. For example, a study by Odlaug et al.¹ found that false positive rates for sterility testing may range up to 2%. Because of the complexities of product sterility testing, the risk of contamination during the test presents a significant risk of failure of the sterility test, thereby resulting in a sterilization process being identified as “failed” when the process parameters meet the validated condition, and the failing test is an environmental or personnel contaminant.

Harmonization of requirements. Clarifying this policy with respect to the results of a sterilization validation performed in accordance with ISO 11137 will harmonize expectations between CDRH and CBER. CDRH has a long history of accepting ISO 11137 validations for all product classifications and the corresponding SAL to demonstrate sterility and thus not requiring any end point sterility testing per USP <71> post sterilization. This approach for devices should be readily accepted for

¹ Odlaug TE, Ocwieja DA, Purohit KS, Riley RM, Young WE. Sterility assurance for terminally sterilized products without end-product sterility testing. *J Parenter Sci Technol.* 1984 Jul-Aug;38(4):141-7. PMID: 6491857.

351 HCT/Ps as the risk profile of a permanent implant is the same regardless of classification or Center responsible for its premarket approval. Thus, in a risk-based framework, a validation conducted in compliance with ISO 11137 sufficiently mitigates the risk and is consistent with ISO 14971, "Risk Management," international standards can play a significant role in risk management by providing requirements for the safety of products or processes. Thus, as described in ISO 14971, conformance to recognized international standards is a valid approach to adequately reducing risk as low as reasonably possible, mitigating the hazard and avoiding patient harm.

Potency testing. When describing the potency testing requirements for BLA products, representatives for CBER have stated that ideally, a potency assay will represent the product's mechanism of action (MOA), which may be very complex. Further, bioassays may be time consuming, expensive, and have variability. Sometimes a single assay alone is not sufficient, and the MOA may never be known. The development of a bioassay is an iterative process. A successful potency assay is based on what FDA thinks is a reasonable MOA proposal. Despite best efforts, often, the package insert for an approved biologic will indicate that the the MOA has not been identified or is unknown. While the determination of the MOA is not a requirement, a final potency test is required, but the potency test, in effect, relies in part in determining the MOA. Additionally, the potency test must be developed and validated in concert with other tests and studies (e.g., stability studies, lot release studies, and comparability). In light of this interactive and iterative process, it would be helpful to receive a decision from CBER related to the adequacy of a product's potency assessment as early in the BLA process as possible. ***We ask that CBER develop additional guidance related to best practices for potency assessment development and commit to earlier and frequent interaction with Sponsors to provide constructive feedback and confirmation of appropriate potency activities and decisions.***

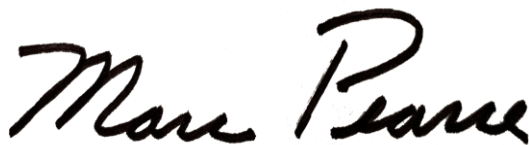
Identity. 21 CFR 610.14 Identity addresses the requirements for identity testing of the contents of a final container of each filling of each lot of Section 351 products. Identity may be established through various methods, including physical or chemical characteristics of the product. It is understood that the Identity requirements for a Section 351 product are in addition to the special controls applicable for Section 361 products in 21 CFR 250, 270 and 290, for Labeling, Records, and Tracking. Given the ambiguity regarding what additional identity tests would be relevant for HCT/Ps, which have much different physical and chemical characteristics than the products defined as Biological products in 21 CFR 600.3 (*any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man*), ***we ask that CBER develop additional guidance related to best practices for HCT/P Identity test requirements and commit to earlier and frequent interaction with Sponsors to provide constructive feedback and confirmation of appropriate Identity testing activities and decisions.***

Required clinical studies. In the FDA's 1998 guidance titled *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, the FDA notes that "[t]he usual requirement for more than one adequate and well-controlled investigation reflects the need for independent substantiation of experimental results. A single clinical experimental finding of efficacy, unsupported by other independent evidence, has not usually been considered adequate scientific support for a conclusion of effectiveness." Especially for products which may have been on the market prior to the close of the recent enforcement discretionary period and for products in which

there are minor differences between the HCT/P as a BLA versus a 361 HCT/P, ***we urge the Agency to consider the body of evidence in totality so that any required prospective clinical trials are narrowly focused*** on the key evidence gaps. We appreciate that the Agency has taken a similar tact with the recent approval of [STRATAGRAFT](#), and we urge the Agency to continue this approach. The Agency has made significant strides in providing guidance for use of real-world evidence to support regulatory decision making; we recommend further collaboration with industry to tease out the nuances of real world data available for human tissues previously marketed solely for homologous uses (361 HCT/Ps).

We hope that you will find this information useful in your deliberations. To ensure continued dialogue and progress on these key issues, ***we request a virtual meeting to further discuss next steps and ways to address these key issues.*** In particular, we are interested in making progress with respect to the inter-related topics of pooling, retention samples, and sterility. The AATB and the TPG stand ready and willing to assist the FDA with its deliberations in any way that you deem appropriate.

Respectfully,



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President & CEO
American Association of Tissue Banks



Joe Yaccarino
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Cc: Peter Marks, M.D., Ph.D.; Jeffrey Shuren, M.D., J.D.