American Association of Tissue Banks®

March 7, 2025

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

Julie Tierney, JD
Deputy Center Director
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Dear Dr. Marks and Ms. Tierney,

The American Association of Tissue Banks (AATB) writes to thank you for the invitation to present at the February 25, 2025, workshop on "Cell Therapies and Tissue-Based Products: A Public Workshop on Generating Scientific Evidence to Facilitate Development," and in particular during "Session 5: Considerations for a Revised Risk-Based HCT/P Framework." As you know, AATB is a professional, non-profit, scientific, and educational organization, and is the only national tissue banking organization in the United States. AATB's membership totals more than 120 accredited tissue banks and over 7,000 individual members. The overwhelming majority of the human tissue distributed for transplants comes from AATB-accredited tissue banks.

AATB and our members have been thinking about a revised risk-based framework for HCT/Ps for many years. We believe such a framework has the potential to:

1. Increase the development of lower risk, innovative HCT/Ps human cells, tissues, and cellular and tissue-based products (HCT/Ps);
2. Reduce the cost and regulatory burden associated with the Biologics Licensing Application (BLA);
3. Increase the number of acceptable claims or approved intended uses for certain products; and
4. Potentially help facilitate reimbursement.

There are also potential benefits to the FDA, including a more efficient review process that requires less staff time compared to the BLA process.

As Ms. Tierney and Dr. Melissa Greenwald, AATB's Chief Medical Officer, discussed during the session, there are three main regulatory pathways currently utilized for HCT/Ps (not including those that are also regulated as drugs). Some products are regulated by the Center for Biologics Evaluation and Research (CBER) solely under 21 CFR Part 1271 and Section 361 of the Public Health Service Act ("361 HCT/Ps"). Some are regulated by CBER under both the 1271 regulations and Section 351 of the Public Health Service Act ("351 HCT/Ps"). Finally, others are regulated by the Center for Device and Radiological Health (CDRH) as devices in instances where the claims sought meet the definition of a device. In general, we think the pathways for 361 HCT/Ps and CDRH-regulated device HCT/Ps are working well, and we therefore recommend FDA leave those as they are.

However, within the 351 category, the regulatory burden does not always reflect the complexity or risk associated with a product. For example, an amnion-derived tissue product that is intended for use as a

"barrier" or "covering" for a wound might be regulated as a 361 HCT/P. However, that very same product for use to aid in healing the same wound would be considered a 351 HCT/P because "wound healing" is not a homologous use according to FDA guidance. As a result, the sponsor of the amnion product used as a "barrier" would be able to market their product without premarket review by the FDA, while the sponsor of the product for "wound healing" must spend years and millions of dollars to go through the BLA process for FDA approval of their product. In an ideal world, the differences in regulatory requirements would be less dramatic for similarly situated products, and the cost of bringing a product to market would scale up depending on the risk/benefit profile of the product.

In developing a new risk-based framework, we recommend FDA focus solely on products regulated as 351 HCT/Ps, and develop a less burdensome process to more expeditiously review low- and medium-risk 351 HCT/Ps. The requirements for low-risk 351 HCT/Ps could be commensurate with what is required for products that go through the 510(k) process, and the requirements for medium-risk 351 HCT/Ps could be commensurate with what is required of products that go through the premarket approval (PMA) process. Currently, 361 HCT/Ps are required to be manufactured following Good Tissue Practice (GTP), while 351 HCT/Ps are manufactured under Good Manufacturing Practice (GMP). We think that low- and medium-risk 351 HCT/Ps in an alternative pathway could be required to be manufactured under GTPs with additional special controls, depending on which category they fall into. Notably, we do not think they should necessarily require following Good Manufacturing Practice.

One category of tissue products that could fit in a low-risk 351 category would be those that are minimally manipulated but for nonhomologous use, and that have preclinical or real-world evidence of safety. For example, an epidermal or amniotic tissue graft with an intended use for wound healing; or a dermal or epidermal graft with an intended use to reduce pain. We understand the FDA will require evidence of safety and efficacy in any products being reviewed under an alternative pathway, but the agency could reduce the burden for such evaluations. Examples include providing for a more tailored approach to pre-clinical requirements for minimally manipulated tissues that have already been used in humans and the clinical claim (e.g., wound healing) requires data, and by allowing sponsors to submit smaller or fewer clinical studies for approval of such products.

A medium-risk 351 category could include tissues for homologous use, combined with another article that raises moderate safety concerns. A second example may be products that are more than minimally manipulated and for nonhomologous use that would also fit in this category. For example, a more than minimally manipulated tissue epidermal or amniotic tissue graft with an intended use for wound healing. As previously stated for the low-risk 351 category, we understand FDA will also require evidence of safety and efficacy for these products. For such medium-risk products, we think there could be a review process with data requirements that are "PMA-like," requiring less evidence than a standard BLA submission. Examples include requiring fewer or smaller clinical trials, and potentially requiring manufacturers to follow GTP instead of, or in addition to, selected aspects of GMP. Regardless of how FDA structures the intermediate pathway, we would like to emphasize the need for regulatory predictability, where companies could have a reasonable expectation of how a product will be regulated before investing in its development.

For example, if the FDA were to establish an intermediate pathway that considers safety concerns as part of the criteria for determining which category a product would fall into, it is important that sponsors should have an understanding up front of what and how the agency considers such safety concerns. Sponsors should also have a clear understanding of the type of evidence that will be required for each pathway, so that they can better determine how much time and money to budget for the

process. Furthermore, faster response times from the FDA Office of Combination Products and Tissue Reference Group, and improvements to the Request for Designation (RFD) and pre-RFD processes would also help provide needed clarity.

Another aspect of regulatory predictability comes from how the new pathway is implemented. While FDA has several implementation options at its disposal, our preference is for rulemaking with notice-and-comment, supported by guidance documents, as necessary. This will allow stakeholders the opportunity to provide feedback and raise concerns the agency may not have considered, and ensure an appropriate balance between safety, access, and innovation. Ideally, any supporting guidance documents would be published initially in draft form for the same reasons already discussed. Legislation would be our secondary preference, as we believe FDA already has the authority to establish alternative pathways and can do so in a more expeditious manner.

There are some potential challenges we already know that FDA and stakeholders will need to address for 351 products falling into low- and medium-risk categories. Among those questions:

1. How to address purity, potency, and identity for small batch human tissue products?
2. How large should safety studies be?
3. How should donor variability be considered in the context of these products?

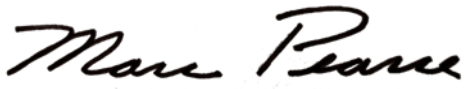
AATB has decided not to comment on how cells and secretions/extracts fit into alternative pathways, but we are aware that an intermediate pathway likely needs to account for those products.

In conclusion, AATB reiterates our appreciation for the opportunity to present during this workshop, and we enthusiastically support the FDA's efforts to establish a revised risk-based framework for certain 351 HCT/Ps. In establishing these pathways, we hope FDA will consider and optimize for:

1. Aligning regulatory burden and the cost of bringing a product to market with the complexity and risk of the product;
2. Balancing both competition and manufacturer differentiation with protection of intellectual property for innovative companies;
3. Ensuring regulatory predictability; and
4. Allowing manufacturers to obtain new claims or indications for products in a less burdensome manner.

We look forward to working with the agency and other stakeholders to develop and implement this framework, and we are eager to learn more about the agency's thinking on this subject.

Respectfully,



Marc Pearce
President & CEO
American Association of Tissue Banks

Considerations for a Revised Risk-Based HCT/P Framework

Melissa Greenwald, MD, FAST

Chief Medical Officer, American Association of Tissue Banks (AATB)

Benefits of Alternative Pathway(s)

Benefits to Industry

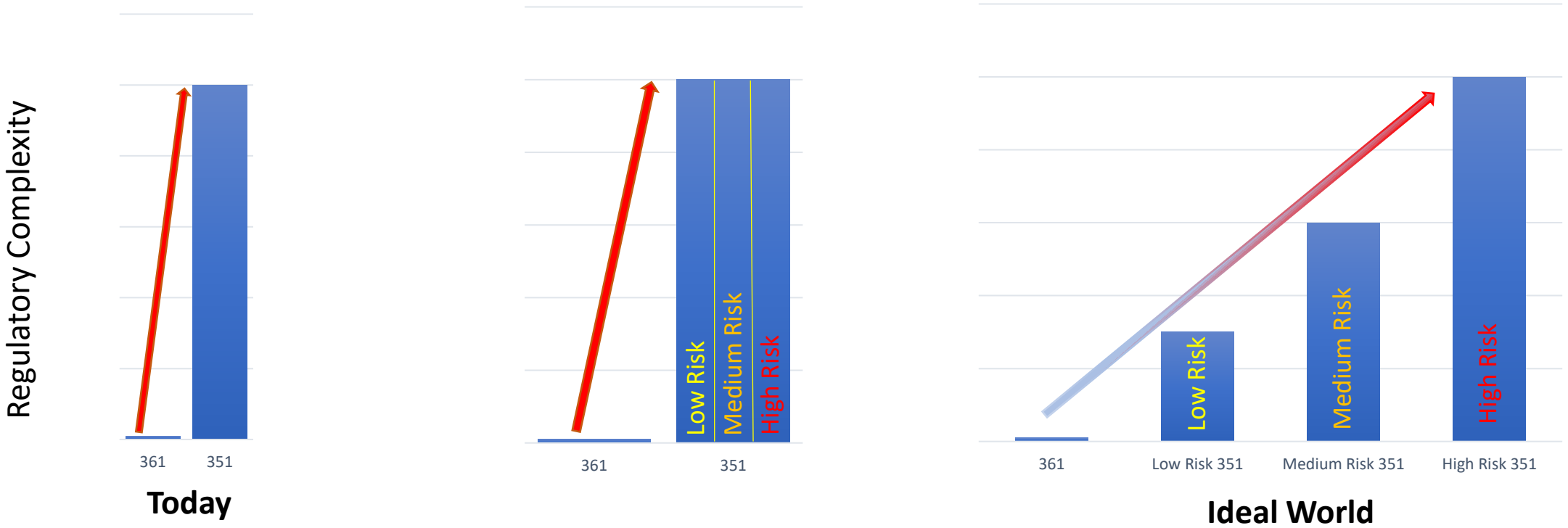
- Incentivize the development of lower risk but potentially impactful, innovative human cells, tissues, and cellular and tissue-based products (or “HCT/Ps”);
- Reduce the cost and regulatory burden associated with the Biologics License Application (BLA);
- Increase the number of acceptable claims or approved intended uses for certain products; and
- Potentially help facilitate reimbursement.

Benefits to FDA

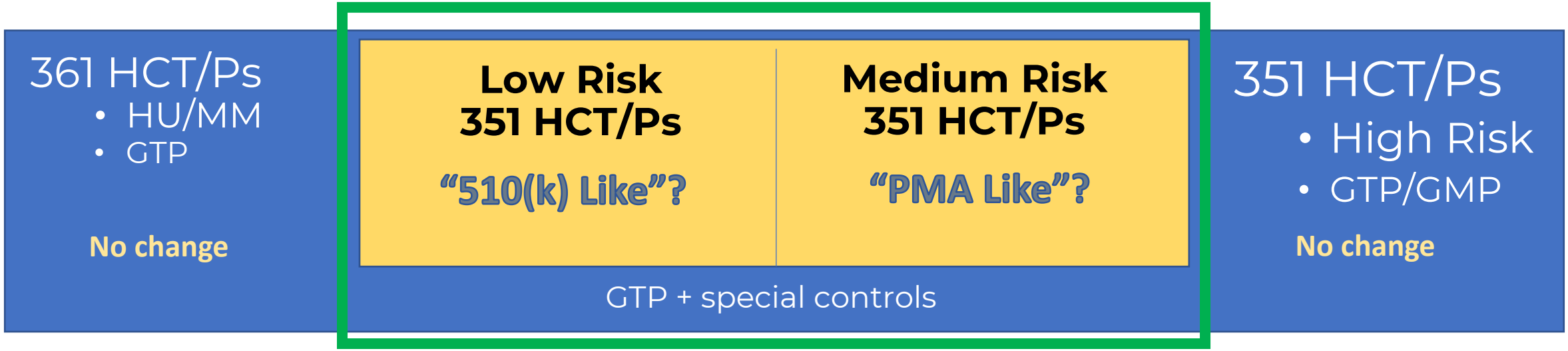
- Improved efficiency: BLA process requires more FDA staff time.

Alternative Pathways for Lower Risk 351 HCT/Ps

- Regulatory Complexity Should Align with Risk:



CBER Potential Regulatory Pathways



- What types of products should be in each box?
- What are the appropriate pre-market requirements for each category of products?

Low Risk “351” Tissue Products

- Possible examples:
  - Minimally manipulated tissue products for nonhomologous use that have preclinical or real-world evidence of safety
    - Epidermal or amniotic tissue graft with an objective intent for wound healing
    - Dermal or epidermal graft with an objective intent to reduce pain in the recipient
- Approval Process:
  - 510(k)-like process?
  - Evidence of safety and (depending on the claim/indication) efficacy?
    - Smaller or fewer clinical studies?
    - More tailored pre-clinical requirements for minimally manipulated tissues that have already been used in humans where the clinical claim (e.g., wound healing) requires data
  - Good Tissue Practice

Medium Risk “351” Tissue Products

- Possible examples:
  - HCT/P for homologous use that includes combination with another article that raises moderate safety concerns
  - More than minimally manipulated HCT/P for nonhomologous use
- Approval Process:
  - PMA-like process?
  - Evidence of safety and (depending on the claim/indication) efficacy?
    - One clinical trial instead of two, or smaller trials?
  - Good Tissue Practice

Regulatory Predictability

- Safety and effectiveness evidentiary requirements
- Manufacturing requirements
- Office of Combination Products/Tissue Reference Group response times
- RFD/pre-RFD improvements
- Notice-and-comment rulemaking vs. legislation

Identifying Potential Challenges

- Purity, potency, and identity requirements
- Size and frequency of various studies
- Donor variability
- Potential uses of real-world evidence, pre- or post-marketing
- Pathway for second, similar (“follow-on”) products to market?
- Cells compared to tissue products
- Would secretions/extracts be acceptable for consideration in the lower risk category or categories?

Questions?