ASSESSING FEASIBILITY OF A STANDARD

for Biological Evaluation of Tissues and Extracellular Matrices Used in Tissue Engineering for In Vivo Studies

Final Report | Oct. 2022

STANDARDS COORDINATING BODY
REGENERATIVE MEDICINE

NEXIGHT GROUP

DISCLAIMER

This report was prepared for the U.S. Food and Drug Administration (FDA), Center for Biologics Evaluation and Research by Nexight Group and The Standards Coordinating Body for Gene, Cell, and Regenerative Medicines and Cell-Based Drug Discovery (SCB) under contract number 75F40120F80487. The information and perspectives contained in this report are those of the authors and should not be attributed to the FDA. The mention of trade names, commercial products, or organizations does not imply endorsement of same by the U.S. Government.

Table of Contents

Introduction

Since the *21st Century Cures Act* was signed into law in December 2016, the U.S. Food and Drug Administration (FDA) has been engaged in ongoing efforts to fulfill its provisions to accelerate medical product development through the advancement of standards. The Standards Coordinating Body for Gene, Cell, and Regenerative Medicines and Cell-Based Drug Discovery (SCB) is supporting the FDA's efforts by coordinating the activities of the regenerative medicine community to accelerate regenerative medicine standards development.

A key element of SCB's support in accelerating standards development is engaging regenerative medicine stakeholders to help assess the feasibility of needed standards using the methods SCB outlined in *Realizing the Promise of Regenerative Medicine Therapies: Strengthening the Standards Development Process*. Assessing a needed standard's feasibility early in the standard advancement process is critical to ensuring efficient use of community resources.

Need Overview: Biological Evaluation of Tissues and Extracellular Matrices Used in Tissue Engineering for In Vivo Studies

Regenerative medicine researchers have growing interest in proteins derived from the extracellular matrix (ECM), a network of macromolecules that support the cellular components of tissues, based on the hypothesis that natural, tissue-derived materials will integrate better with host tissues during transplantation compared with synthetic biomaterials. However, the benefits of naturally derived ECM proteins in tissue engineering remain mostly hypothetical, due in large part to a lack of standard approaches to the assessment of these materials and their performance after transplantation. Current analytical methods are limited in scope to specific applications, preventing a comparative assessment of various tissue-engineered products.

After this area of standard need was identified, SCB assembled a working group to further assess the priority and feasibility of the needed standard. In partnership with Nexight Group, SCB developed this report to outline the results of its feasibility assessment of potential standards for biological evaluation of tissues and ECMs. The report includes input from a facilitated meeting in June 2022. See below for a breakdown of meeting participants by stakeholder group.

June 2022 Meeting Attendance by Stakeholder Group

Count	Stakeholder Type
7	Industry
10	Academia
2	Associations/Public-Private Partnerships
3	SCB
2	Nexight Group
3	Affiliation not given

Structure

The feasibility assessment considered four factors: technical feasibility, expert availability, implementation feasibility, and other related factors. Together, these factors offer a comprehensive overview of whether a standard is scientifically ready to advance and has sufficient buy-in from experts who are willing to support the standard advancement effort and community stakeholders who will ultimately adopt the standard.

This report includes a summary of findings from facilitated discussions, a description of the opportunities and challenges for each feasibility factor, and an outline of next steps.

Summary of Findings

Meeting participants proposed various potential sub-topics for standardization within the overarching need area:

- Definitions for ECM composition and microstructures
- Metrics for successful integration with host tissue
- Preclinical in vivo models
- Appropriate characterization methods based on ECM sources and properties
- Comparison of outcomes from different matrix types (e.g., acellular matrix, synthetic matrix)

The group determined that the most valuable approach for an initial standard would be to **develop a flowchart breaking down tissue and ECM products into different categories** based on input material and/or intended function (e.g., mechanical functions, metabolic functions) and offering key considerations for each subtype, including recommended assays and related standards. After completing this initial standard, it may be valuable to develop standards specific to the individual product subtypes.

The meeting participants primarily discussed technical and implementation feasibility issues for a potential standard and did not identify any significant barriers that would prevent a standard's development.

Technical Feasibility

Standards require strong scientific and technical bases to build community consensus. If too many unanswered technical questions remain at the time of standard development, the standard may be held up indefinitely until the field matures. Technical feasibility assesses whether an adequate technical and scientific foundation exists for creating the standard and seeks to ensure that the standard will serve its intended purpose.

The meeting participants identified some knowledge gaps that will require further discussion and consideration but did not identify any technical barriers they felt were significant enough to prevent the development of a useful standard.

OPPORTUNITIES	BARRIERS

• **Relevant standards that could be leveraged** for this effort include:
  ○ ASTM F2211-13(2021), Standard Classification for Tissue-Engineered Medical Products (TEMPs)
  ○ ASTM F3354-19, Standard Guide for Evaluating Extracellular Matrix Decellularization Processes
  ○ ASTM F3510-21, Standard Guide for Characterizing Fiber-Based Constructs for Tissue-Engineered Medical Products
  ○ ASTM F3224-17, Standard Test Method for Evaluating Growth of Engineered Cartilage Tissue Using Magnetic Resonance Imaging
  ○ ASTM WK3551, New Guide for the Assessment of Demineralized Bone without Excipient
• A standard **advising on proven ways to qualify techniques for cell counting and viability testing** for tissues and ECM would fill a critical gap for product developers.
	• It will not be possible to make a standard for every possible application, but **an overly vague standard would not provide much value**, so it will be important to strike a balance in the standard's level of specificity.
	• Various knowledge gaps within the community **will require further discussion to determine if sufficient technical consensus exists** for a standard to provide additional clarity. Examples include:
	  ○ How to assess if decellularization has successfully removed undesired biological materials while retaining desired structures and properties
	  ○ Effect of measuring fragmented (i.e., nonfunctional) proteins on the validity of assessments
	  ○ Minimum number of growth factors for proteomic assessment and how to determine their functionality
	  ○ Acceptable levels of remnant detergents in decellularized tissue
	  ○ How sterilization affects product performance
	  ○ How testing requirements should change as operations scale (e.g., should proteomics testing be conducted on every batch of samples during manufacturing?)

Expert Availability

Standards development requires committed technical experts who can advance the potential standard and help communicate the standard's value to the regenerative medicine community. If there is insufficient interest from experts in the community, the working group may be unable to obtain the necessary technical information to include in the standard. Likewise, buy-in from an SDO is needed to publish a formal standard, although best-practices documents and other informal guides can be produced independently.

Meeting participants did not identify any major expert availability barriers for the standard and will continue to explore this issue as the scope of the potential standard is defined in more detail. Future discussions will also assess appropriate SDOs to develop a potential standard.

Implementation Feasibility

Implementation feasibility considers factors that influence an individual firm's adoption of the standard: incurred costs; the standard's compatibility with existing equipment, materials, and technology; and required in-house expertise. If a standard is developed that does not have the support of the community, adoption rates may ultimately be too low for the standard to have any significant impact.

Meeting participants identified one potential area of concern for implementation feasibility: **existing manufacturers of tissues or ECM may be resistant to do additional testing** recommended by a standard if the benefit is unclear. However, this could be addressed through considering what benefit(s) the standard could provide and ensuring the standard clearly communicates the benefits to users. Meeting participants did not identify any other major implementation feasibility barriers. They believed a standard would generally be welcomed by the community as it would provide clarity on common areas of uncertainty and help stakeholders avoid spending time on unnecessary testing.

OPPORTUNITIES	BARRIERS
• A standard could provide valuable input not only on what assays are needed for a given application, but also what assays are not needed—which can **save organizations time and effort in justifying the decision not to conduct a test** (e.g., for tumorgenicity). • Product developers would welcome **more prescriptive guidelines on selection of assays**, including advice on procedural steps such as how many samples to prepare, as there are many options for assays and unclear criteria for choosing among them. • It would be **especially valuable to get regulatory buy-in for a standard** (e.g., pursuing recognition by the Voluntary Consensus Standards Recognition Program for Regenerative Medicine Therapies). Regulatory support would help build confidence in new technology.	• Manufacturers of existing ECM or tissue products **may not want to change or increase their testing and characterization, unless there is a likely benefit** (e.g., safety, efficacy, marketing, regulatory).

Other Feasibility Factors

Several other factors—including development costs, time to develop, accessibility, and legal feasibility—can impact the feasibility of developing and adopting a potential standard.

The meeting participants did not identify any major additional feasibility barriers.

Next Steps

The feasibility assessment determined that there are few technical, implementation, expert availability, or other barriers to a standard for ECM and tissue product evaluation. Based on the feasibility assessment outcome, the group plans to pursue advancement of a **standard categorizing different types of ECM and tissue products** and offering a flowchart advising on major considerations for protocols and best practices while using assays for each product type.

The group will hold additional discussions to further explore standard feasibility and define the best scope for a standard.

Next steps for the feasibility assessment effort are described below.

Goals for 2022–2023

- **Assemble a working group** and seek relevant expertise.
- **Conduct discussions with the working group** to confirm whether to move forward with the creation of a standard categorizing different types of ECM and tissue products and further refine its scope.
- **Develop a standard scope** with working group experts to determine the focus and extent of a potential standard.
- **Identify interested SDOs** and formalize a plan to advance the standard within a particular SDO. Once the scope of a potential standard is finalized, SCB will reach out to contacts at relevant SDOs to evaluate their interest.
- **Make a final assessment** of whether the standard should be advanced, researched further through independent efforts, or held for future reconsideration. Based on the feasibility assessment, SCB expects the standard to move forward if community enthusiasm and participation remain high.
- **If the standard is expected to move forward,** SCB will begin to outline the potential standard and support its advancement through the relevant SDO development process.