Assessing Feasibility of a Standard

FOR PRODUCT POTENCY AND FUNCTIONALITY MEASUREMENT METHODS

Final Report

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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.

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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: Product Potency and Functionality Measurement Methods

Potency is a quantitative measure of a product's ability to affect a desired therapeutic result in patients. Identity, purity, cell content, health, function in tissue-engineered constructs, and stability of therapy-component cells all contribute to a product's potency.

Due to the complexity and varying mechanisms of action in regenerative medicine products, researchers have difficulty identifying and developing consistent and effective methods for measuring product potency, leading to uncertainty about effective dosing. There is also a need for standards to help researchers and product developers navigate the complexities of determining function in tissue-engineered constructs.

Currently, there is a lack of specific regulatory guidance for assessing potency and limited sharing of potency test results. The regenerative medicine community would benefit from specific strategies to improve comparability and consistency of data from clinical trials and increase data collection and sharing to support correlations between lab-based assays with clinical outcomes.

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 product potency and functionality measurement methods. The report includes input from two facilitated meetings in December 2021 and January 2022, attended by 22 experts across multiple stakeholder groups. See below for a breakdown of meeting participants by stakeholder group.

December 2021 and January 2022 Meeting Attendance by Stakeholder Group

Count	Stakeholder Type
9	Industry
1	Standard Developing Organization (SDO)
3	Academia
4	Associations/ Public-Private Partnerships
4	Government
1	Industry/Government
3	SCB
2	Nexight Group

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

The meeting participants identified seven major potential sub-topics for standardization:

1. Method used to assess killing activity of T-cells or cytokine release
2. Standard method for selecting reference material
3. Advice on establishing correlation between lab-based tests and clinical activity using approved reagents and supplies
4. Definition of potency for tissue-engineered medical products (TEMPs) and bioprinting applications
5. Best practices for performing validation using a matrix approach to potency
6. Framework for establishing potency assays
7. Outline of differences between pharmaceutical potency and regenerative medicine potency (e.g., potency variance for autologous cell therapy)

The meeting participants determined that technical feasibility is a significant barrier for the topic of potency as a whole because of the lack of scientific maturity and the rapid pace of change in the space, particularly for assays.

In light of these concerns, the meeting participants concluded that a potency standard would not be feasible in the foreseeable future. They proposed **shifting the focus of standardization efforts from potency to functionality**, which is a more technically mature topic area. Functional assays are often used as a surrogate means of assessing potency, and their standardization could contribute to the overall advancement of product potency understanding for the regenerative medicine field.

The feasibility assessment participants believed that the field could benefit from white papers on various topics that address gaps in common understanding of potency and functionality and clarify fundamental terminology specific to cell therapy (e.g., assays versus bioassays). These white papers could serve as precursors to potential standards developing organization (SDO) technical reports or standards (e.g., standards for specific functional assays).

Meeting participants proposed the following topics for potential white papers:

White Paper Topic: Definition and Approach for Potency and Functionality Assessment for TEMPs

Because potency for cell therapy products receives the most attention from the regenerative medicine field, TEMPs manufacturers often struggle to understand what aspects of potency are relevant to their products. The feasibility meeting participants felt that it would be valuable to develop a document outlining general considerations for TEMPs manufacturers to use in potency assessments and expanding on the unique aspects and needs of TEMPs as they relate to potency.

White Paper Topic: Case Studies of Known Potency Tests for Approved Products

The feasibility meeting participants determined that the regenerative medicine field would benefit from a white paper presenting examples of the potency tests used for specific FDA-approved regenerative medicine products. Such a white paper would demonstrate the range and areas of overlap of potency tests currently in real-world use and spur discussion among the community that could help move the field closer to standard readiness.

White Paper Topic: Data Sharing to Support Identification of Measurements Predictive of Clinical Outcomes

Currently, there is no single study that provides sufficient data to establish correlations between laboratory measurements and clinical outcomes. A white paper would explain the need for data sets that span different products and labs and would outline the challenges to data sharing. By promoting data sharing in the regenerative medicine community, the white paper would support the pooling of data that could push the field closer to being able to see patterns that could inform the identification of measurements predictive of clinical outcomes.

White Paper Topic: Fit-for-Purpose Assessment of Functional Assays

Using ISO 23033:2021, General requirements and considerations for the testing and characterization of cellular therapeutic products as a model, this white paper would walk through the considerations of selecting a functional assay that is fit-for-purpose in assessing potency. This white paper could help regenerative medicine product developers improve the efficiency of their products' regulatory reviews by preventing them from wasting time and resources on inappropriate assays.

White Paper Topic: Validation of Functional Assays

To help improve the consistency and value of measurements, this white paper would provide advice and considerations for developing and validating specific functional assays (e.g., cytokine release assays, tumor cell killing assays) using a matrix approach. Improved measurement consistency would be valuable for enabling effective comparison of shared data.

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.

Rather than focusing on a specific sub-topic, the technical feasibility discussion focused on the overall feasibility of standards for potency and functionality measurement methods.

OPPORTUNITIES	BARRIERS

• **A white paper could push the conversation on potency assays forward**, using current FDA guidance as a starting point.
• There is value in **assessing interaction of multiple measurands** to develop more valuable potency assays.
• **Addressing a more technically mature topic related to potency** could be more feasible than trying to address potency directly.
  ○ E.g., ensuring consistency in product characteristics to address issues such as variability in the same autologous cell therapy assay among differently aged patients.
• There is an opportunity to help address potency needs by **standardizing functional assays used in assessing potency** (e.g., cytokine release assays).
	• **There is a lack of scientific consensus and established regulatory guidance** on accepted potency assessment methods, as well as gaps in the understanding of the underlying biology.
	• **Potency is often product-specific,** as well as being a significant part of intellectual property (IP). **Companies would likely be reluctant to share enough detail** to be valuable for informing a standard on this topic.
	• Potency tests should be reflective of mechanism of action, **but often there is no ethical way to study mechanism of action in humans.**
	• An individual product may have **multiple mechanisms of action**.
	• **The inherent heterogeneity** in each individual product and lot makes standard potency assessment methods impractical.
	• **Correlating potency assays with clinical outcomes would be desirable for a standard but is not currently possible** with the level of knowledge in the field.
	  ○ Siloing of data may make it difficult to connect lab measurements to patient-specific outcomes.
	  ○ Patient outcomes may also be influenced by factors unrelated to potency (e.g., sepsis).
	• **Assays in the field are constantly changing** and those in use today may no longer be used five years from now.

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.

The feasibility assessment participants did not think that the topic would be ready to advance to an SDO at this stage due to the technical feasibility concerns described in the previous section. Future discussions will assess if there are any gaps in expertise in the working group that should be filled before development of any white paper(s).

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.

The meeting participants believed that, while standards focused on product potency are often requested by the regenerative medicine community, it would not be feasible to develop a standard that the community would welcome at this stage due to lack of consensus on measurement methods.

OPPORTUNITIES	BARRIERS
• The community may be open to white papers that could **help identify current gaps in the scientific understanding of potency.**	• The **community is not currently in agreement** on the best potency measurement methods for specific use cases. • Current FDA **guidance on potency is not sufficiently detailed to support consensus** on a standard.

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, while the field is not yet mature enough for standards to be developed on product potency and functionality measurement methods, the regenerative medicine community would welcome a preliminary resource, such as a white paper. In addition, the assessment concluded that future standardization efforts should focus on functional assays as a means of assessing potency rather than addressing potency directly.

The feasibility assessment participants determined that white papers on the following topics would help identify and address knowledge gaps in the community and spur productive discussions:

- Definition and approach for potency and functionality assessment for TEMPs
- Case studies of known potency tests for approved products
- Data sharing to support identification of measurements predictive of clinical outcomes
- Fit-for-purpose assessment of functional assays
- Validation of functional assays

Next steps for the feasibility assessment effort are described below.

GOALS FOR 2022–2023

- **Seek additional working group participants** for the development of the white papers.
- **Conduct discussions with the working group** to select which white paper topic(s) to move forward and determine how to prioritize the white paper topic(s).
- **Encourage stakeholders in the community to organize an interlaboratory study** to gather data on functional assay validation, potentially leveraging the National Institute of Standards and Technology (NIST) Flow Cytometry consortium for resourcing.
- **Develop white paper(s) on selected topics** to support the community in filling gaps in order to move toward standard readiness.
- **Publish the white paper(s)** and seek feedback from the community.
- **Pursue publication of a manuscript in a high-impact journal** describing the overarching challenges to potency measurement and introducing the idea of functional assays to measure potency and the need for increased data sharing.
- **Reassess whether standards should be advanced**, researched further through independent effort, or tabled for future reconsideration.