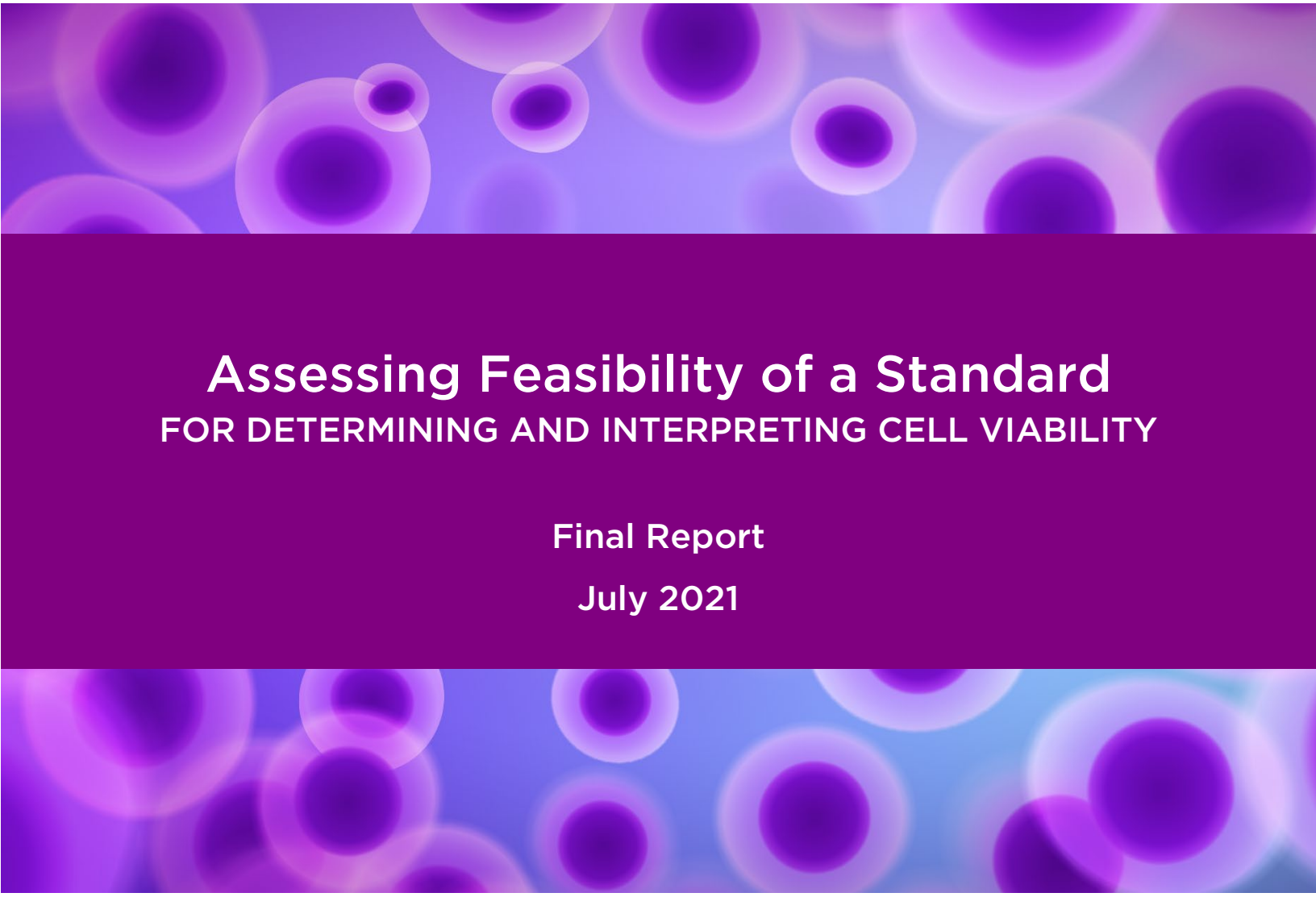

Assessing Feasibility of a Standard

FOR DETERMINING AND INTERPRETING CELL VIABILITY

Final Report

July 2021

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 ensure efficient use of community resources.

Need Overview: Determining and Interpreting Cell Viability

It is difficult for researchers to identify the most appropriate method (e.g., assay) for assessing cell viability within a given therapy or cell type due to a lack of consensus around measurements, terminology, and testing parameters. In addition, test methods can be difficult to interpret due to a lack of understanding of what assays measure and how measured parameters correlate with cell viability. Standards in this area could better enable researchers to select reproducible assays that yield accurate and precise cell viability results.

After this 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 has developed this report to outline the results of SCB's feasibility assessment for the potential standard on determining and interpreting cell viability. The report includes input from two facilitated meetings in April and May 2021 attended by 14 experts across multiple stakeholder groups. See below for a breakdown of meeting participants by stakeholder group.

April/May 2021 Meeting Attendance by Stakeholder Group

Count	Stakeholder Type
4	Academia
6	Industry
1	Professional Society
2	Government
2	SCB
2	Nexight Group
1	Affiliation Not Given

STRUCTURE

The feasibility assessment considered four main factors: technical feasibility, expert availability, implementation feasibility, and other related factors. Together, these factors represent a comprehensive overview of whether a standard is scientifically ready to advance and has sufficient buy-in from experts supporting the standard advancement effort and the 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 group identified two major potential sub-topics for standardization:

- **Cell viability terminology** that establishes subcategories of viability based on common use cases
- **Considerations for assay selection and interpretation of results** for different use cases

A potential standard for cell viability could incorporate both subtopics, using subcategory terminology as a foundation for the assay selection considerations. The participants planned to focus an initial standard on cell therapy applications; the standard could later be adapted to tissue engineering and other biologics (e.g., manufacturing of antibodies and other proteins). The most significant challenges to standardization identified by the group included difficulty in achieving a consensus on cell viability terminology due to the complexity of the concept and the potential that organizations that have already invested in specific assays may have difficulty implementing the standard. However, the group felt that these barriers would be surmountable.

The **Next Steps** section discusses actions focused on advancing the standard that have been taken since the feasibility assessment meetings or that are planned for the future.

Technical Feasibility

Standards require a strong scientific and technical basis 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 constructing the standard and seeks to ensure that the standard will serve its intended purpose.

During the feasibility meeting, participants identified two sub-topics that may be ready to move forward to standardization. These sub-topics are described in the sections below.

SUB-TOPIC: CELL VIABILITY TERMINOLOGY

There are various potential ways to define and measure the well-being of cells, including factors such as membrane integrity, molecular markers, and ability to replicate. These varying definitions and related assays are often relevant for different use cases (e.g., viability for routine cell culture, monitoring cell manufacturing processes, and cell therapy product release) but are generally simply applied as cell viability. It would be valuable to establish standard terminology for cell viability (i.e., cell well-being) that divides it into specific subcategories by use case, such as “viability based on trypan blue membrane integrity” and “viability based on adenosine triphosphate (ATP) metabolic activity.” Because there is a lack of consensus on definitions used amongst the various standards developing organizations (SDOs)

and companies, engagement by SDOs and companies in development of a terminology standard is needed. It would also be useful to define terms related to common viability metrics to ensure that the considerations outlined in the standard can be clearly understood.

STANDARD OBJECTIVE: Create standard definitions of cell viability subcategories and other key cell viability terminology.

OPPORTUNITIES	BARRIERS
• Consensus definitions for cell viability concepts could **prevent confusion among stakeholders** who may be using terms to mean different things.	• **Changing terminology may be difficult,** as certain terms are already in use by FDA, industry, academia, and suppliers. To create an effective standard, experts from many different areas and organizations would need to be involved in the development process. • **Certain aspects of defining viability may be difficult to agree on** due to the complexity of the concept, such as whether a static or dynamic definition should be used (e.g., a cell may have appropriate membrane integrity but be metabolically nonviable). • **Defining what is and is not a subcategory within cell viability** will require further discussion by experts (e.g., whether cell viability should be more narrowly defined based on truly "dead" cells with no potential for life, or more broadly defined as a continuum of cell health that includes apoptosis and other measures of cell health within scope.

SUB-TOPIC: CONSIDERATIONS FOR ASSAY SELECTION AND INTERPRETATION OF RESULTS

Cell viability is a complex topic, and there is often uncertainty around the most reliable and appropriate assays for a given use case, as well as assay parameters, data types to measure, stock types and testing environments, timing of sample collection, and other variables. Regenerative medicine product developers would benefit from a standard that identifies the criteria for cell viability for a particular use case and provides guidelines on the assays, measurements, and methodologies that could best satisfy those criteria.

STANDARD OBJECTIVE: Establish a set of fit-for-purpose decision-making process recommendations for selecting cell viability assays and methodology for cell therapy applications.

OPPORTUNITIES	BARRIERS
• The standard could help product developers **describe what they are trying to measure and how they plan to use the information**, which would enable clearer communications with regulators and improve data comparability. • The standard could help clarify common points of confusion, such as **pre- and post-thaw considerations for release assays versus in-process measurements.** • **The standard could advise on potential reference and control materials** for a given assay. • **There is likely sufficient scientific consensus** to develop a general cell viability framework that would be uniform between different analytical tools. • **A standard on this sub-topic would be widely applicable** to all cell therapy products and many different aspects of cell therapy product manufacturing processes, enabling it to have a large impact on the field. • Subsequent parts in the standard could provide a **closer look at considerations for specific viability assays.**	• **A given assay may perform differently with different cell types,** which could complicate development of comprehensive assay considerations. • Some **scientific challenges exist in determining reliable indicators of cell viability** (e.g., some cells with damaged membrane integrity can recover). • **Reference materials would require further scientific cooperation and consensus** on United States Pharmacopeia (USP)-defined assays. The field should continue to address these challenges to advance cell viability standards in the future.

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.

Participants proposed several potential SDOs for consideration:

- International Organization for Standardization (ISO)
- AABB
- USP, European Pharmacopoeia (Ph. Eur.), or other pharmacopeias

During the feasibility meeting, participants focused on what additional expertise is most needed in the standard working group. They identified the following stakeholder groups whose input would be valuable:

- Regulators
- Industrial bioprocessing professionals
- Cancer researchers
- Developers of assay kits, reagents, and equipment (e.g., Thermo Fisher Scientific, Pierce Biotechnology, Roche, ChemoMetec)
- Therapeutic product developers
- International Society for Advancement of Cytometry and Association of Biomolecular Resource Facilities (ABRF), which are linked to core facilities where assays are developed

Implementation Feasibility

Implementation feasibility considers factors that may 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 feasibility meeting participants believed that the most significant implementation concerns would be for late-stage products using legacy methods for viability assays, but that this concern could be mitigated by focusing on an assessment of the pros and cons of potential approaches rather than offering a rigid protocol.

OPPORTUNITIES	BARRIERS
• A **standard that is flexible** (i.e., protocol-based but not prescriptive) is likely to be successful. • **Highlighting incentives for following the standard** may improve the chances of successful implementation. • **Startups working on new products would likely have a relatively easy time adopting the standard** because they would not need to do comparability or bridging studies.	• **Current products under development or on the market** may still be using methods that are no longer considered best practices by the community (e.g., manual trypan blue). This could lead some stakeholders to be resistant to a standard that recommends changing these methods, which would require the use of additional resources. • If the standard's **recommended assays are too costly, complex, or inaccessible, it may hinder implementation.**

Other Feasibility Factors

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

The feasibility meeting participants did not identify any major additional feasibility barriers not included in the other factors. Participants noted that due to the complexity of cell viability, this topic might ultimately require multiple standards to adequately cover the subject matter. They also identified a possibility of disputes between organizations if stakeholders following the standard produced different viability outcomes from established methods.

OPPORTUNITIES	BARRIERS
• **A multi-volume standard** could cover general considerations first and then move on to more specific topics (protocols, specific use cases, etc.) as more volumes are added. • **Development time should not be a concern.** The timeline for development of a standard in this area should allow for the standards to be relevant and impactful after publication (even if this process takes a few years).	• **Regulators have identified a need to narrow down the number of assays used by different companies for Investigational New Drug (IND) applications,** but this may be challenging to accomplish through a standard. • If the standard's recommendations produce a different result from existing in-house processes for evaluating viability (e.g., 90% viable versus 95% viable), **there may be technical and regulatory ambiguity around how to determine which result is valid.**

Next Steps

The feasibility assessment found that overall, there are few significant barriers for technical feasibility, expert availability, implementation feasibility, and other feasibility factors for a cell viability standard, and that it should be feasible to proceed with a standard provided it is possible to obtain sufficient participation in the working group from stakeholders with the expertise outlined in this report. The group determined that a standard establishing a definition for cell viability and providing fit-for-purpose assay considerations for cell therapy applications would likely be a good starting point, and subsequent standards could expand on specific test methods and cover additional application areas.

Since the initial feasibility assessment meetings, the working group has initiated a new project with ISO and formalized a plan to advance the standard within ISO/TC 276 WG 3. The project plan, scope, and outline were presented to ISO at the June 2021 meeting, and the experts in attendance agreed to begin a new project (NP) ballot. A form 4 and NP ballot will be initiated in August 2021.

The following projected dates for standard development are estimates only since development of a standard depends on ISO timelines.

GOALS FOR 2021–2025

- **Ongoing: Seek additional working group participants**, focusing on the expertise needs identified in the feasibility report. SCB will reach out to relevant organizations individually through national meetings, national organizations, and other methods.
- **Summer 2021: Develop Working Draft (WD)** to submit for comment period and balloting. The initial WD will be drafted through both the SCB working group and international drafting team

from ISO/TC 276 WG 3. There may be comment periods within ISO during this timeframe. The final WD will be submitted to undergo a committee draft (CD) ballot.

- **2022: Develop CD** to submit for comment period and balloting. The CD will be drafted through both the SCB working group and international drafting team from ISO/TC 276 WG 3. There may be comment periods within ISO during this timeframe. The final CD will be submitted to undergo a draft international standard (DIS) ballot.
- **2023: Develop DIS** to submit for comment period and balloting. The DIS will be drafted through both the SCB working group and international drafting team from ISO/TC 276 WG 3. There may be comment periods within ISO during this timeframe. The final DIS will be submitted to undergo a Final Draft International Standard (FDIS) ballot.
- **2023: Develop FDIS** to submit for comment period and balloting. The FDIS will be drafted through both the SCB working group and international drafting team from ISO/TC 276 WG 3. There may be comment periods within ISO during this timeframe.
- **2024: Submit standard to ISO Central Secretariat** for finalization and publication. The ISO central secretariat will check the FDIS for formatting and adherence to ISO rules. SCB will revise the document based on any requested changes and resubmit for publication.
- **2025: Publication of standard** anticipated to occur through ISO. The document will be available for public purchase through the typical ISO mechanisms.
- **2025: Potential development of implementation curriculum** for the published standard. SCB will conduct feasibility studies to determine if development of an implementation curriculum would be appropriate.