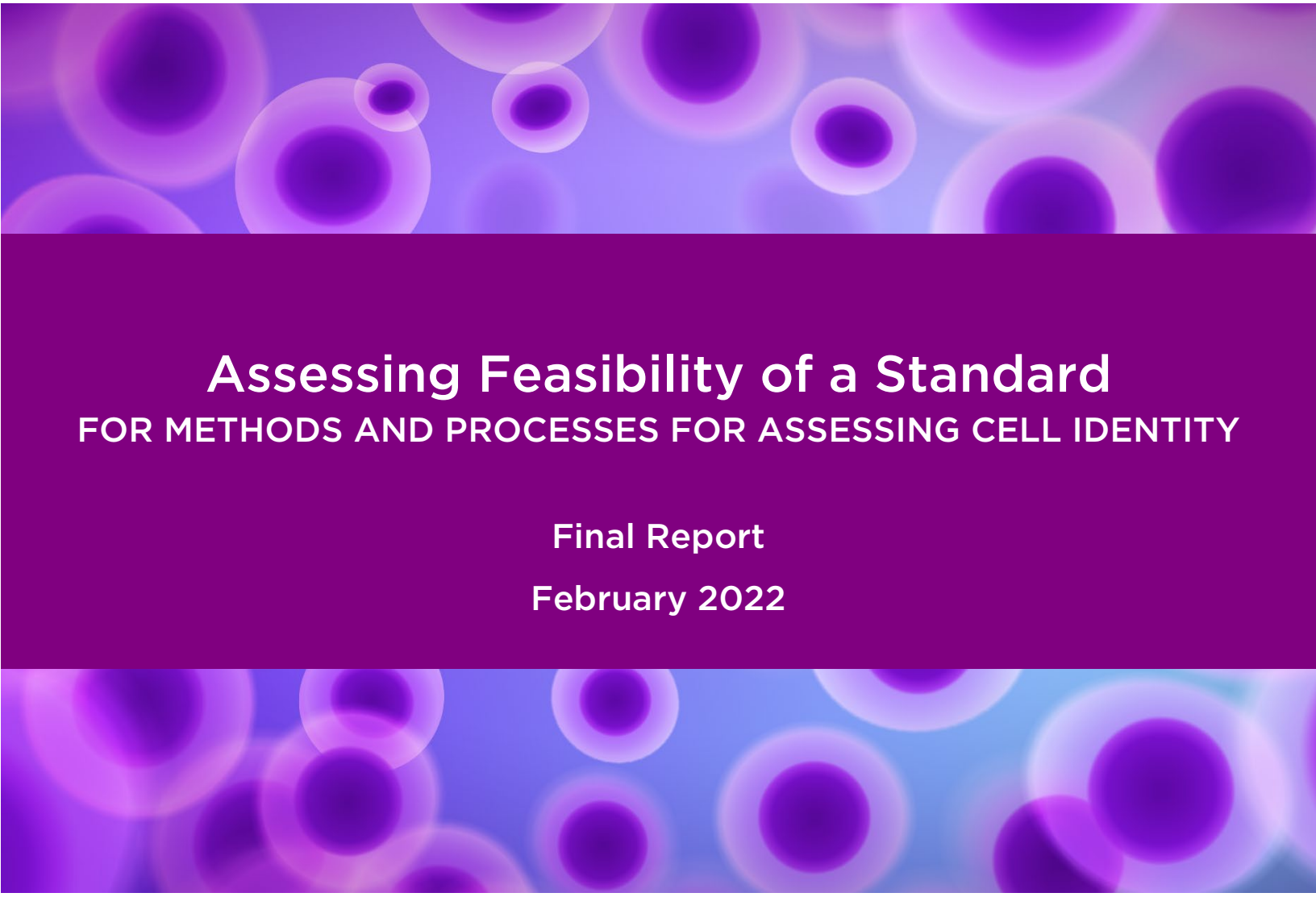

Assessing Feasibility of a Standard

FOR METHODS AND PROCESSES FOR ASSESSING CELL IDENTITY

Final Report

February 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.

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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: Methods and Processes for Assessing Cell Identity

A cell's identity can be defined differently across the scientific community (e.g., gene expression, function, potential, lineage). A common approach to cell identity is to determine the distinct pattern of gene expression that gives rise to a cell type's unique structure and function through the control of protein production and modification. Assessment of the identity of cells is valuable in various regenerative medicine therapy applications (e.g., determining successful differentiation of a pluripotent cell or providing a surrogate measure for potency).

However, there are multiple methods and processes for assessing cell identity, each with their own benefits, drawbacks, and special considerations. In addition, the lack of robust quantitative methods limits the ability to connect cell identity to critical quality attributes (CQAs). Developing a standard in this area could help researchers and product developers identify the most effective assessment approach for their use cases and better understand factors that could influence their findings, such as environmental variations and heterogeneity in cell population.

After this area of standard need was identified, SCB assembled a working group to further assess the priority and feasibility of a potential standard. In partnership with Nexight Group, SCB has developed this report to outline the results of its feasibility evaluation of potential standards for methods and processes for assessing cell identity. The report includes input from two facilitated meetings in December 2021 and January 2022, attended by 14 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
4	Industry
1	Standard Developing Organization (SDO)
3	Academia
2	Public-Private Partnership
1	Industry/Government
3	Government
2	SCB
3	Nexight Group

STRUCTURE

The feasibility assessment considered four factors: technical feasibility, expert availability, implementation feasibility, and other related factors. Together, these elements 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 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 meeting participants identified two major potential sub-topics for standardization:

1. Terminology
2. Product-based approaches for assessing identity

The meeting participants determined that these sub-topics should be combined into a two-part standard, with an initial part introducing relevant terminology and a second part showing users how to apply the product-based approaches to their work.

The meeting participants did not find any significant barriers to developing the standards but did note that one key aspect of an ideal standard—defining CQAs as a form of identity—is not yet scientifically mature enough to be feasible for users to carry out. Meeting participants believed that a standard could still address this important issue by advising industry to characterize products to the best extent possible using current technology, creating a baseline for defining CQAs and establishing a reference point for cell identification to build upon in the future.

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 adequate technical and scientific foundations exist for creating the standard and seeks to ensure that the standard will serve its intended purpose.

During the feasibility meeting, participants discussed the technical feasibility of two sub-topics, described below, that may be ready to move forward.

SUB-TOPIC: TERMINOLOGY

The topic of cell identity has various interrelated and overlapping terms, including:

- Cell identity
- Cell state
- Cell attributes (e.g., mobility)
- Cell niches
- Cell type
- States of cell cycle, maturation, differentiation, and senescence
- Donor age
- Length of freezing
- Passaging (e.g., method of passaging, number of passages and what constitutes one passage)
- Intended use
- Purity
- Heterogeneity

In addition, these definitions can differ depending on the subject under discussion (e.g., single cells versus populations of cells, or a clonal population versus a polyclonal population of cells).

There is also confusion around basic concepts such as when, if, and how acquired heterogeneity changes the identity of a given cell population, and whether there is a need for fidelity between cell identity and intrinsic biological potential.

A terminology standard could help clarify these basic definitions and concepts and offer users a foundation for solid understanding of cell identity assessment.

STANDARD OBJECTIVE: Develop a set of common terms and definitions to clarify the basic concepts and considerations of cell identity.

OPPORTUNITIES	BARRIERS
• **The Nomenclature Committee on Cell Death (NCCD) regularly updates a document on cell death terms.** These definitions could be leveraged for a cell identity terminology standard. • A standard that clarifies cell identity definitions could **better equip industry to begin identifying CQAs** by providing a common understanding of underlying concepts.	• **Common complications around cell identity definitions would need to be resolved** for experts to come to a consensus for a standard (e.g., establishing a clear distinction between cell identity and cell function, two terms that are often conflated). • Careful research will be needed to ensure the standard does not **contradict existing medical terms.**

SUB-TOPIC: PRODUCT-BASED APPROACHES FOR ASSESSING IDENTITY

There are three major approaches to cell identity assessment: genetic, phenotypic, and functional. One or more of these approaches may be appropriate depending on the product or use case, and which would be most valuable is not always clear to product manufacturers. In addition, complicating factors such as heterogeneity of cell-based products often leave manufacturers uncertain of what to measure and how to best interpret those measurements.

While it is common for manufacturers to evaluate surface markers or degree of differentiation to confirm identity, an ideal standard in this area would help push the field forward by encouraging more comprehensive, product-tailored identity assessment of cells and cell populations. A standard could accomplish this by providing guidelines for how, when, and why to identify a cell, including a framework for quantifying heterogeneity. In addition, a standard could advise on a staged approach for incorporating CQAs into future identity assessments as technology matures.

STANDARD OBJECTIVE: Develop a general-concept standard outlining a product-based approach to confirm the presence of the cell type essential to the particular therapy. Such a standard would also include approaches for quantification of the cell type used for the therapy as well as assessment of the principal cell function needed for the therapy.

OPPORTUNITIES	BARRIERS
• **The AABB Standards for Cellular Therapy Services address similar concepts** and could serve as a starting point for a potential standard. • An identity standard addressing quantification of heterogeneity and purity—which is not commonly included in manufacturers' cell identity assessments despite the fact that the necessary technology exists—could help **drive the field forward.**	• The **potential criteria for cell identification are complex**, including cell functions and activities, location of cells in tissues, and what cells they divide to produce. This complexity could impede agreement on basic principles. • **Scientific knowledge is currently insufficient to incorporate CQAs into identity assessment** (i.e., correlate heterogeneity or cell properties to CQAs); however, the standard could address how to pursue this as a future goal. • Because the field is still developing, **the full variation of different cell types is unknown**, but even without this comprehensive information, a standard would still be valuable to the regenerative medicine community. • While technology currently exists for quantifying heterogeneity (e.g., high dimensional flow cytometry), there is **currently no technology for assessing heterogeneity of tissue stem cells, specifically**.

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 not be able to obtain the necessary technical information to include in the standard. Likewise, buy-in from a standards developing organization (SDO) is needed to publish a formal standard, although best-practices documents and other informal guides can be produced independently.

The decision on which SDO(s) may take up the development of this standard is still pending. Potential SDOs discussed by the meeting participants include:

- AABB
- Foundation for the Accreditation of Cellular Therapy (FACT)
- International Organization for Standardization (ISO)

The feasibility meeting participants identified the following stakeholder groups whose input would be valuable to the standard effort:

- Cell biologists
- Epidemiologists—particularly those with experience assessing speciation shifts and jumps
- Instrumentation experts (e.g., flow cytometry, cell analysis)
- Manufacturers
- Materials experts
- Molecular biologists—particularly those with experience in RNA-Seq and proteomics
- Pathologists
- Regulators
- Researchers
- Statisticians
- Tissue cell biologists
- The International Alliance for Biological Standardization (IABS)

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 does not have the support of the community, adoption rates may ultimately be too low for the standard to have significant impact.

The meeting participants did not identify any significant implementation barriers for either of the potential standard sub-topics. They anticipated that industry would welcome the standard as a tool to improve consistency in assessing cell identity.

OPPORTUNITIES	BARRIERS
• **The standard would be inexpensive to implement**—in the range of $1,000–2,000 total. • The standard would likely save money in the long run by **accelerating regulatory approval of products and improving reproducibility.** • The standard could help **improve communication between suppliers and users** of regenerative medicine products, which will benefit patients by increasing efficiency and reducing errors. • The lexicon standard could help **unify the language used in publications, minimize variation in interpretation, and improve understanding**.	• There is a risk common to all new standards that **people may assume the standard is mandatory and view it negatively as a result**; education and messaging will be important to address this.

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 meeting participants did not identify any major additional feasibility barriers.

Next Steps

The feasibility assessment found that, overall, there are few significant barriers to technical feasibility, expert availability, implementation feasibility, and other feasibility factors for a standard on methods and processes for assessing cell identity.

The group determined that a two-part standard on terminology and product-based approaches for assessing identity would be a good starting point for standardization. They believe that a standard on these topics would be a valuable complement to existing standards such as ISO 23033:2021, General Requirements and Considerations for the Testing and Characterization of Cellular Therapeutic Products, and ISO/CD 23511, General Requirements for Cell Line Authentication.

Next steps for the feasibility assessment effort are described below.

GOALS FOR 2022–2023

- **Assemble a working group and seek relevant expertise,** focusing on the expertise areas identified in the feasibility report. The working group will also work to provide feedback on current standards efforts underway with complementary topics.
- **Conduct discussions with the working group** to confirm whether to move forward with the creation of a two-part standard on the sub-topics identified in the report (terminology and product-based approaches for assessing cell identity) and further refine their scope.

- **The working group will inventory existing standards and nomenclature** to ensure harmonization and avoid clashes or overlap.
- **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.
- **Request historical review from executive agency partners** to leverage their lessons learned (e.g., through biologics standards) and develop a standard that can effectively evolve with technological innovation.
- **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.
- **Working group members will draft articles for journals** to promote the use of the completed standard to a broader audience.