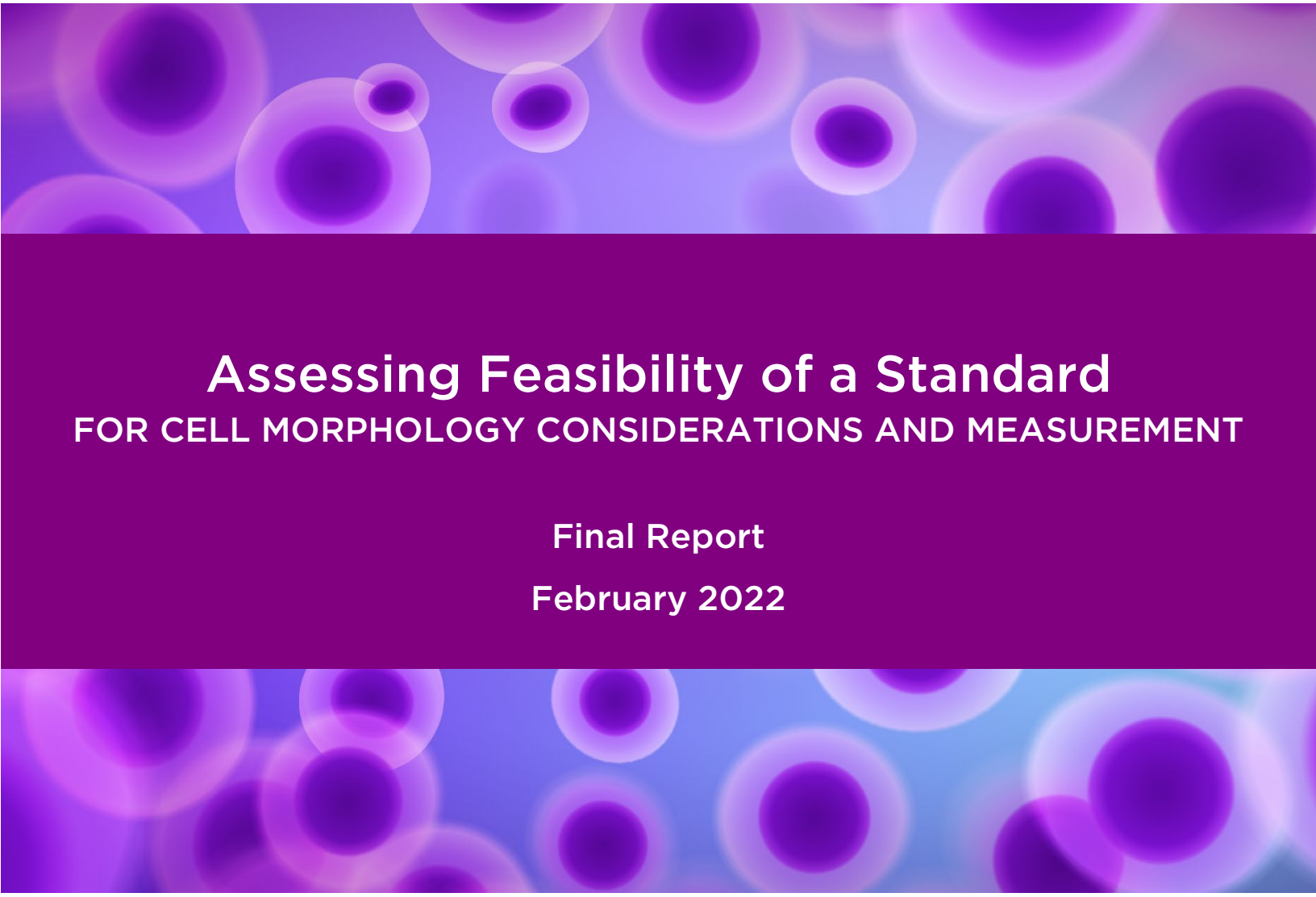

# Assessing Feasibility of a Standard
## FOR CELL MORPHOLOGY CONSIDERATIONS AND MEASUREMENT

**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: Cell Morphology Considerations and Measurement

Cell behavior, performance, and function is influenced by a cell's morphology—its shape, form, structure, and size—and its environment (e.g., ex vivo, in vitro, in vivo). Limited knowledge of cell morphology (e.g., for different cell types), how best to measure it for a given application, and how it relates to cell behavior and performance inhibits progress toward researching and developing new therapies for use in patients.

Two related standards are currently under development:

- ISO/CD 23511, Biotechnology — General requirements for cell line authentication
- ISO/AWI 24479, Biotechnology — Minimum requirements for cellular morphological analysis — Image capture, image processing, and morphometry

Additional standards in this area could promote increased understanding of how to mitigate/respond to the effects of morphology and environment during cell therapy product development.

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 has developed this report to outline the results of its feasibility assessment of potential standards for cell morphology considerations and measurement. 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 |
|---|---|
| 5 | Industry |
| 2 | Government |
| 3 | Academia |
| 2 | Public-Private Partnership |
| 1 | Professional Association |
| 1 | Standards Developing Organization (SDO) |
| 2 | SCB |
| 3 | 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 discussed various factors related to cell morphological characterization and analysis, such as the minimum image quality necessary to define different morphological features, as well as challenges inherent to three-dimensional and time-course imaging. Participants felt these considerations were mostly within the scope of the ISO standard on morphological analysis currently in development.

Participants proceeded to discuss applications of cell morphology data. Although links between morphological characteristics and regenerative medicine product potency are not well established, the use of cell morphology as a surrogate measure for quality-control purposes was deemed highly valuable because morphology assays can often be performed rapidly. It was noted, however, that cell morphology measurements are of limited usefulness on their own and must be coupled with other measures, such as cell-surface markers. To that end, participants discussed the following areas to standardize for **correlative analysis of cell morphology data**:

1. Data collection methods, including which techniques to use and which parameters to measure
2. Data reporting elements and metadata
3. Appropriate statistical and informatics approaches to correlative data analysis

Because these considerations would be highly application-specific, participants determined that it would be helpful to conduct a survey of investigators currently integrating cell morphological characterization into their work. The following questions were proposed for a potential survey:

- What morphological features are you measuring?
- What assays and techniques are you using?
- What equipment are you using?

- What is your segmentation strategy?
- What application are you applying cell morphology data to?
- Why do you consider cell morphology important to your application?
- What do you consider to be the limitations of cell morphology data for your application?
- Are you interested in sharing your images and 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 adequate technical and scientific foundations exist for creating the standard and seeks to ensure that the standard will serve its intended purpose.

| OPPORTUNITIES | BARRIERS |
|---|---|
| • A standard for morphological measurements could help to characterize **heterogeneity or consistency** within cell populations, as well as characterize changes in a cell population over time.<br>• Establishing methods to measure morphological heterogeneity or consistency could help in determining **release criteria for cell therapeutic products**.<br>• **Large amounts of image data have already been generated** that could serve as a basis for developing standardized analysis techniques.<br>• A document outlining **which areas are not mature enough to standardize** could still provide value to the community. | • Many morphological characteristics are **poorly defined and often assessed subjectively** by human observers.<br>• Different image thresholding and segmentation strategies can produce **different data from the same set of images**.<br>• Effective recommendations may be **limited to specific applications**.<br>• There is currently **little data directly supporting a link between morphological parameters and product potency**.<br>• Tools and techniques for handling **large image datasets** are limited, particularly in the case of time-course imaging. |

## 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 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 participants determined that the group needs more engagement from experts on the morphological assays currently in use.

The participants identified some researchers engaged in work related to cell morphology measurements:

- NIST is working on morphometric image analysis of cell populations.
- FDA has done work linking the morphology of mesenchymal stem cells (MSCs) to performance.
- A research group published a recent paper on morphology as a potential critical quality attribute for cellular therapies.
- NIH has developed a selection process for iPSC clones.
- NIBSC published a 2020 paper that noted that the abnormal morphology of certain iPSC cell lines seemed to affect pluripotency.
- The MUHC Neurology Institute is managing the new Brain Canada iPSC-CRISPR translational platform.

## 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.

| OPPORTUNITIES | BARRIERS |
|---|---|
| • Morphology data standards would be **helpful to organizations that are creating manufacturing plans.**<br>• Morphology data standards would not be burdensome to the community and would most likely **cut time and costs to organizations that implement them**.<br>• As **many of the standards discussed are application specific**, implementation would mainly focus on organizations manufacturing products within a given application's scope and would not impact many other products.<br>• **Data management and reporting standards would be easy to implement** with low costs and would help ease communication barriers and data comparison.<br>• Organizations would **save time and cost by implementing data management standards**. | • **High-resolution and high-magnification techniques may be too expensive** for some users.<br>• Because **the value of morphological measurements as a quality control metric for regenerative medicine products is not firmly established**, it would be important that any recommendations be for research purposes rather than industrial applications. |

## 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 meeting participants determined that a standard on morphology data management would be feasible, but they needed further input from the community to narrow down the specific focus and scope among the specific application-dependent standards that might be needed. Next steps for the feasibility assessment effort are described below.

### GOALS FOR 2022–2023

- **Conduct a survey of active practitioners** assessing cell morphology in relation to cell characterization or regenerative medicine products.
- **Create a consolidated list** of current efforts related to cell morphological characterization.
- **Convene a follow-up meeting** to discuss findings from the above.
- **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. There is potential to reach out to ISO/TC 276 to develop the standard in conjunction with their current cell morphology standard (ISO/AWI 24479, Biotechnology — Minimum requirements for cellular morphological analysis — Image capture, image processing, and morphometry); however, the decision is pending further discussion with the working group.

- **Make a final assessment** of whether the standard should be advanced, researched further through independent efforts, or held for future reconsideration.
- **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.