ASSESSING FEASIBILITY OF A STANDARD

for Methods for Assessing Gene Therapy Product Activity and Comparability

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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 order number 75F40122F80406. 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.

SCB developed this report in partnership with Nexight Group to outline the results of its feasibility assessment of potential standards for gene therapy product activity and comparability.

Need Overview: Gene Therapy Product Activity and Comparability

The rapid proliferation of regenerative medicine therapies has spurred development of a wide array of gene therapy products. Currently, there is no agreed-upon framework in place for assessing product performance. In addition, changes during manufacturing (e.g., change in facility) can impact product quality and safety and require manufacturers to perform comparability studies to ensure the product has not significantly changed.

There is currently no accepted method for conducting studies on comparability, as these attributes will vary from product to product. The lack of standardized comparability assays makes it challenging to build understanding around potential manufacturing changes. This slows the progress of innovation and leads to confusion among patients and clinicians in making treatment decisions with products that do make it to market.

Process

Phase 1: Initial Priority and Feasibility Assessments

After this area of standard need was identified, SCB assembled a working group to further assess the priority and feasibility of the needed standard. SCB conducted two facilitated meetings—one in December 2022 and one in January 2023. See below for a breakdown of meeting participants by stakeholder group.

December 2022 and January 2023 Meeting Attendance by Stakeholder Group

Count	Stakeholder Type
10	Industry
2	Academia
3	Regulatory
3	SCB
2	Nexight Group

Feasibility Assessment Factors

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.

- **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.
- **Expert availability** assesses whether there is sufficient interest from experts in the community to advance the potential standard, as well as buy-in from potential standards development organizations (SDOs) to publish a formal standard.
- **Implementation feasibility** considers factors that influence an individual firm's adoption of the standard such as costs; the standard's compatibility with existing equipment, materials, and technology; and required in-house expertise.
- **Other feasibility factors** include development costs, time to develop, accessibility, and legal feasibility.

Phase 2: Community Workshop for Detailed Need Assessment

FDA co-organized a workshop in November 2023 with SCB and the United States Pharmacopeia (USP) to build on the results of the feasibility assessment and identify specific subtopics that are feasible to standardize and would make a significant positive impact on the regenerative medicine field.

The workshop was a hybrid two-day event held at USP headquarters in Rockville, MD. It was attended by more than 50 in-person stakeholders and 180 virtual stakeholders from industry, academia, SDOs, and government agencies, among other regenerative medicine stakeholder groups.

Each day centered around a breakout session that offered participants a chance to engage in **detailed discussions of standards needs for gene and cell therapy product assessment.** After identifying needs, the groups voted on potential standards that would have the greatest positive impact in the field.

Findings

During the initial feasibility meetings, participants discussed the feasibility of standardization around the main topics of product activity and comparability, noting that standardization would be difficult at a high level due to the sheer number of critical quality attributes (CQAs) and different potential ways to measure them. In addition, they determined that attempting to standardize certain cell lines

and assays would not be feasible due to the amount of variability in what a therapy developer would need. However, they thought that some subtopics would be feasible to standardize, particularly if they focused on considerations for decision making that would be applicable to a broad range of products. Participants agreed that the following two sub-topics would have the greatest potential for standardization:

1. Methods for selecting and developing assays
2. Framework for selecting cell lines appropriate for the intended tissue model or disease model

After assessing each potential sub-topic, the group concluded that it would be most beneficial to focus specifically on a standard advising on how to how to select, implement, and validate assays. These initial discussions are described in depth in **Appendix: Detailed Phase 1 Findings.**

FDA identified a need to **further refine the scope of the standards needs identified during Phase 1 with input from the community** about current challenges and gaps, which was accomplished through the community workshop. The Phase 2 workshop focused on narrowing the assay selection and development topic from Phase 1 to focus on a specific assay or set of assays. Workshop participants identified the following three priority topics:

1. Empty/full/partial capsid characterization
2. Genome titer assays
3. Standardizing infectivity for adeno-associated viruses (AAVs), adenoviruses, and other viral vectors

Challenges and Standards Needs

The workshop included a broad discussion of challenges associated with gene therapy development. Some of the key challenges that emerged included:

- Difficulty ensuring clearance of helper viruses due to their similarity to adenoviruses and a need for reliable helper virus removal methods and common limits on levels of residual helper virus
- Variability in assays and methods for measuring full and empty capsids, including uncertainty around determining safe levels of empty capsids
- Difficulty defining partial capsids and a need for alignment on a consistent definition
- Lack of clear metrics to define viral vector quality
- Variability in the use of microphysiological systems (MPS) and cell-based assays to assess gene therapies (e.g., cell culture methods, cell sources, characterization approaches)

The group then examined the challenges they had identified and developed a list of potential standards that would address each challenge. They ranked the identified topics by priority; the full list of identified topics in order of priority includes:

1. Empty/full/partial capsid characterization
2. Genome titer assays
3. Standardizing infectivity for AAVs, adenoviruses, and other viral vectors
7. Total AAV capsid particle concentration
8. Post translational modifications in AAVs
9. Standards on in-process testing, particularly focused on the vector stability profile

4. Standards for impurities in the manufacturing process
5. Potency assays
6. Ultracentrifugation approaches
10. MPS characterization
11. Aggregation assessment

Priority Topic 1: Empty/Full Partial Capsid Characterization

Gene therapy product developers often struggle to identify a safe level of empty or partial capsids due to uncertainty about their impact on patients and difficulty comparing across products as a result of assay variability. A standard in this area would be valuable to establish assay best practices and allow for more meaningful cross comparisons.

Components of a Standard

A standard on this topic could address:

- Definitions of full/empty or possibly partial capsids
- Guidance on how to obtain, use, and characterize reference materials
- Pros and cons of different assay methods and advice on appropriate use cases for a given method
- How to report empty/full capsid results
- How to assess and address genome truncation within capsids
- Method for measuring empty/full capsids
- Interpretation of varying results among different methods (e.g., analytical ultracentrifugation [AUC] vs. charge detection mass spectrometry [CDMS])

Potential Barriers to Standardization

Feasibility Assessment Factor	Description of Barrier
Implementation Feasibility	Potential industry concerns about how specifications are defined and the implementation timeline
	Industry reluctance to change established practices
	Cost barriers and resource constraints in adopting the standard (e.g., obtaining new instrumentation)
	A need for new technologies or methods to apply the standard and training on how to use them
	Data integrity and compliance gaps for software packages used for new technologies

Stakeholders to Involve in Standards Advancement

Stakeholders could include manufacturers of all sizes, including startups; contract development and manufacturing organizations (CDMOs); biorepositories such as the American Type Culture Collection (ATCC); global regulators; and academia.

Priority Topic 2: Standards for Genome Titer Assays

There are three major methods for assessing genome titer—quantitative polymerase chain reaction (qPCR), droplet digital polymerase chain reaction (ddPCR), and digital polymerase chain reaction

(dPCR). Product developers are often uncertain about the benefits, drawbacks, and best use cases for each method. A standard advising on method selection and other considerations for how to best conduct these assays would help to ensure product quality and consistency.

Components of a Standard

The group identified two standards that would be needed:

- A standard on the **use of reference materials** covering their availability, use, characterization, methodology, and creation
- A **methodology standard** covering terminology and best practices for activities such as assay selection, interpretation, and validation

Potential Barriers to Standardization

Feasibility Assessment Factor	Description of Barrier
Implementation Feasibility	Developers who already have technology in place may be reluctant to make changes
	How to deviate appropriately
	Implementation cost
	Software required for data acquisition
Other Feasibility Factors	How the standard would age with current technology and revision cycles

Stakeholders to Involve in Standards Advancement

Stakeholders could include reference materials developers, raw materials manufacturers, and drug manufacturers of all sizes; CDMOs; and heads of chemistry, manufacturing, and controls (CMC), assay development, or other process development roles.

Priority Topic 3: Infectivity for Viral Vectors

The complexity of the steps involved in assessing infectivity of viral vectors leads to a great deal of variability in assay results. A standard on this topic could help with increasing predictability and consistency of assays and their interpretation from batch to batch and across different labs and manufacturers.

Components of a Standard

The needed standards identified for this topic were similar to those for Priority Topic 2:

- A standard on the **use of reference materials** covering their availability, use, characterization, methodology, and creation
- A **methodology standard** covering terminology and best practices for activities such as assay selection, interpretation, and validation

Potential Barriers to Standardization

Feasibility Assessment Factor	Description of Barrier
Technical Feasibility	Uncertainty around whether there is clear consensus on the method/topic
Implementation Feasibility	Difficulty developing software needed for data acquisition
	Difficulty bridging/transitioning to the standard
Other Feasibility Factors	Concern around how the standard would age with rapid changes in technology
	Variation among cell lines and their ties to licensing agreements

Stakeholders to Involve in Standards Advancement

Stakeholders could include reference materials developers, raw materials manufacturers, and drug manufacturers of all sizes; CDMOs; and individuals in process development roles such as heads of CMC or assay development.

Next Steps

SCB plans to organize new working groups to further assess the feasibility of the prioritized topics for standardization and potentially advance them to SDOs for development. SCB will focus initially on the **empty/full/partial capsid characterization** topic, which was the highest priority subtopic identified.

Next steps for the standard advancement effort are described below.

Goals for 2024–2025

- **Assemble a working group and seek relevant expertise,** focusing on the expertise areas identified in the feasibility report.
- **Conduct discussions with the working group** to confirm whether to move forward with the creation of a standard and further refine the standard's scope.
- **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.

Appendix: Detailed Phase 1 Findings

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 discussion identified the two sub-topics that would be most feasible to pursue: methods for selecting, developing, and validating assays, and a framework for selecting cell lines appropriate for the intended tissue model or disease model. Although some technical barriers were identified, such as the product-specific nature of potency, the feasibility assessment group believed that these would not be a major concern for standards within the selected subtopics. Additional input will be needed from other community stakeholders on which assays to prioritize for standardization.

OPPORTUNITIES	BARRIERS
• There is an opportunity to **teach product developers how to select proper assays and cell lines**. There are many approaches to choose from, and a **guide or framework on how to select the right one** for a product would be helpful. • There are universally measurable physicochemical properties that can be used as potential CQAs to **develop assays**. • Analytical characterization has a lot of **flexibility** even in well-established fields, such as the mAb industry.	• **There are few existing standards on these topics** that could be referenced or leveraged to develop new ones. • **Product potency is product-specific** and cannot be standardized aside from generalized approaches. • Product activity and comparability depend on the **modality of the therapy**. ○ E.g., a standard that would apply to an AAV-based gene therapy product would probably not apply to a lentiviral-based product.

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 meeting participants thought that sufficient expertise exists in this area and recommended reaching out to the following groups of stakeholders:

- Organizations producing cell lines
- Institutions (both academic and commercial) developing vectors
- The Bespoke Gene Therapy Consortium

- The National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL), which has a soon-to-launch viral vector program
- Assay developers
- Companies (e.g., Illumina, Bio-Rad) that could provide examples of internal controls used for these products
- FDA

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 significant impact.

The meeting participants noted that FDA's support will be critical for this standard to be used. Standards on how to select appropriate assays and cell lines would be invaluable for smaller companies or academic teams that do not have the bandwidth to make customized assays to test their products.

OPPORTUNITIES	BARRIERS

• A standard framework for selecting cell lines or assays would benefit all stakeholders and not require a large investment.
  ○ Smaller companies and teams could leverage frameworks on selecting cell lines or assays to **help them make decisions quicker** and save limited resources.
  ○ Larger companies or organizations would gain **an additional resource for decision-making**.
	• Assays or cell lines could potentially be standardized, but **organizations tend to produce their own** as needed.
	• **Regulatory agency recognition of the approach** will be important for encouraging adoption.

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.