Assessing Feasibility of a Standard
FOR LENTIVIRAL VECTORS

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 ensure efficient use of community resources.

Lentiviral Vectors

Lentiviruses are commonly used as a vector to treat genetic diseases due to their unique ability to stably integrate into non-dividing cells to replace abnormal gene variants. However, use of lentiviral vectors presents challenges such as difficulty in consistently assessing viral vector titer or transduction efficiency between varying sponsors and the risk of unexpected delayed effects. Standards could help stakeholders develop more consistent testing methods to enable more comparable measurements from lab to lab and improve the safety and effectiveness of lentiviral vectors.

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 lentiviral vectors. The report includes input from two facilitated meetings in December 2020 attended by eight experts across multiple stakeholder groups. See below for a breakdown of meeting participants by stakeholder group.

December 2020 Meeting Attendance by Stakeholder Group

Count	Stakeholder Type
7	Industry
1	Professional Society
2	SCB
2	Nexight Group

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 three major potential sub-topics for standardization:

- Titration assays and methodology
- Titer measurement improvement and terminology
- Replication competent lentivirus (RCL) testing

Among these, they agreed that titration assay and methodology standards were the highest priority. The most significant challenges to standardization identified by the group included resistance to change among larger companies with more established testing methodologies. However, the group believed that most stakeholders would ultimately recognize the potential benefits of a standard, such as filling knowledge gaps, facilitating innovation, and simplifying regulatory approval.

Further input will be sought from the working group to confirm that there is support behind these three standard topics, as discussed in the **Next Steps** section.

Technical Feasibility

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. Standards require a strong scientific and technical basis in order 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.

During the feasibility meeting, participants identified three sub-topics that may be ready to move forward for standardization, which are described in the sections below. The technical feasibility discussion focused primarily on issues related to the highest-priority sub-topic, titration assays and methodology.

SUB-TOPIC: TITRATION ASSAYS AND METHODOLOGY

Measurement of lentiviral vector titers differs from lab to lab, both through the use of different titration assays and differing methodology or environments (e.g., blood versus tissue). Variations can include vector pseudotyping, cell culture format, volume, cell type, timing of exposure to viral particles, and differences in measuring expression of transgene or copy number. A standard in this area could help ensure consistency and comparability of measurements and their interpretation. Participants believed that functional titration in particular is urgently in need of standardization, but that standards for both functional and physical titration would be valuable.

STANDARD OBJECTIVE: Create a standard framework to help stakeholders choose appropriate titration assays and methods for their needs.

OPPORTUNITIES	BARRIERS
• There is a need for standardization of the approach to **methods for the assessment and quantification of critical quality attributes (CQAs) such as titer, and/or residual host-cell or plasmid DNA.** • A vesicular stomatitis virus G (VSV-G) vector standard and/or other physical reference standards could be **broadly applicable across multiple cell lines and sponsors.**	• **Stakeholders may have difficulty agreeing on a cell type for transduction assays** that would be broadly applicable. • Numbers derived from integration titration assays are dependent on the conditions used; more work is needed to **investigate and characterize how different conditions and environments can impact the end result.**

SUB-TOPIC: TITER MEASUREMENT IMPROVEMENT AND TERMINOLOGY

Transducing unit is a functional titration measure that varies based on factors such as the target cells and the calculation method used to obtain it. Because of this, stakeholders often use the term to mean different things. Additionally, the current methods for assessing virus titers have a low level of measurement assurance. Improvements in best practices and the creation of documentary and physical reference standards would improve titer measurements and would enable clearer communication between stakeholders.

STANDARD OBJECTIVE: Develop standard terminology, improve best practices, and develop documentary and physical reference standards to support titer measurement improvement.

OPPORTUNITIES	BARRIERS
• It would be valuable to **establish clear definitions for terminology** applicable to lentiviral vectors (e.g., transducing units, functional titer). • There is an opportunity to **improve the application and increase the use of best practices** for the measurement of titer, in addition to **creating documentary standards**. • **Physical reference standards** could help bridge differences in and improve the quality of transducing unit methods and help to determine the suitability of assay(s) for intended purpose, while increasing sponsors' confidence in the quality of their testing methods. • There is a need to establish **measurement assurance and appropriate orthogonal measurements** for batch-to-batch consistency.	• The varying methods used to calculate transducing units **are difficult to compare.** • Standards **need to be compatible with existing methodology.** • The measurement of titer requires the use of cell-based methods, **which are difficult to control and automate.**

SUB-TOPIC: RCL TESTING

It is critical to test lentiviral vectors for RCL, a marker of uncontrolled replication ability, before therapeutic use to avoid adverse outcomes such as the development of tumors. Existing regulatory guidance for RCL testing primarily focuses on T-cell therapies, leading to uncertainty around the appropriate level and types of testing for other applications.

STANDARD OBJECTIVE: Create a risk-based framework for selecting and validating RCR/RCL testing methods.

OPPORTUNITIES	BARRIERS
• A risk-based RCL testing approach would offer a **significant benefit to organizations developing RCL assays** for products not covered under existing guidance. • It would be valuable to **establish a standard quantity of material for testing** (such as for adenovirus) because current testing methods lack scalability.	• **Numerous products and formats would need to be covered** by a potential standard. • **Because U.S. Food and Drug Administration (FDA) guidance already exists on this topic**, it would be difficult to introduce a new standard.

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 in order 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. During the feasibility meeting, participants focused on what additional expertise is most needed in the standard working group. They identified the National Institute of Standards and Technology (NIST) and National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) members as key stakeholders whose input will be critical. In addition, they identified the following stakeholder groups:

- **Manufacturers,** who could potentially drive development for reference standards:
    - OxfordBiomedica
    - Lentigen
    - AGC Biologics (formerly MolMed)
    - FinVector
    - Novartis
    - Gilead
    - Orchard Therapeutics
- **Service Providers**
- **Academia,** including vector core facilities and universities with good manufacturing practice (GMP) vector capabilities. Participation by these organizations could help labs align with industry standards early in their projects. In particular, the participants proposed reaching out to the following organizations:
    - University of California, Los Angeles (UCLA) Vector Core, Los Angeles
    - King's College, London
    - Indiana Clinical and Translational Sciences Institute (CTSI)
    - San Raffaele University School of Medicine, Milan

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 feasibility meeting participants predicted that members of the community would welcome lentiviral vector standards if the standards are simple and easy to adopt. They predicted that smaller companies with fewer entrenched processes would benefit the most from a standard.

OPPORTUNITIES	BARRIERS
• Once a standard has been set up across different organizations, there would likely be **no additional major costs.** • Academic labs would benefit from **a standard's ability to help demonstrate that a product is manufacturable;** using standards could help them make a case for funding and address potential development challenges. • A standard would **promote innovation and save companies effort** spent re-discovering effective testing or measurement processes.	• Historically, stakeholders have been **resistant to adopting new ways of testing**, so messaging about the benefits of the standard would be important. • Organizations with well-established methods and systems differing from the proposed standards (e.g., focusing on multiplicity of infection [MOI] rather than physical titer) **may have an additional burden in implementing the standard.**

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. They concluded that a potential lentiviral vector standard would have minimal intellectual property (IP) concerns and there would be no anticipated incompatibilities with existing legal frameworks.

OPPORTUNITIES	BARRIERS
• **IP is not a major concern**; organizations typically use arbitrary conditions from historical practice.	• Some **materials licenses may be needed for limited use of cells,** but participants did not see this as a major barrier.

Next Steps

The feasibility assessment found that overall, there are few significant barriers for technical feasibility, expert availability, implementation feasibility, and other feasibility factors. Participants agreed that the sub-topic of titration assays and methodology would make the most sense to address first, because it is a high priority standard need likely to be well received by the regenerative medicine community.

Next steps for the feasibility assessment effort are described below.

GOALS FOR 2021

- **Seek additional working group participants,** focusing on the expertise areas identified in the feasibility report, which include specific manufacturers, service providers, and academic organizations.
- **Continue discussions with the working group** to confirm whether to move forward with the creation of a terminology document, the titration assay sub-topic, and/or other sub-topics identified in the report. The SCB working group focused on this potential standard will review

the report and will come to a decision on which of the specific standard sub-topic areas to pursue during its upcoming meetings.

- **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 be able to move forward as long as community enthusiasm and participation remains high.
- **If the standard will move forward,** SCB will begin to outline the potential standard.