Assessing Feasibility of a Standard

FOR A FRAMEWORK FOR GENE DELIVERY METHODS AND GENE EDITING TOOLS

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.

Need Overview: Framework for Gene Delivery Methods and Gene Editing Tools

As gene therapy is a relatively new and continually evolving subsector in the field of regenerative medicine, there is often insufficient consensus around appropriate tools and methods for a given application, which can result in potential safety risks, such as misidentification of genetic material or incorrect removal/insertion processes. Opportunity exists to improve the safety of gene therapy products by developing guidelines for selecting appropriate tools and gene delivery methods and establishing best practices for their use.

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 for potential standards to provide a framework for gene delivery methods and gene editing tools. The report includes input from three facilitated meetings in April 2021 attended by 15 experts across multiple stakeholder groups. See below for a breakdown of meeting participants by stakeholder group.

April 2021 Meeting Attendance by Stakeholder Group

Count	Stakeholder Type
1	Academia
11	Industry
1	Public-Private Partnership
2	Government
2	SCB
2	Nexight Group

STRUCTURE

The feasibility assessment considered four 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 meeting participants identified four major potential sub-topics for standardization:

1. Off-target effects
2. Quality of reagents
3. Acceptable amount of residual-free guide RNA *ex vivo*
4. Genome stability

Of these sub-topics, two were identified as the best candidates to move forward due to their relative priority and readiness for standardization: **off-target effects** and **quality of reagents.** The meeting participants determined that technical feasibility is a significant barrier for both subtopics due to a lack of consensus in the community on specific measurement needs and solutions. While the group believed this barrier would be surmountable, they did not believe a standard would be immediately feasible.

The group proposed that an appropriate first step would be to develop a white paper addressing one or both sub-topics. A white paper defining common challenges would provide the community with a chance to give feedback on their needs and share solutions they have developed. Input gathered in development of the white paper would inform creation of a standard better tailored to real-world needs and best practices and more likely to be embraced by the community.

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 creating the standard and seeks to ensure that the standard will serve its intended purpose.

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

SUB-TOPIC: OFF-TARGET EFFECTS

The genome editing community lacks sufficient best practices for assessing off-target effects. There is a lack of technical understanding and agreement surrounding issues related to **how much of the genome needs to be sequenced** when looking for off-target effects, as well as **how much confidence to have in the result** based on the percentage of the genome that was sequenced. The community also lacks a framework for **validating new methods** to ensure they produce valid and consistent results.

A standard in this area could help organizations arrive at solutions for these challenges by identifying best practices and areas of technical consensus, which organizations could refer to rather than spending significant time and resources testing measurement methods and designing method validation approaches in house. Arriving at proven, reliable measurement approaches for detecting off-target effects would also improve patient safety and foster public confidence in gene-edited therapeutics.

Additionally, clarity and agreement on the best practices for detection, methods, and thresholds for off-target effects will bring the regenerative medicine community closer to addressing other significant challenges, including:

- Detecting and mitigating risk of chromosomal translocations
- Unintended integrations of a sequence into the genome
- Assessing whether or not gene delivery or editing has been successful

STANDARD OBJECTIVE: Develop a framework for detecting off-target effects—including appropriate parameters for genome sequencing, recommended methods, and characteristics to measure based on use case—and best practices for validating new off-target measurement methods.

OPPORTUNITIES	BARRIERS
• Various companies **are already actively working in the genome editing space** and would benefit from even a preliminary resource such as a white paper. • The **NIST Genome Editing Consortium is working concurrently on reference materials and benchmark data** that could help support development of a documentary standard.	• There is **not yet consensus in the community** on the answers to key scientific questions in this sub-topic (e.g., interpreting results, the consequences of specific off-target changes); a white paper could promote discussion and sharing of best practices. • Organizations **lack incentives and direction to encourage them to collect and share the data** that would be needed for a standard; a white paper could also help with this challenge by helping to focus the community on a narrow set of key problems. • Because off-target effects impact the whole genome editing field, **a single standard could likely not address all relevant issues**; more input from the community is needed to identify an appropriate scope for a standard. • Many organizations have spent significant time and resources developing in-house methods and may have **difficulty coming to consensus on method recommendations or defining criteria that applies broadly to all relevant methods**.

SUB-TOPIC: QUALITY OF REAGENTS

While FDA guidance exists for viral vectors, there is no similar guidance for non-viral vectors such as lipid nanoparticles. **Quality varies widely in reagents used in gene-edited therapy products,** and the field

would benefit from a **comprehensive list of desired quality attributes for reagents.** Such a list could specify identity, purity, and potency testing guidelines; methods for establishing and communicating stability protocol; and other quality considerations such as ensuring that packaging maintains a consistent charge to avoid unintended reactions with the reagent.

STANDARD OBJECTIVE: Develop a list of recommendations for characteristics relevant to reagent quality and provide recommendations on appropriate methods to measure these characteristics.

OPPORTUNITIES	BARRIERS

• Several **related standards could be leveraged** when developing a standard on reagents:
  ○ ISO/TS 20399-1, Ancillary Materials Present During the Production of Cellular Therapeutic Products
  ▪ Part 1: General Requirements
  ▪ Part 2: Best Practice Guidance for Ancillary Material Suppliers
  ▪ Part 3: Best Practice Guidance for Ancillary Material Users
  ○ ISO/FDIS 23033, General Requirements and Considerations for the Testing and Characterization of Cellular Therapeutic Products
  ○ ISO 20688, Nucleic Acid Synthesis
  ▪ Part 1: Requirements for the Production and Quality Control of Synthesized Oligonucleotides
  ▪ Part 2: General Definitions and Requirements for the Production and Quality Control of Synthesized Gene Fragment, Gene, and Genome
	• The **impact of some quality attributes is still unknown,** which limits the ability to provide specific recommendations. For example, there is not yet a precise understanding of how much a 10% variation in lipid nanoparticle purity could affect potency.

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 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 following stakeholder groups whose input would be valuable:

- Inventors of core off-target methods
- Pathologists who can provide input on how long to follow up with patients for off-target concerns
- Organizations that make gene editing reagents

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.

SUB-TOPIC: OFF-TARGET EFFECTS

The meeting participants did not identify any significant implementation barriers for an off-target effects standard, but they noted that it will be important to avoid making the standard overly strict, as strict standards are costly to implement and can limit innovation.

OPPORTUNITIES	BARRIERS
• Provided the standard is not overly strict and prescriptive, the working group anticipated it would **save product developers money** by enabling them to focus time and resources on the most critical tests. • The standard would also **save time and reduce uncertainty for small companies** who would otherwise be uncertain how risky their off-target effect detection approach is. • The standard could help encourage **contract development and manufacturing organizations (CDMOs) to adopt new technology** by providing a better understanding of what tests are needed for off-target effect detection.	• A strict standard **prescribing specific methods would likely be expensive and cumbersome** to implement and could **impede technological advances**.

SUB-TOPIC: QUALITY OF REAGENTS

The meeting participants did not identify any significant implementation barriers for a reagent standard, but they thought that more information is still needed from experts on the potential impact of a standard on reagent suppliers. Additionally, it is unclear if this standard need could be met by using several existing standards, or if it would be better to add lipid nanoparticle considerations to existing

standards in future updates. The meeting participants, however, believed that a white paper or standard would be received positively by the community and would be beneficial in further defining the key challenges.

OPPORTUNITIES	BARRIERS
• A standard could lead to **potential savings for therapeutic product developers** by ensuring more consistent quality of materials. • Participants believed the **community would welcome effort toward standardization** in this area because it would help address recurring concerns about reagent quality.	• Participants were **not sure of the economic impact of the standard on reagent suppliers**; more input is needed from the community.

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 not included in the other factors. One consideration the group identified is that the FDA may soon release additional guidance related to genome editing, so it would be important to coordinate with the FDA to avoid overlap.

OPPORTUNITIES	BARRIERS
• **Intellectual property (IP) is not anticipated to be a concern for off-target measurement methods**; companies are generally willing to share information.	• Guidance for genome editing is listed on the 2021 CBER-FDA guidance agenda; coordination with FDA may be necessary to ensure **work toward standardization harmonizes with any in-progress guidance**. • **IP issues could be a concern for lipid nanoparticles**, but specific stakeholders in the space may be willing to share knowledge for a reagents standard.

Next Steps

The feasibility assessment determined that while **the field is not yet mature enough for standards** on gene delivery methods and genome editing, **the genome editing community would welcome a preliminary resource such as a white paper.** A white paper would also spur discussion on specific standards needs and encourage stakeholders to share knowledge and data that could contribute to a future standard. The working group determined that the off-target effects sub-topic is higher priority

than reagent quality due to its safety implications and should be prioritized for a white paper. However, SCB will continue to assess the issue of reagent quality and seek input from additional subject matter experts on lipid nanoparticles to determine the path forward. Based on preliminary information, it is likely that this issue will be addressed through a white paper that defines the issue and educates the community on existing standards that are applicable for some reagent quality issues.

Next steps for the feasibility assessment effort are described below.

GOALS FOR 2021 – 2022

- **Ongoing: Seek additional working group participants**—focusing on the expertise needs identified in this report—for the development of the white paper on off-target effects and to better understand and make actionable the issues surrounding lipid nanoparticle reagent quality.
- **Late 2021: Develop a white paper on off-target effects** that defines the common challenges, creates a venue for conversation and sharing of internal solutions and best practices among stakeholders, and educates the community on the state and needs of the technology. The white paper will be revised based on input from FDA and additional relevant experts.
- **Mid 2022: Publish the white paper on off-target effects** and seek feedback from the community on standards needs and potential solutions to common challenges.
- **Late 2022: Reassess** whether standards should be advanced, researched further through independent effort, or tabled for future reconsideration. SCB believes that the data gathered from the community through the white paper development process may reduce or remove the current technical barriers to feasibility and make it possible to proceed with standard advancement.