Assessing Feasibility of a Standard

FOR EVALUATING PRE-EXISTING IMMUNITY TO ADENO-ASSOCIATED VIRUSES

Final Report

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STANDARDS COORDINATING BODY

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 75F40119P10294. 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.

SCB's gene therapy sector working group identified the need for a standard for assessing pre-existing antibody-mediated immunity to adeno-associated viruses (AAVs) in early 2018, and gene therapy stakeholders prioritized this area for standards advancement through a community-wide survey in early 2019. AAVs are a promising vehicle of delivery for gene therapy treatments due to their non-pathogenic nature and relatively low rate of immune response. However, patients who do have a pre-existing immunity to AAVs may be unable to fully benefit from these therapies and can face additional treatment complications. Pre-existing immunity to AAVs presents a significant challenge to the safety and efficacy of AAV-based treatments for the general population, but there is currently no common language or standard process for evaluating pre-existing AAV immunity prior to attempting treatment.

After this standard need was identified, SCB assembled an AAV 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 pre-existing immunity to AAVs. The report includes input from the AAV project working group discussions, as well as from a facilitated meeting in August 2019 attended by 38 experts across multiple stakeholder groups. See below for a breakdown of meeting participants by stakeholder group.

August 2019 Meeting Attendance by Stakeholder Group

Count	Stakeholder Type
16	Industry
4	Academia
2	Government
1	Professional Society
7	Standards Developing Organization (SDO)
3	Affiliation not Given
2	SCB
3	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 members 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

Pre-existing immunity to AAVs is a broad area, and no single standard can address every consideration within this topic. This feasibility assessment sought to determine sub-topic areas ready for standardization. While five sub-topics were identified that would be valuable to standardize within AAV, two of these appeared ready to advance based on discussion during the feasibility meeting:

- **A language and terminology standard** establishing and defining common terminology for use in evaluating AAV immunity
- **A validation standard** providing guidance for accurate use of assays, including evaluating whether an assay used for assessing pre-existing AAV immunity is fit for purpose

The technical challenges for these sub-topics are possible to overcome through expert discussion and appropriate scoping of the standards, and both sub-topics can provide strong foundations for other standards work. A language and terminology standard would facilitate communication about the complex topics involved in evaluating pre-existing AAV immunity, and a validation standard would make the data collected across the field more useful and comparable.

Further input will be sought from the working group to confirm that there is support behind these two 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.

Technical feasibility was the primary focus of this feasibility assessment. Because technical feasibility challenges are often driven by external factors in the field itself, addressing these challenges requires extensive input from the community.

GENERAL CHALLENGES TO TECHNICAL FEASIBILITY

The topic of pre-existing immunity to AAVs and other vectors used in gene therapy is very complex and is not yet fully understood scientifically. There are issues within basic immunology that still need to be addressed, such as cases where patients may have combinations of AAV antibodies that lead to unclear testing results.

However, during the feasibility meeting, experts from industry, academia, and government identified five sub-topics that may be ready to move forward for standardization. The potential opportunities and feasibility challenges associated with standardizing these sub-topics are discussed in the tables below.

SUB-TOPIC: LANGUAGE/TERMINOLOGY

Currently, organizations involved in assessing pre-existing immunity to AAVs often use different terms for the same concepts, such as describing neutralizing assays using cell lines as either transduction assays or uptake assays. This lack of a common language can lead to confusion and make it difficult to discuss technical needs.

STANDARD OBJECTIVE: Create a list of terms and definitions related to pre-existing AAV immunity.

OPPORTUNITIES	BARRIERS
• A language and terminology standard would **provide a useful starting point for pre-competitive dialogue** and help facilitate clear communication as stakeholders from across different sectors and geographies collaborate on specific technical standards. Common terminology would provide a foundation for **industry and regulators to communicate effectively,** which is important for product safety. • This standard **would not need to be narrowed to a specific serotype or capsid,** allowing a single, broadly applicable standard to be produced relatively quickly. • The standard could leverage the efforts of the American Society of Mechanical Engineers (ASME), which has expressed interest in creating a regenerative medicine lexicon (see **Expert Availability**).	• **Pre-existing immunity touches on numerous perspectives and expertise areas,** including biotechnology, manufacturing, pharmaceuticals, diagnostics, and immunology. Individuals from these varied disciplines **may have difficulty reaching consensus,** and it may be challenging to ensure that all perspectives are represented during standard development. • However, **the technical barriers to developing this standard are low overall** because most terminology in the field is generally agreed upon and barriers to consensus for terminology can usually be overcome with discussion by experts.

SUB-TOPIC: VALIDATION OF ASSAYS

There are many variables involved in selecting and validating assays for assessing pre-existing immunity, including the type of test to use and how to interpret and compare results. Clinical trial designers often find it difficult, time consuming, and costly to independently design a validation process for assays to test for pre-existing immunity. Independent validation processes can also hinder the ability to compare collected data across different organizations.

STANDARD OBJECTIVE: Provide guidance on the accurate use of assays, including considerations to determine if the assay chosen is fit for purpose.

OPPORTUNITIES	BARRIERS
• As new assays to assess pre-existing immunity are developed and implemented, there is a need to **ensure accuracy and validity of the data produced.** A validation standard would help address this need. • There are **two major test types for assessing pre-existing immunity**—enzyme-linked immunosorbent assays (ELISA), which measure antibodies, and cell-based assays that measure neutralizing activity. A standard could discuss **how to determine and perform the most appropriate assay** and provide important points to consider for the selected test. • The standard could **help resolve common questions** about setting up assays for optimal results. • **Existing standards have been developed for measuring neutralizing antibody response to protein therapies,** which could be used as a reference point for a potential AAV standard. • By improving data quality and comparability, a validation standard would **advance the foundational knowledge needed to pursue other standards,** as well as for the field in general.	• **Scientific understanding of how to use circulating or total antibodies** in determining true naïve status versus delay of reaction is still limited, which would make it difficult to provide clear guidance in this area. • Several key questions for successful assessment of pre-existing immunity are also still being explored, such as **how to ensure an ELISA is measuring the correct population of antibodies, identify false positives, and determine whether results correlate with actual neutralization activity**. This information could not be included in a standard until the questions are resolved within the field. • There are also likely to be some **intellectual property (IP) concerns about assay specifics,** which would limit the ability to discuss detailed assay considerations in a standard.

SUB-TOPIC: ANTIBODY REFERENCE MATERIAL

Creating a high-quality reference material for use in assay validation is critical for effective assessment of pre-existing AAV immunity. Clinical trial designers need a reference material that is representative of relevant antibodies and is not prohibitively expensive to generate.

REFERENCE MATERIAL OBJECTIVE: Create a material (polyclonal serum or collection of recombinant monoclonals) that can be used to validate assays for their ability to detect desired antibodies.

OPPORTUNITIES	BARRIERS
• A reference material **for needed populations of antibodies** would improve the assay validation process for clinical trial designers. • There are different advantages to using monoclonal versus polyclonal antibodies—monoclonal antibodies are more specifically targeted, while polyclonals provide better cross-reactive detection. **It may be possible to combine both desired qualities** by creating a panel of monoclonals that functions as a polyclonal. • **Epitope mapping could potentially be used** to determine the most effective reference material to cover the main epitopes. • **The American Type Culture Collection (ATCC) has created AAV reference materials** for specific serotypes that could be leveraged for this effort. • **The National Institute for Biological Standards and Control (NIBSC) is working on a monoclonal panel** that could be tied into a standard effort.	• There are **still many unknowns regarding which antibodies are most relevant to clinical results,** so a truly representative antibody reference material may not yet be possible. • Key data is still needed that would be valuable in developing an effective reference material, such as **the number and serotypes of different antibodies that are generated** for a serotype, and **patient-derived antibody sequences** related to capsid proteins. • Multiple reference materials would need to be created, as a **single reference material would not be relevant to all AAV serotypes and capsids**. • The subject matter expert community would also need to **clearly identify the desired technical objective of this potential standard area**, as the community seems to still have varying perspectives on the purpose/application of the assay to be standardized within this topic (e.g., a panel of all potential neutralizing antibodies, product-specific antibodies, cell lines to use for neutralizing antibody assays, etc.).

SUB-TOPIC: AAV SEROTYPE-SPECIFIC STANDARDS

Each AAV serotype produces a unique immune response which may involve a different set of antibodies and neutralization mechanisms. Effective testing of pre-existing immunity requires clinical trial designers to understand these factors and identify the most relevant test methods for the serotype they are using.

STANDARD OBJECTIVE: Establish a set of considerations specific to individual AAV serotypes that suggests appropriate assays and testing methods.

OPPORTUNITIES	BARRIERS
• Standards **aimed at specific serotypes and capsids would be highly valuable** to help researchers tailor their approach to ensure they are utilizing the most appropriate methods to test for the right antibodies. • Transduction of genetic material for therapeutic purposes using AAV vectors is complex, with **multiple factors impacting success beyond the presence of relevant antibodies.** A serotype-specific standard would allow detailed consideration of these factors. • **Some patients independently seek seropositivity testing** prior to participating in AAV trials. A standard would increase the comparability and accuracy of these test results, increasing patient safety.	• It is important to determine whether **antibodies for specific serotypes and capsids are neutralizing or non-neutralizing.** Efforts to explore this question are still ongoing and cannot be included in a standard until they are resolved. • Due to genetic similarities between capsids, **an immune response may result even if there is no prior exposure.** There is still a need to better understand mechanisms that cause these cross-reactivity responses in order to provide detailed guidance on how to obtain meaningful assay results. • Each serotype standard will **need to be prioritized in order to allocate the appropriate time and resources** needed to develop them, and currently it is uncertain which serotypes will have the most impact.

SUB-TOPIC: LIMIT OF DETECTION/ANTIBODY TITER THRESHOLD

The field currently lacks a clear understanding of the antibody titer threshold that is predictive of poor therapeutic results. This makes it difficult to interpret when the titer level detected by a pre-existing AAV immunity assay should be the basis for exclusion from a clinical trial.

STANDARD OBJECTIVE: Offer guidance on acceptable limits of detection to determine patient exclusion from AAV trials.

OPPORTUNITIES	BARRIERS
• A titer threshold standard could provide guidelines for **interpreting levels of IgG versus IgM and anti-drug antibodies versus neutralizing antibodies,** helping clinical trial designers make more nuanced interpretations of assay results. • Guidelines for titer thresholds could also help clinical trial designers determine **when to adjust dosing levels or use pre-existing immunity for patient stratification** within the clinical trial, rather than excluding patients from participating. • Providing guidance for **data collection best practices, such as time points for testing,** would help in determining primary versus secondary reactions more effectively. Testing soon after exposure is important for gathering meaningful results.	• Providing detailed guidelines for limit of detection **may be dependent on answering the questions raised in other sub-topics,** such as appropriate antibodies to test for and the assay methodology. • **The ability to predict adverse events after AAV exposure is still limited**—for example, activation of IgG has triggered renal damage in patients. Detailed knowledge of what causes these events is important for providing meaningful guidance about patient exclusion from trials. • **All patients have some immune response to AAVs,** but the timing and degree of that response differs. Scientific understanding of the clinical significance of these differences may not yet be mature enough to support development of a standard on this sub-topic.

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.

RELEVANT SDOS

The decision on which SDO(s) may take up the development of this standard is still pending. During the feasibility meeting, participants discussed potential candidates and standard development mechanisms.

OPPORTUNITIES	BARRIERS
• Potential SDOs that work on similar regenerative medicine standards include **the Parenteral Drug Association (PDA), ASTM, and NIBSC.** • **The International Organization for Standardization (ISO) is also a possibility** and could be approached through the U.S. Technical Advisory Group (TAG) for ISO/TC 276. • **ASME is working on a lexicon** for the bioengineering space, with future plans for a regenerative medicine lexicon. There may be an opportunity to advance the AAV terminology standard as part of ASME's ongoing work in this area.	• Currently, **no SDO has expressed definitive interest in the standard,** so the working group would need to continue to actively approach potential candidates.

NEEDED EXPERTISE

The AAV standard working group generally has the right expertise needed to move forward, but it could benefit from additional perspectives and input from specific disciplines.

OPPORTUNITIES	BARRIERS
• The current project working group has a broad cross-section of relevant expertise and perspectives, including **product manufacturers, industry representatives, and clinical and academic researchers.** • The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use **(ICH) or ISO could be invited to participate to help ensure global harmonization and international availability** of the standard.	• Additional expertise is needed from **pre-clinical and diagnostic companies** that are involved in product development and/or pre-screening of patient candidates for clinical trials. • The standard effort could also benefit from the involvement of **patient advocacy groups to help working group members better understand how viable patient populations are assessed.** • More **immunology expertise and additional academic perspectives** could also help enhance the standard effort.

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 overall, members of the community would expect to benefit from the standard and would readily adopt it. They felt that any associated implementation costs would be minimal and would be outweighed by the value of improved testing methodology that would allow more efficient and effective pre-existing immunity screening.

OPPORTUNITIES	BARRIERS
• Standards that improve AAV screening ability (e.g., assay methods, kits, reagents) would be expected to **increase clinical trial efficiency** by excluding patients who do not meet certain criteria, ultimately improving time to market. • Additionally, **patient enrollment in trials would be expected to rise** due to higher rates of positive outcomes. • Materials costs for assays tend to be low, and researchers are motivated to obtain the most robust tests they can, so **cost is not expected to inhibit adoption.**	• While assay materials are usually not costly, the **expertise necessary to run additional or more complex assays** may be a barrier to adoption for some organizations. • Some assays are proprietary and reflect significant time and investment. Standard developers would **need to be conscious of avoiding post-competitive differentiators.**

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. A potential AAV standard would be relatively low cost to develop, and the standard working group has already conducted research to help harmonize it with existing U.S. and international regulations.

OPPORTUNITIES	BARRIERS
• In preparation to draft a white paper on AAV standards needs, the working group **conducted research on existing standards and assessed numerous regulatory documents,** including FDA guidance, guidelines from the European Medicines Agency (EMA), and guidance	• Expected barriers in this area are low; however, **coordination of the project does require SCB resources.** Currently, SCB is devoting one fifth of the time of a technical program manager to this project, plus travel costs to SDO meetings.

from the UK Scientific Advisory Committee on Genetic Modification (SACGM). Once work begins on a standard, this preparation will help to fit the standard into existing regulatory frameworks and avoid duplication of effort. • Expert discussion suggested that the **standard has potential for international adoption.** For instance, there are multiple companies in the UK that have expressed interest in AAV standardization. • The standard is being developed using volunteer resources and existing data, so **estimated costs are minimal.**	

Next Steps

The feasibility assessment found that overall, there are few significant barriers for expert availability, implementation feasibility, and other feasibility factors. The level of technical feasibility varies by sub-topic, but the sub-topics of Language/Terminology and Validation of Assays may be ready to move forward based on the expert discussion.

Next steps for the feasibility assessment effort are described below.

GOALS FOR 2020

- **Invite input from the community** on this feasibility report.
- **Release a draft white paper to the public** discussing AAV standard needs and seek additional community input.
- **Identify interested SDOs** and formalize a plan to advance the standard within a particular SDO.

GOALS FOR 2021

- **Make a final assessment** of whether the standard should be advanced, researched further through independent effort, or wait for future reconsideration.
- **If the standard will move forward,** begin to outline the potential standard.