ASSESSING FEASIBILITY OF A STANDARD

for Defining Aspects of a Certificate of Analysis for Ancillary Materials

Final Report | Feb. 2023

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.

Need Overview: Certificates of Analysis for Ancillary Materials

A certificate of analysis (COA) is a paper or electronic document detailing product specifications. COAs include data from analytical testing performed by a quality assurance body (either internal or external to the manufacturing organization) to ensure that product parameters of each batch or lot fall within expected values.

Precision manufacturing processes with high efficiency and low waste require consistency in the quality of ancillary materials. There is currently no standard process for the evaluation or presentation of COAs across ancillary material suppliers, making it difficult for regenerative medicine manufacturers to ensure reproducibility, comparability, and consistency in their products.

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 developed this report to outline the results of its feasibility assessment of potential standards for COAs for ancillary materials. The report includes input from facilitated meetings in December 2022 and 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
7	Industry
2	SDO
3	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 group discussed various information gaps that a COA standard could address:

- Which components should be considered ancillary materials and which should be excluded (e.g., single-use systems, IV bags and other disposable plastics)
- Types of ancillary materials (i.e., low- vs. high-risk categories, animal- vs. human-derived components) and how material type affects testing requirements
- Template for information to include in a COA
- Testing recommendations, including the recommended stringency level and information ancillary material suppliers should share (e.g., measurement units, assays) for the following tests:
    - Identity tests
    - Functionality tests
    - Sterility tests, including sterility assurance level of terminally sterilized products (e.g., 10^{-3} or 10^{-6})
    - Mycoplasma tests
    - Particulate tests, including guidelines on what particulates are safe
    - Virus tests
    - Endotoxin tests

The group believed that these sub-topics would be best addressed by developing a **single standard that provides recommendations on a broad range of considerations for developing ancillary material COAs.** Such a standard could help to decrease variation in ancillary materials among suppliers, address concerns from regulators regarding inconsistency of information available on ancillary material quality, and improve the clarity of communications between ancillary material suppliers and users.

The group identified implementation feasibility as the most significant barrier to standardization. They anticipated potential pushback from ancillary materials suppliers who may view the additional testing and reporting recommended by the standard as burdensome. However, the group thought this barrier would be surmountable if representatives from ancillary materials supplier organizations were involved in the development of the standard. Early involvement would give them a chance to share concerns and ensure that standard recommendations would be realistic for their organizations to implement.

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 meeting participants identified some concerns related to inconsistency in existing standards and potential difficulties with testing specific subtypes of ancillary materials but did not identify any technical barriers they felt were significant enough to prevent the development of a useful standard.

OPPORTUNITIES	BARRIERS

• **Relevant standards that could be leveraged** for this effort include:
  ○ ISO 20399, Ancillary materials present during the production of cellular therapeutic products and gene therapy products
  ○ ISO 20399-1:2018, Ancillary materials present during the production of cellular therapeutic products — Part 1: General requirements
  ○ ISO 20399-2:2018, Ancillary materials present during the production of cellular therapeutic products — Part 2: Best practice guidance for ancillary material suppliers
  ○ ISO 20399-3:2018, Ancillary materials present during the production of cellular therapeutic products — Part 3: Best practice guidance for ancillary material users
  ○ USP <1043>, Ancillary Materials for Cell, Gene, and Tissue-engineered Products
• A standard could **encourage more stringent testing** than is currently common (e.g., for sterility and mycoplasma).
	• There are **conflicts in existing standards** (e.g., ISO, USP) **regarding what is considered an ancillary material.** It will be necessary to come to an agreement on which components to include as ancillary materials in the standard.
	• **Some ancillary materials may not be compatible with existing assays** (e.g., serum is often too complex for an identity test to be informative).
	• Ancillary materials suppliers **could have difficulty anticipating all the potential end use cases** to inform the performance tests they should develop.
	• **Functionality tests have a high degree of variability** and may be challenging to standardize; this could potentially be addressed by including sections on different material types in a standard.

Expert Availability

Needed Expertise

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 feasibility assessment participants believed it would be important to reach out to the following groups to involve them in the development of the standard:

- Ancillary materials suppliers (e.g., suppliers involved in Bioforum's Cell and Gene Therapy Raw Materials Phorum)
- Stakeholders involved in functional testing
- Regulators

Relevant SDOs

The decision on which SDO(s) may take up the development of this standard is still pending. The group discussed potential candidates, including the United States Pharmacopeia (USP) and International Organization for Standardization (ISO), and noted that an ISO standard may receive more international adoption.

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 major implementation feasibility barrier identified by the group was potential pushback from ancillary materials suppliers in response to new testing expectations created by the standard. The feasibility assessment group believed this barrier could be overcome by including ancillary materials suppliers in the standard development process and soliciting their input on the tests that would be realistic to implement.

OPPORTUNITIES	BARRIERS
• It is often **more efficient and effective for ancillary materials suppliers to test their own products** rather than having end users develop tests for the broad range of ancillary materials they use in their processes. • **Following the standard could provide a competitive advantage** for ancillary materials suppliers who choose to do so. • There is an opportunity to pursue FDA support for the standard by submitting it for review by the **Voluntary Consensus Standards Recognition Program for Regenerative Medicine Therapies**.	• Ancillary materials suppliers may push back because **the standard would add to their required release testing**.

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 group noted that ancillary materials suppliers may have concerns related to sharing intellectual property (IP) associated with testing processes, particularly identity testing. This concern could be addressed along with the implementation barrier described above by involving ancillary materials suppliers in the standard development process to give them a chance to help shape the standard's recommendations.

Next Steps

The feasibility assessment determined that there are few significant technical, implementation, expert availability, or other barriers to a standard for COAs for ancillary materials. Based on the feasibility assessment outcome, the group plans to pursue advancement of a broad standard **addressing the different considerations for developing ancillary material COAs**, including types of ancillary materials, tests that should be performed, and testing information that should be recorded in the COA.

The group will hold additional discussions to further explore standard feasibility and define the best scope for a standard.

Next steps for the feasibility assessment effort are described below.

Goals for 2023–2024

- **Assemble a working group and seek relevant expertise,** particularly from ancillary materials suppliers and experts involved in functional testing. The working group will also work to provide feedback on current standards efforts underway with complementary topics.
- **Conduct discussions with the working group** to confirm whether to move forward with the creation of a standard on considerations for developing ancillary materials COAs.
- **Publish the feasibility report** and invite input from the regenerative medicine community. SCB will make the report publicly available on its website to promote interest in the standard advancement project and increase the visibility of the feasibility assessment process.
- **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. The group is currently considering proposing the topic as a potential standard to ISO.
- **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.