ASSESSING FEASIBILITY OF A STANDARD

for Guidelines for Interoperability for Regenerative Medicine Equipment and Software

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STANDARDS COORDINATING BODY
REGENERATIVE MEDICINE

NEXIGHT GROUP

DISCLAIMER

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Table of Contents

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: Guidelines for Interoperability for Regenerative Medicine Equipment and Software

The development and manufacture of regenerative medicine therapies involves numerous highly complex technologies and processes, including sensors and imaging, data analytics and data management, cell culture and incubation, and product storage and delivery; all of these technologies and processes must operate at a high standard to ensure product efficacy and safety.

For regenerative medicine therapies to be commercially viable, automation and interoperability of hardware and software are critical to:

- Reduce the amount of paper-based or manual data entry for product manufacturing processes, which is associated with additional cost, contamination risk, and labor
- Enable more advanced analysis of the complex data required to assess products, potentially providing new process or operational insights to streamline production of therapies

For these reasons, standards for interoperability have the potential to reduce costs and increase availability and consistency of regenerative medicine products, as well as allow smaller or newer product developers to more easily enter the market.

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 interoperability for regenerative medicine equipment and software. The report includes input from a facilitated meeting in June 2022. See below for a breakdown of meeting participants by stakeholder group.

June 2022 Meeting Attendance by Stakeholder Group

Count	Stakeholder Type
4	Industry
1	Academia
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 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 meeting participants identified **data integration** as the priority subtopic for standardization within the overall interoperability need area. Currently, regenerative medicine manufacturers spend a disproportionate amount of time manually transcribing data from devices (e.g., cell counters, imaging devices) that either lack a means of outputting data or have a proprietary data management system that does not allow direct data transfer to other equipment. In addition, operators in sterile production rooms face difficulties completing paper records and computer keyboard operations due to gowning.

A standard promoting open data and communication protocols and data models could help product manufacturers carry out **more rapid, comprehensive, continuous data assessment and analysis** for cell, gene, and tissue products to better understand causes of variability and improve quality, compliance, and efficiency of overall manufacturing processes. In addition, a standard on this topic would help avoid **transcription errors and contamination risks** from movement of paper records in and out of clean rooms.

The group discussed a potential multi-step approach to developing a data integration standard:

1. Complete a series of case studies assessing common devices to classify their usage, capability, and structure for data management, integration, and compliance and use the findings to help systematize an approach to data integration
2. Identify specific incentives that might compel suppliers of such equipment to extend their integration capability (e.g., the shift to continuous verification using integrated data could reduce the burden related to traditional qualification efforts)
3. Develop technical guidelines (e.g., for metadata, data dictionary, unified namespace, Internet of Things [IoT]-based protocols) that specify parameters and formatting to enable easily searchable, compatible data exports from equipment and make it possible to share data to use for analysis

The meeting participants determined that **implementation barriers would be the most significant** for this standard, as equipment vendors benefit commercially from the use of proprietary data management systems. Additionally, many regenerative medicine product developers have already integrated non-interoperable equipment into their processes and would have difficulty changing systems.

The meeting participants concluded that these barriers are surmountable, but it will be important to consider opportunities to incentivize suppliers and industry to extend data integration capabilities.

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.

While the meeting participants identified some technical barriers that would apply to a comprehensive data integration standard impacting equipment functionality, they believed that a standard related solely to exports of metadata would be technically feasible at this stage.

OPPORTUNITIES	BARRIERS

• Various existing standards could be leveraged as references for a potential data integration standard:
  ○ HL-7 hospital standards for transferring data between healthcare providers
  ○ Lab equipment standards for systems communication and data formatting (e.g., SiLa, AnIML)
  ○ Manufacturing equipment standards for communication protocols and information models (e.g., EtherNet/IP, OPC UA)
• **Some equipment vendors may already be interested in allowing their devices to connect to other systems** but lack technical guidance on the protocols to enable plug-and-play integration. A standard could lower the compliance burden for suppliers and industry to encourage them to move toward integration (e.g., by lowering upfront validation efforts for systems incorporating the standard due to the ability to demonstrate continuous verification).
  ○ The efforts of BioPhorum's Plug-and-Play project team may serve as a useful model; these include a white paper and Plug and Play standard and data models for single-use equipment.
• **A standard focused on metadata would allow flexibility and support innovation,** as it would not force the use of a specific technology and would only require common data outputs.
• **A standard calling for development of export functionality would be less technically demanding for equipment vendors** compared with one calling for more comprehensive functional changes.
• **A data integration standard could help streamline and systematize product manufacturing** by helping companies better understand the data vocabulary and the interrelationships among equipment.
	• Regenerative medicine manufacturing operations are often built around legacy equipment that is **deeply integrated into existing processes and difficult to switch out.**
	• Operational changes to regenerative medicine manufacturing can have unexpected impacts on **complex and interdependent processes.** A data integration standard would need to consider the system in its totality.
	• The need for interoperability **has a wide scope**, including cell manufacturing automation systems, benchtop devices such as cell counters and flow cytometers, cold chain storage, and transactional systems (manufacturing execution system [MES], laboratory information management system [LIMS], electronic quality management system [eQMS], etc.), each of which would have its own requirements and interdependencies.
	• **Industry has been slow to adopt newer technologies that can aid data integration** (e.g., RFID, optical character recognition [OCR], artificial intelligence [AI]) due to the compliance burden and lack of supplier readiness to understand how to qualify systems for pharmaceutical manufacturing.

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 feasibility assessment participants believed that it would be important to **reach out to equipment vendors** to include them in further discussion related to standard advancement. As the creators of the systems impacted by the potential standard, equipment vendors would have valuable input about barriers, needs, and potential impacts of the specifications within a standard. It may also be beneficial to seek expertise from **IoT/Industry 4.0 bodies outside of the pharmaceutical industry** to draw on their insights and ensure alignment with their work (e.g., CESMII, a non-profit institute working on smart manufacturing topics across all industries).

In addition, the group intends to pursue wider biopharmaceutical industry involvement and buy-in from suppliers and manufacturers (see Implementation Feasibility).

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 believed that while a data integration standard would offer operational efficiencies to regenerative medicine product manufacturers, there would be a **significant challenge in incentivizing suppliers and regulated companies to make the changes** needed to adhere to a standard. They felt this barrier may be surmountable but could require regulatory support (e.g., a dedicated regulatory approval channel promoting the standard's use). In addition, it will be important to get early buy-in from major vendors and involve them throughout the standard development process. Another option to increase buy-in would include **narrowing the scope of the effort to a highly specific and targeted goal**, such as standardized imaging output/data structure.

OPPORTUNITIES	BARRIERS

• The standard could facilitate a data-centric approach that would **support more systemized and continuous regulatory oversight** compared with a traditional audit-based approach.
  ○ There may be potential for a regulatory pathway or incentive supporting the standard's use, similar to Process Analytical Technologies (PAT) and Quality by Design (QbD).
  ○ The work of the ISPE Validation 4.0 Special Interest Group could inform these efforts.
• **Involving major vendors early in the standard development process** could help ensure their support and increase overall community buy-in.
• **Narrowing the scope of the initial standard effort** (e.g., to standardized imaging output/data structure) could help increase industry buy-in by ensuring the goal of the effort is concrete and achievable.
• In the long term, a data integration standard could **reduce the level of effort related to data analysis, validation, and audits.**
• The standard could be **used as a marketing tool** for companies that adopt it (i.e., saying a product is backed by the expertise that went into the standard).
• **IoT-based approaches** (e.g., use of sensors to interface with cloud technologies) may be leveraged as a reference to develop a cost-effective approach for interoperability.
• **An interoperability standard could reduce the burden on industry caused by manual data transcription**—employees often spend hours of working time each day recording and inputting data.
	• Integrating systems can be **costly and burdensome** even for companies that would benefit from the operational efficiencies.
	  ○ Small companies may lack the budget to complete these integrations.
	  ○ Larger companies may struggle due to having invested significantly in legacy equipment that uses proprietary data management systems.
	• **Companies may prefer to continue to use paper-based transcription** for data because they perceive operational changes as risky and disruptive. To counter this perception, it could be valuable to emphasize the long-term cost benefits of moving away from a paper-based system.
	• It will be **important to avoid making the standard too prescriptive**, as this could stifle innovation and discourage the standard's use.

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.

Next Steps

The feasibility assessment determined that there are few significant barriers to technical feasibility and expert availability for the data integration standard. While significant implementation feasibility barriers exist, the group believes it is worth continuing to explore strategies to overcome these barriers.

The group intends to pursue advancement of a standard focused on data export guidelines as a first step to promote open sharing of data across regenerative medicine manufacturing equipment.

Next steps for the feasibility assessment effort are described below.

Goals for 2022–2023

- **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 on data integration.
- **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.