Assessing Feasibility of a Standard
FOR CELL COLLECTION FOR CELL THERAPIES

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.

Cell Collection for Cell Therapies

The collection of high-quality cells is a cornerstone of manufacturing safe, effective cell therapy products. As more companies have entered the cell therapy field, they have developed their own unique methods and requirements for cell collection processes, which vary widely. Collection facilities have expressed a need for standardization to help improve organizational efficiency and product quality. Without standardized processes for cell collection, personnel at individual collection centers are expected to follow divergent requirements specific to different cell therapy companies. This can lead to variation in starting material quality for cell collection processes and increased risk of error.

The standard advancement project originated when Be The Match BioTherapies reached out to SCB to address differing collection protocols at apheresis centers. SCB validated the issue with other companies in the industry and held a stakeholder workshop where cell collection was a primary topic. SCB then 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 cell collection for cell therapies. The report includes input from a facilitated meeting in December 2020 attended by 19 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
2	Academia
1	Professional Society
6	Healthcare
2	Standards Developing Organization (SDO)
1	Affiliation Not Given
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 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

The group identified nine potential sub-topics for standardization:

- Cell collection parameters
- Method for requesting collection volume
- Quality systems, including change control
- Short term post-collection storage criteria
- Apheresis product testing prior to shipping
- Minimum requirements for facilities/equipment (e.g., CD34 enumeration ability)
- Pre- and post-collection testing of apheresis products
- Accreditation to consolidate/centralize audits
- Change management—how industry manages changes with sites

The group agreed that cell collection parameters were the highest priority sub-topic to standardize. The most significant challenges to standardization identified by the group included:

- Existing manufacturer requirements which may conflict with a standard
- Potential for a standard to impact parameters already written into existing FDA licensure agreements for commercial products

However, the group determined that it would be possible to overcome these barriers with sufficient buy-in from FDA and manufacturers.

While discussion focused primarily on the cell collection parameters sub-topic, the group also identified another high-priority sub-topic, establishing standards for requesting collection volume, and discussed potential technical barriers to standardization in this area.

Further input will be sought from the working group to confirm that there is support behind these standard sub-topics and to evaluate potential additional sub-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 discussed technical feasibility barriers to two sub-topics that may be ready to move forward for standardization, which are described in the sections below.

SUB-TOPIC: CELL COLLECTION PARAMETERS

There is a high potential for variation in start- and end-of-collection procedures, including collection start and end times, use of stripped or unstripped tubing, methods for clamping and segmenting tubing, length of tubing, number and location of heat seals, and methods of clamping and sealing of bags. Establishing standard approaches to these procedures will help apheresis centers reduce the number of steps that vary by manufacturer and ensure a more consistent collection product.

STANDARD OBJECTIVE: Create a standard that establishes consistent start- and end-of-collection procedures for apheresis centers.

OPPORTUNITIES	BARRIERS
• A standard could be designed to reduce the variation in apheresis collection requirements by **establishing standard approaches and collection parameters to reduce the number of variable steps**. • The creation of **an industry standard leukapheresis manual/standard operating practices (SOP) template** would reduce errors and misunderstandings in the communication of variable cell collection parameters.	• Some apheresis centers may have an existing documented procedure **requiring cell collection parameters to come from manufacturers.** • Companies with collection parameter requirements that differ from the standard **may still expect apheresis centers to follow their parameters.**

SUB-TOPIC: METHOD FOR REQUESTING COLLECTION VOLUME

Manufacturers often make collection requests in terms of overall blood volume to process rather than specifying the end goal (e.g., obtaining a specific number of CD34+ cells). A standard approach to framing collection volume requests in terms of the desired end component could help apheresis centers meet the volume targets needed for cell therapy manufacturing with minimal waste.

STANDARD OBJECTIVE: Develop a framework for making collection volume requests based on the desired end component of collection.

OPPORTUNITIES	BARRIERS
• A standard would **provide apheresis centers with more flexibility** to determine the blood volume they need to process to obtain sufficient numbers of target cells. • Identifying a collection goal that enables targets to be met at a lower collection volume would **improve patient safety.**	• Industry may have arrived at blood volume targets based on clinical trial results submitted for regulatory review and be **reluctant to deviate from their validated process.** • Some sites **lack the capability to measure certain cell types** (e.g., they may be limited to CD34+).

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, an SDO is needed in order to publish a formal standard, although best practices documents and other informal guides can be produced independently. Buy-in from a plurality of SDOs is also important to ensure broad support for the standard.

RELEVANT SDOS

The decision on which SDO(s) may take up the development of this standard is still pending. The group proposed the following potential SDOs:

- AABB
- American Type Culture Collection (ATTC)
- American Society for Apheresis (ASFA)
- Foundation for the Accreditation of Cellular Therapy (FACT)
- Joint Accreditation Committee of ISCT-EBMT (JACIE)

NEEDED EXPERTISE

The group agreed that most of the expertise needed to develop a standard is already available within the current working group. However, they believed that additional expertise from apheresis nurses could be valuable when considering mechanics of collection process variables such as location and number of seals. One participant with experience as an apheresis technician offered to contact colleagues with relevant expertise if more input is needed. The professional society ASFA was identified as another potential resource, with membership including nurses and directors and work centering around guidelines and education related to apheresis collection. Additionally, the group determined that they should seek input from a downstream group (e.g., cell processing labs that isolate and prepare cells for storage) on start- and end-time parameters and identified an international collection standards subcommittee that could provide feedback. Other areas of expertise that could benefit the working group include regulatory and quality assurance (QA) experience.

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 adopting a standard for collection parameters would come with short-term costs, including rewriting SOPs and updating software. However, they felt that these costs would ultimately be outweighed by savings from higher success rates in collection processes, leading to less loss of material.

OPPORTUNITIES	BARRIERS
• Stakeholders have been skeptical that standardization is possible for cell collection practices, so a standard would **demonstrate the possibility of successful collaboration.** • Collections deviating from manufacturing parameters can result in extra management work and documentation (e.g., developing exception reports). A standard would **help reduce these exceptions and save time and effort.**	• Collection centers are wary of additional work from new requirements, so **framing the standard as an optional way to save effort will be important.**

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.

One major feasibility barrier identified by the group was that a standard could impact parameters already written into existing FDA licensure agreements for commercial products. While this barrier could add additional time and effort to standard development, the group believed it would be surmountable if FDA is able to provide feedback and help advise on updates to licensure agreements.

OPPORTUNITIES	BARRIERS
• Standards for collection parameters are **not expected to create any intellectual property (IP) concerns.**	• Some parameters (e.g., tubing length) may be written into **FDA licensure agreements, which can be time consuming and burdensome to update**; input from FDA could mitigate this 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. The most significant barrier the group identified was the potential for a standard to conflict with parameters written into FDA licensure agreements for commercial products. However, the group believed this barrier could likely be overcome with sufficient input from FDA on approaches to updating licensure agreements. Participants agreed that the sub-topic of cell collection parameters would make the most sense to address first, because it would be relatively simple to standardize these routine processes and would provide significant benefits in improving the quality and consistency of collection products.

Next steps for the feasibility assessment effort are described below.

GOALS FOR 2021

- **Continue discussions with the working group:** In addition to the biweekly working group calls, SCB is setting up a quarterly clinical call to seek input from those in clinical roles within apheresis centers to ensure that these critical stakeholders can weigh in on the standard.
- **Seek and evaluate potential additional sub-topic recommendations:** The working group plans to address the cell collection parameters sub-topic first, as well as a standardized template for leukapheresis manuals. The working group has identified onboarding and training, environmental control and monitoring, and audits as additional potential sub-topics for future consideration.
- **Seek additional working group participants,** focusing on the expertise needs identified in the feasibility report. SCB will present at the annual ASFA meeting in May to invite additional membership. SCB will also reach out to people who completed the cell collection survey and ask them if they would like to join the working group. The Parenteral Drug Association (PDA), ASFA, and AABB are also reaching out to their stakeholders to recruit additional members for the working group.
- **Develop a proposal for PDA** and await official acceptance as a work item. SCB anticipates that PDA will draft and publish the standard through a consensus-based process, then FACT and AABB will incorporate components of this PDA standard into their standards, accreditation, and audits. The goal of this strategy is to provide harmonized requirements to both the industry partners and the apheresis centers collecting for them.
- **Once the standard is accepted as a work item,** begin to outline and draft the proposed standard(s).
- **Reach out to FDA for advice** on the best approach for updating licensure agreements. SCB plans to show FDA the draft document once it has reached a stage where the recommendations have been agreed upon by many different people in the community, including apheresis centers.