STANDARDS DEVELOPMENT FOR
REGENERATIVE MEDICINE THERAPIES

COMMUNITY PERSPECTIVES: NEEDED STANDARDS IN REGENERATIVE MEDICINE

December 2020

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 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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ABOUT THIS REPORT

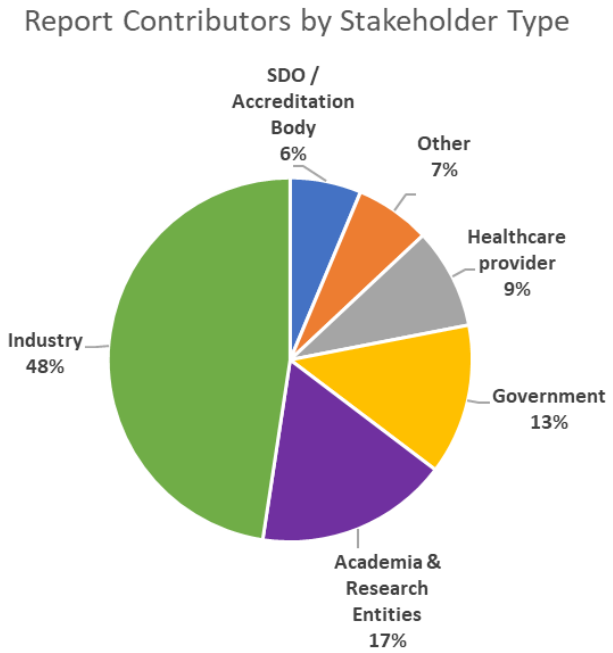
The *21st Century Cures Act*—signed into law on December 2016—directed the U.S. Food and Drug Administration (FDA) to accelerate medical product development through the advancement of standards. The Standards Coordinating Body (SCB) has been supporting this need by identifying existing and in-development standards relevant to regenerative medicine, recommending ways to strengthen standards development processes in this field, and coordinating community input on specific standards advancement efforts.

Who Should Use This Report

This report is intended for regenerative medicine product manufacturers, researchers, clinicians, regulators, patient advocates, and other stakeholders who are interested in engaging in the standards development process to support the advancement of standards that could drive improved safety and efficiency in the regenerative medicine field.

In partnership with Nexight Group, SCB released *The Regenerative Medicine Standards Landscape* report (originally released in Spring 2018 and updated in Spring and Fall of 2019 and Fall of 2020), which outlines more than 250 standards relevant to regenerative medicine that companies can use to improve their operations. In assessing the standards landscape, the community also identified a strong need for more standards specific to regenerative medicine.

The objective of this *Community Perspectives: Needed Standards in Regenerative Medicine* report is to outline standards needs identified by the community that could have the greatest benefit to the field and improve the safety and quality of regenerative medicine products.



To develop this report, we implemented identification and prioritization process improvements outlined in *Realizing the Promise of Regenerative Medicine Therapies: Strengthening the Standards Development Process*. Throughout 2018 and early 2019, SCB and Nexight Group gathered feedback and input from **more than 250 regenerative medicine stakeholders** for this report through expert interviews, a community-wide survey, and community prioritization exercises at the *Realizing the Benefit of 21st Century Cures through Standards Development Workshop* and several other smaller-scale workshops in conjunction with other industry events.

This is a living document; it will be updated periodically as standards needs are met, technology evolves, and new needs emerge.

EXECUTIVE SUMMARY

Regenerative medicine therapies—including cell, gene, and tissue engineering therapies—are an emerging field of medicine with many promising products in development that could help manage and potentially cure many conditions and diseases that are intractable, chronic, and even terminal. The regenerative medicine field is currently at a key tipping point, with disruptive innovation pushing the boundaries of science, the first products established in the market, and many more products poised to move toward commercialization.

Regenerative medicine has relatively few existing standards compared with more mature medical fields, leaving researchers and manufacturers to solve the complex challenges of clinical translation and scaling of commercial products independently. Furthermore, regenerative medicine products are highly personalized and are often made of constantly changing living cells, which creates unique difficulties with establishing common practices for comparing test results and ensuring consistent product quality and safety.

The benefits of standards address many of these challenges. To support the growth of this field and the success of emerging therapies, the regenerative medicine community must advance new standards targeted at the field's most pressing needs. Without standards in place to support safe, efficient, and scalable practices and reduce the burden on companies seeking regulatory approval for their products, many promising therapies may be unable to successfully transition from the research phase to commercially viable products.

Needed Standards Identified by the Community

To help stakeholders better understand and address regenerative medicine standards needs, **this report outlines 44 areas identified and prioritized by the regenerative medicine community where standards could yield significant benefits to the field.** The report is intended to help align awareness and action around standards needs so that individuals are inspired to act and the community can work together on advancing and developing the standards that can make the greatest difference. This list of standards needs is non-exhaustive and new needs will continue to be identified as the field moves forward.

The following table provides an overview of the standards needs detailed in this report, including the associated functional area from product development through administration and the relevant regenerative medicine sectors that would be impacted by standards development.

Note: These standard needs have been renumbered in the December 2020 version of the report to incorporate nine new standards needs identified by the community.

	Area of Standard Need	Cell Therapy	Tissue Engr.	Gene Therapy
Bioprocessing and Production	[C1] Ancillary Materials	X	X	X
	[C2] Cell Collection Procedures	X	X	
	[C3] Cell and Tissue Therapy Manufacturing Equipment Requirements	X	X	
	[C4] Knowledge Standard for Cell Types	X	X	
	[C5] Methods and Processes for Cell Identity & Cell Line Authentication	X	X	
	[C6] Establishing Consistency in the Management System for Processing and Handling of Cells for Regenerative Medicine New	X	X	X
	[G1] Framework for Gene Delivery Methods & Gene Editing Tools			X
	[G2] Standards Regarding Ethical Considerations of Gene Therapy			X
	[T1] Characterization of Scaffold Materials		X	
	[T2] Donor Tissue Sterilization		X	
	[T3] Bioprinting Specifications		X	
Analytics & Testing Methods	[C7] Cell Counting Methods	X	X	X
	[C8] Determining & Interpreting Cell Viability	X	X	
	[C9] Defining Aspects of a Certificate of Analysis for Ancillary Materials New	X	X	X
	[G3] Methods for the Evaluation of Endogenous T-Cell Therapies			X
	[G4] Viral Vector Gene Quantification			X
	[G5] Establishing Comparability Between Assays for Measuring Human Immune Response to Viral Vectors New			X
	[G6] Best Practices for Conducting Off-Target Analyses for Gene Editing Products New			X
	[T4] Correlation of Decellularization Measurements and Clinical Outcomes for Tissue Engineered Products New		X	
Product Quality and Characterization	[C10] Human Cell Characterization	X	X	X
	[C11] Product Potency Measurement	X	X	X
	[C12] Test Methods to Measure Sterility, Mycoplasma, and Adventitious Agents	X	X	X
	[C13] Acceptable Particulates in Regenerative Medicine Products	X	X	X
	[C14] Release Criteria for Regenerative Medicine Products	X	X	X
	[C15] Consistent Language and Testing Practices for Sterility Testing Methods	X	X	X
	[C16] Guidelines for Vector Characterization, Design, and Validation for Use in Cell and Gene Therapy Products New	X		X
	[G7] Revisiting Applicability of Standards for Replication-Competent Retrovirus (RCR) Testing			X
	[G8] Methods for Assessing Product Activity and Comparability			X
	[T5] Biological Evaluation of Tissues and Extracellular Matrices Used in Tissue Engineering for in Vivo Studies New		X	

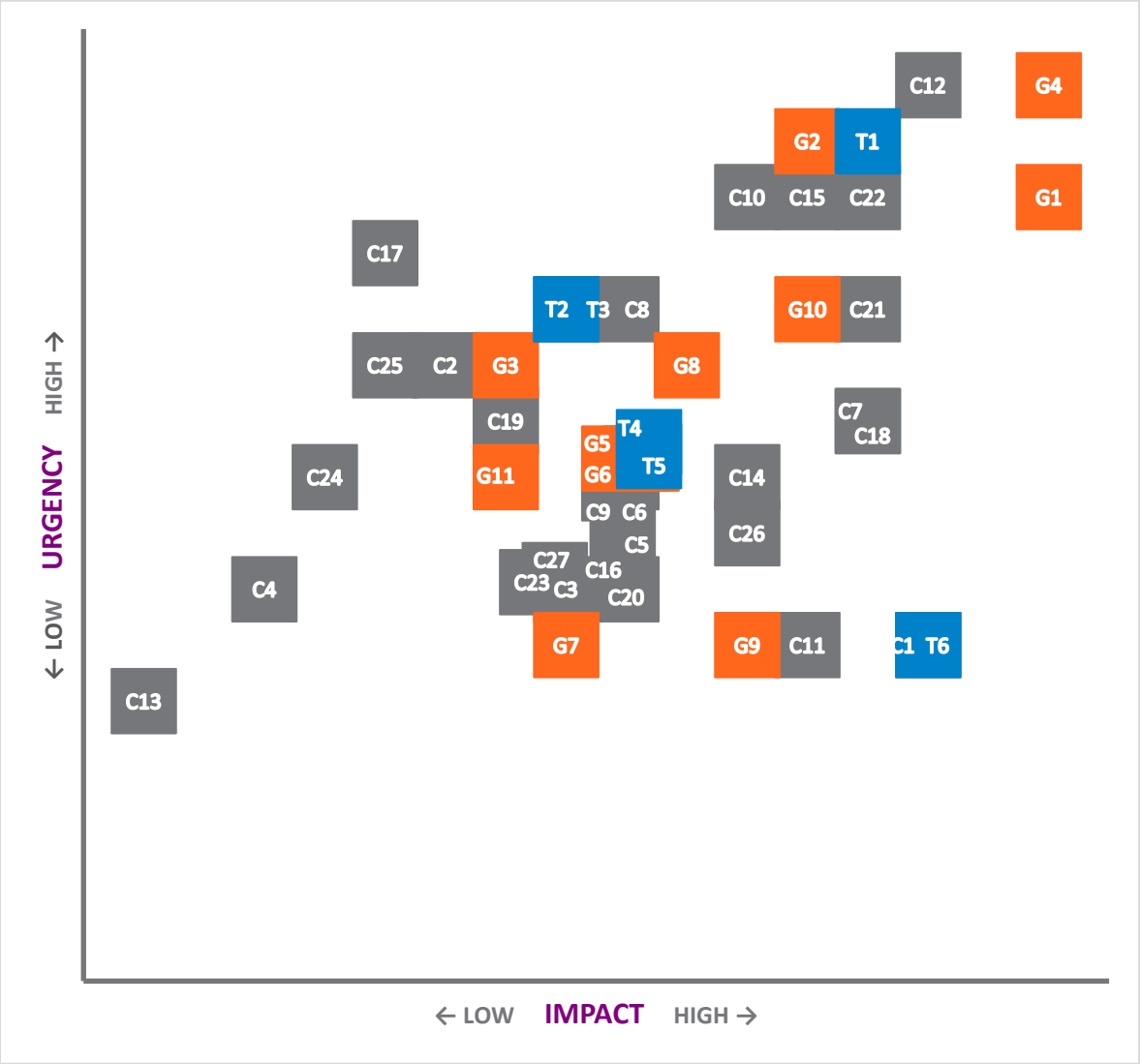
	Area of Standard Need	Cell Therapy	Tissue Engr.	Gene Therapy
Logistics and Compliance	[C17] Chain-of-Identity / Chain-of-Custody Recording	X	X	X
	[C18] Labeling Standards Specific to Regenerative Medicine Products	X	X	X
	[C19] Data Acquisition	X	X	X
	[C20] Cryopreservation Methods	X	X	X
	[C21] Regenerative Medicine Product Packaging	X	X	X
	[C22] Transportation Standards for Regenerative Medicine Products	X	X	X
	[C23] Regenerative Medicine Terminology New	X	X	X
Preclinical Studies	[C24] Animal Models for Safety Testing and Product Activity Evaluation	X	X	X
	[G9] Methodology for Collecting & Evaluating Biodistribution Data			X
	[G10] Development of Consistent Validation Methodology for Gene Therapy Manufacturing Processes			X
Clinical Trials	[C25] Clinical Trial Interpretation with Unknown Cell Specific Doses	X	X	X
	[C26] Safety Training and Education for Clinicians Administering Therapies	X	X	X
	[C27] Patient Data Security New	X	X	X
	[G11] Evaluating Pre-existing Immunity to Adeno-associated Virus (AAV) Vectors			X
	[T6] Product Integrity Testing Methods		X	

The community rated the relative priority of each of these needs based on their potential impact to the field and the urgency with which a need must be addressed:

- **Impact** is defined as the difference a needed standard could have on the regenerative medicine community, product development, and ultimately on patient care. This includes the extent to which addressing this need could improve safety/quality, accelerate the time to market or development of a product, lower the cost to develop products, and improve patient access and care.
- **Urgency** refers to the difference that acting now versus later could make to the quality and safety of regenerative medicine products.

COMMUNITY PRIORITIZATION OF STANDARDS NEEDS

These prioritization results are based on input received from approximately 60 stakeholders from various groups within the regenerative medicine community, including industry, public-private partnerships, government agencies, standards developing organizations (SDOs), academia, and healthcare providers. These results have not been peer reviewed but are intended to provide a snapshot of perspectives from the community.



How to Use this Report

This report is intended as a resource for the broad regenerative medicine community to focus and align their efforts to advance needed regenerative medicine standards. Bringing these standards to fruition will take collaborative effort from across the whole regenerative medicine community, and SCB will not necessarily be the leading organization to move all these efforts forward. SCB's role is to support and coordinate key standard advancement initiatives by different stakeholders in order to drive momentum and prevent duplication of work. Standards needs identified in this report may not be ready for immediate action and will need to undergo further feasibility assessments to determine their readiness for standards development and implementation.

Next Steps for Standards Advancement

As community stakeholders identified needed standards, they also weighed in on potential next steps for addressing these current needs. These next steps intend to help further define the need among affected stakeholders, assess the feasibility of developing a standard and its potential for adoption, and identify whether the solution is optimally addressed through a single standard or a series of standards focused on more specific aspects of the need. The next steps outlined will likely evolve as individuals and groups take action. Common next steps include:

- Solicit input from the broad regenerative medicine community on existing best practices and pain points
- Identify the stakeholders most affected by the standards to involve them in the standards development process
- Conduct research or round-robin studies to answer key questions that must be addressed for a standard to be feasible for development or adoption
- Contribute to related existing efforts, such as joining an SCB-supported standards advancement project or participating in a Standards Developing Organization technical committee

Factors to consider when advancing standards include:

- **Achieve stakeholder consensus for critical standards** — To be widely adopted across the regenerative medicine community, standards must be developed with input from a variety of stakeholders to ensure the standards are feasible, practical, and flexible. Consensus-based standards development processes may be effective for some types of standards.
- **Focus expertise on additive standards efforts** — As an emerging field, regenerative medicine has a limited number of experts with experience relevant to each specific standards need. To maximize the limited time of these experts, it is essential that new efforts leverage existing standards and do not overlap with existing efforts. Not only will this ensure that the community's expertise will be focused on those areas most needed, but it will also ensure that a standards need isn't addressed with a number of hyper-focused or sub-par standards focused on similar issues.
- **Support innovation while standardizing** — Because companies' commercial success lies in their ability to develop innovative, safe, effective, and reliable products, they may be protective of business processes that give them a competitive edge. To accelerate advances in

regenerative medicine, standards should focus on the precompetitive space so as not to limit or inhibit innovation related to company-specific intellectual property.

- **Ensure compatibility of U.S. standards with international efforts** — Consensus and buy-in is improved when standards are developed with international guidelines and policies in mind. Ensuring compatibility between U.S. and international standards and participating in the development of standards in global forums, is critical for helping companies in the industry maintain a global competitive edge.
- **Prioritize standards with the greatest potential impact and need** — While there is benefit in developing some regenerative medicine standards specific to one sector or functional area, focusing on developing standards that address common industry needs across functional areas and applications can have a more significant impact.

How to Get Involved in Standards Development

STANDARDS COORDINATING BODY
REGENERATIVE MEDICINE

Standards are essential to the continued innovation and success of regenerative medicine therapies. To help SCB identify and advance the standards that matter to you or learn more about how you can work with specific Standards Developing Organizations (SDOs), contact us today:
https://www.standardscoordinatingbody.org/contact

REPORT STRUCTURE

This report contains two main sections and two appendices:

Sector Summary Sections: An overview of standards needs is provided for each of the regenerative medicine sectors:

- **Cell therapy:** Products made from living, whole cells that are injected into a patient in order to treat a disease.
- **Gene therapy:** Products that aim to correct or compensate for defective versions of genes by delivering a healthy copy into patients' cells.
- **Tissue engineering:** Products made from scaffolds, cells, and/or biologically active molecules to create new, functional tissue or whole organs.

Each of the sector-specific sections begins with an overview of key themes across standards needs, a summary of potential areas where standards would be beneficial, and related efforts under way in the regenerative medicine community that can help address these needs. Each sector-specific section also contains a table with high-level descriptions of the objectives of standards in each area and links to the detailed description of each standards need.

Many of the standards needs listed in this report describe challenges common to multiple regenerative medicine sectors. In particular, all of the standards needs in the cell therapy section relate to common regenerative medicine process or quality concerns and are therefore also applicable to the tissue engineering and/or gene therapy sectors. These standards are included in the summary tables for each sector they apply to and are labeled as "crosscutting."

Detailed Standards Needs by Functional Area: Detailed, 1–2-page descriptions of each standard need are included in this section, categorized based on the following functional areas:

- **Bioprocessing and Production:** The design and development of processes, materials, and equipment for manufacturing products from raw/ancillary biological materials (e.g., the characterization of starting materials such as cells, gene therapy vectors, and biomaterials).
- **Analytics and Testing Methods:** The tools and methods used to detect, measure, and/or monitor the properties and state of regenerative medicine product components.
- **Product Quality and Characterization:** The measurements and guidelines needed to convey well-defined quality attributes of materials used in regenerative medicine therapies and provide a clear understanding of their intended use.
- **Logistics and Compliance:** The processes and protocols surrounding the coordinated collection, manufacturing, and administration of cells and other therapy products across the supply chain.
- **Preclinical Studies:** The testing of a drug, procedure, or other medical treatment in animals before clinical trials in humans can be started.
- **Clinical Trials:** The research studies that determine whether a regenerative medicine strategy, treatment, or device is safe and effective for human use.

Each of the standards needs listed in this section begins with an overview of the topic area and the challenge that could be addressed by standardization. Next, it describes the potential for standardization, including the objective of the standard and possible areas to standardize (e.g., specific tests or processes). The description also provides links to related efforts, showing steps that the regenerative medicine community has already taken toward standardization in this area. Each description ends with a list of suggested next steps for stakeholders interested in addressing the standards need.

The applicable regenerative medicine sector(s) and functional area for each standards need are indicated by purple icons.

SCB-Coordinated Projects

Several of the standards needs listed in this report are currently being addressed in whole or in part through an SCB-coordinated standards advancement project. These needs are labeled with the SCB icon:

If you are interested in joining one of these projects, you can contact SCB to join a working group.

Appendix A. Methodology: Describes the research methodology that Nexight Group and SCB followed when developing the report.

Appendix B. Report Contributors: Lists the individuals who provided input used in the creation of the report.

SECTOR SUMMARIES

Cell Therapy

Cell therapy involves administering **living, whole cells to a patient** as a method for treating disease. Cell therapy products can be derived or reprogrammed from stem cells or can be engineered from other cell types. To create **products made from dynamic, living cells that are safe, effective, and produce consistent results**, the cell therapy sector is working to **deepen understanding of cell attributes and functions**.

Crosscutting Standards:
Due to the maturity of the cell therapy field and the fact that cells are the building blocks of many regenerative medicine products, **all cell therapy standards are crosscutting** and also apply to the gene therapy and/or tissue engineering fields.

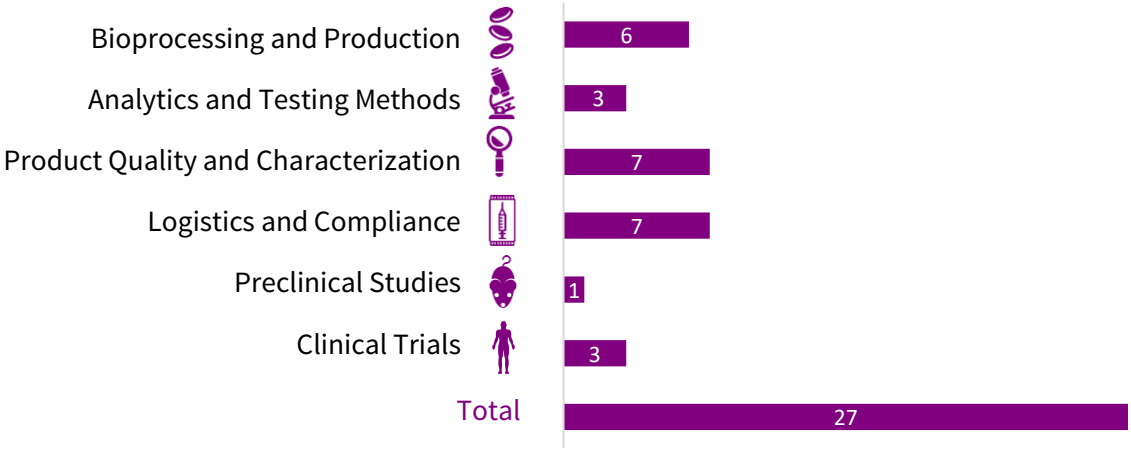
KEY THEMES:

- Many of the needs in this sector are interrelated.
- A core challenge of cell therapy is cell characterization—defining critical quality attributes (CQAs) and optimal testing methods to ensure that cell therapy products are safe and effective.
- Several other standards needs relate to better understanding individual areas of CQAs: identity, cell counting, and viability.
- Other key challenges include mitigating the potentially harmful effects of foreign agents in cell therapy products (e.g., microbes, particulates) and working around short product shelf lives.
- Criteria for method selection (i.e., which assay to use and when to use it) will help improve efficiency and consistency in cell therapy production.

POTENTIAL AREAS TO STANDARDIZE:

- Management systems for processing and handling cells for regenerative medicine
- Best practices to ensure patient data security
- Certificate of analysis (COA) requirements for ancillary materials

CELL THERAPY STANDARDS NEEDS BY FUNCTIONAL AREA



RELATED EFFORTS

- SCB is coordinating standards advancement projects on many of these standards needs: cell characterization, ancillary materials, cell collection, cell manufacturing equipment, cell counting, cryopreservation, and rapid microbial testing methods (RMTMs).
- ISO, ASTM, USP, PDA, and FACT are involved in ongoing standards development for different cell therapy sector needs.

SUMMARY OF PRIORITIZED STANDARDS NEEDS – CELL THERAPY SECTOR

This section provides a brief description of each of the cell therapy sector standards needs prioritized by the regenerative medicine community. **Each need listed below links to a detailed description** of the challenge, standardization opportunity, and efforts related to the standards need.

All needs prioritized for the cell therapy sector are **applicable to the tissue engineering and/or gene therapy sectors** and can also be found in the summary of prioritized standards needs lists for these sectors when relevant.

Bioprocessing and Production

- **[C1 - Crosscutting] Ancillary Materials:** Create guidelines for evaluating ancillary materials to reduce the burden of fit-for-use studies and ensure lot-to-lot consistency
- **[C2 - Crosscutting] Cell Collection Procedures:** Establish streamlined cell collection requirements that ensure consistency, safety, and comparability in final cell therapy products
- **[C3 - Crosscutting] Cell and Tissue Therapy Manufacturing Equipment Requirements:** Set defined minimum requirements, enabling reduced manufacturing costs and increased production outputs
- **[C4 - Crosscutting] Knowledge Standard for Cell Types Used in Therapeutic Products:** Increase understanding of how to mitigate/respond to the effects of cell morphology
- **[C5 - Crosscutting] Methods and Processes for Cell Identity and Cell Line Authentication:** Establish consistent reporting practices to increase confidence in published data
- **[C6 - Crosscutting] Establishing Consistency in the Management System for Processing and Handling of Cells for Regenerative Medicine:** Create guidelines for the implementation of processing systems for cells for regenerative medicine to assist manufacturers in ensuring product quality and consistency across the industry

Analytics and Testing Methods

- **[C7 - Crosscutting] Cell Counting Methods for Regenerative Medicine Therapies:** Provide clearly defined criteria for use across cell-counting assays to improve comparability
- **[C8 - Crosscutting] Determining and Interpreting Cell Viability:** Enable researchers to design and use cost-effective assays that yield accurate and precise cell viability results
- **[C9 - Crosscutting] Defining Aspects of a Certificate of Analysis for Ancillary Materials:** Establish consistent analytical testing methods and COA formats for various ancillary materials that allow manufacturers to compare materials from different sources

Product Quality and Characterization

- **[C10 - Crosscutting] Human Cell Characterization:** Set guidelines for defining a cell's critical quality attributes (CQAs) and how to measure these CQAs to assess that the cell is fit-for-purpose
- **[C11 - Crosscutting] Product Potency Measurement Methods:** Establish guidelines for measuring potency and developing appropriate potency assays for different products
- **[C12 - Crosscutting] Test Methods to Measure Sterility, Mycoplasma, and Other Adventitious Agents:** Clarify when to use different test methods and how to interpret results
- **[C13 - Crosscutting] Acceptable Particulates in Regenerative Medicine Products:** Increase knowledge of potential particulate types, acceptable thresholds, particulate effects, and mitigation strategies
- **[C14 - Crosscutting] Release Criteria for Regenerative Medicine Products:** Define minimal appropriate release criteria to allow researchers to reliably demonstrate product quality and safety compliance
- **[C15 - Crosscutting] Consistent Language and Testing Practices for Sterility Testing Methods:** Clarify appropriate use cases for different methods and set consistent terminology
- **[C16 - Crosscutting] Guidelines for Vector Characterization, Design, and Validation for Use in Cell and Gene Therapy Products:** Establish guidelines to harmonize manufacturers' characterization, design, and validation processes to lower barriers to understanding and mitigating existing complications

Logistics and Compliance

- **[C17 - Crosscutting] Chain-of-Identity / Chain-of-Custody Recording:** Establish consistent product handling practices and digital information documentation for tracking products
- **[C18 - Crosscutting] Labeling Standards Specific to Regenerative Medicine Products:** Create a universal labeling system that accounts for different processing systems, technology, and local languages
- **[C19 - Crosscutting] Data Acquisition:** Create protocols to increase data quality, make data easier to share, and establish mechanisms to safeguard intellectual property and patient privacy
- **[C20 - Crosscutting] Cryopreservation Methods:** Establish best practices and a flexible framework for decision-making for cryopreservation methods and processes
- **[C21 - Crosscutting] Regenerative Medicine Product Packaging:** Define acceptable packaging materials and practices to prevent post-packaging contamination and ensure product sterility, stability, and safety
- **[C22 Crosscutting] - Transportation Standards for Regenerative Medicine Products:** Establish parameters for the control and consistency of packaging, handling, storage, and tracking of regenerative medicine therapies
- **[C23 Crosscutting] - Regenerative Medicine Terminology:** In consultation with major organizations in the fields of regenerative medicine research and development, create a document providing standard definitions for basic regenerative medicine terminology

Preclinical Studies

- **[C24 - Crosscutting] Animal Models for Safety Testing and Product Activity Evaluation:** Increase access to animal model data to enable cross-comparisons of, and confidence in, testing results

Clinical Trials

- **[C25 - Crosscutting] Clinical Trial Interpretation with Unknown Cell-Specific Doses:** Broaden understanding of cell activity and variation over time
- **[C26 - Crosscutting] Safety Training and Education for Clinicians Administering Therapies:** Establish comprehensive training requirements to equip clinicians with skills needed to administer products safely and effectively
- **[C27 - Crosscutting] Patient Data Security:** Establish a standardized guide for HIPAA compliance during the cell and gene therapy manufacturing and administration process to increase patient safety and reduce the cost and time associated with product development

Gene Therapy

Gene therapy involves **modifying the expression of a patient's genes and/or repairing abnormal genes using recombinant DNA technology.** Gene therapy products are delivered using viral or non-viral vectors that administer specific nucleic acids (DNA or RNA) into the cell for expression and replication. This sector's key challenge is to better understand and control how products interact wit the human body by defining variables related to **delivery mechanisms, gene editing methods, and dosing**.

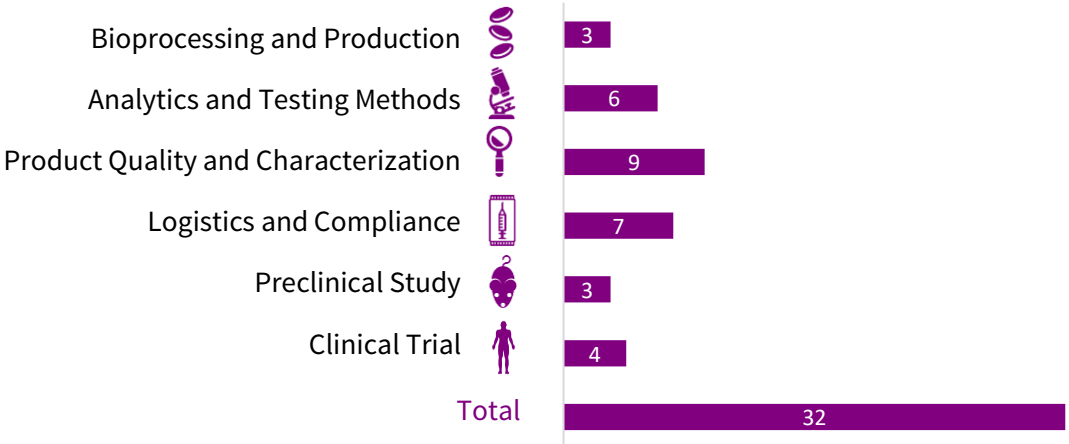
KEY THEMES:

- Delivery of appropriate doses of vectors to patients is a foundational challenge that could be addressed through vector quantification standards.
- The factors that cause adverse reactions in gene therapy patients (e.g., immune response to T-cell therapy products or complications from replication-competent retroviruses [RCRs]) must be better understood.
- The sector also needs robust best practices for gene editing tool selection and use to support overall safety and effectiveness of products.

POTENTIAL AREAS TO STANDARDIZE:

- Methods for gene editing tool selection
- Selection of potency assays for determining safe dose
- Protocols for patient monitoring after infusion
- Factors for selection of biodistribution methods
- Methodology for screening patients for immunity to adeno-associated virus (AAV) vectors

GENE THERAPY STANDARDS NEEDS BY FUNCTIONAL AREA



RELATED EFFORTS

- SCB is coordinating a standard advancement project on evaluating pre-existing immunity to AAVs.
- FDA has released draft and final guidance on related areas, including retroviral vector-based human gene therapy products and vector biodistribution.
- The National Institutes of Health (NIH) is active in this area and has created a Somatic Gene Editing Program and guidance addressing gene therapy ethical concerns.

SUMMARY OF PRIORITIZED STANDARDS NEEDS – GENE THERAPY SECTOR

This section provides a brief description of each of the gene therapy sector standards needs prioritized by the regenerative medicine community. **Each need listed below links to a detailed description** of the challenge, standardization opportunity, and efforts related to the standards need.

Bioprocessing and Production

- **[G1] Framework for Gene Delivery Methods and Gene Editing Tools:** Develop guidelines for selecting and using appropriate tools and gene delivery methods
- **[G2] Standards Regarding Ethical Considerations of Gene Therapy:** Create consensus-based ethical guidelines reflecting perspectives of a broad and diverse collection of stakeholders
- **[C1 - Crosscutting] Ancillary Materials:** Create guidelines for evaluating ancillary materials to reduce the burden of fit-for-use studies and ensure lot-to-lot consistency

Analytics and Testing Methods

- **[G3] Methods for the Evaluation of Endogenous T-Cell Therapies:** Define acceptable evaluation methods for monitoring and mitigating common complications arising from T-cell therapy
- **[G4] Viral Vector Gene Quantification:** Establish consistent measurement procedures and reporting requirements that ensure accuracy of quantification results
- **[G5] Establishing Comparability Between Assays for Measuring Human Immune Response to Viral Vectors:** Develop a standard approach to pre-existing immunity assay development, selection, and evaluation to enhance patient safety, quality of clinical trial data, and eventually efforts to circumvent the impact of pre-existing immunity
- **[G6] Best Practices for Conducting Off-Target Analyses for Gene Editing Products:** Establish standards for monitoring off-target mutation effects in gene therapy patients to improve patient safety and the development of predictive off-target screening methods
- **[C7 - Crosscutting] Cell Counting Methods for Regenerative Medicine Therapies:** Provide clearly defined criteria for use across cell-counting assays to improve comparability
- **[C9 - Crosscutting] Defining Aspects of a Certificate of Analysis for Ancillary Materials:** Establish consistent analytical testing methods and COA formats for various ancillary materials that allow manufacturers to compare materials from different sources

Product Quality and Characterization

- **[G7] Revisiting Applicability of Standards for Replication-Competent Retrovirus (RCR) Testing:** Expand guidelines for safe and efficient testing and create a framework for incorporating new test methods
- **[G8] Methods for Assessing Product Activity and Comparability:** Establish best practices for measuring product performance and assuring comparability
- **[C10 - Crosscutting] Human Cell Characterization:** Set guidelines for defining a cell's critical quality attributes (CQAs) and how to measure these CQAs to assess that the cell is fit-for-purpose
- **[C11 - Crosscutting] Product Potency Measurement Methods:** Establish guidelines for measuring potency and developing appropriate potency assays for different products

- **[C12 - Crosscutting] Test Methods to Measure Sterility, Mycoplasma, and Other Adventitious Agents:** Clarify when to use different test methods and how to interpret results
- **[C13 - Crosscutting] Acceptable Particulates in Regenerative Medicine Products:** Increase knowledge of potential particulate types, acceptable thresholds, particulate effects, and mitigation strategies
- **[C14 - Crosscutting] Release Criteria for Regenerative Medicine Products:** Define appropriate release criteria to allow researchers to reliably demonstrate product quality compliance
- **[C15 - Crosscutting] Consistent Language and Testing Practices for Sterility Testing Methods:** Clarify appropriate use cases for different methods and set consistent terminology
- **[C16 - Crosscutting] Guidelines for Vector Characterization, Design, and Validation for Use in Cell and Gene Therapy Products:** Establish guidelines to harmonize manufacturers' characterization, design, and validation processes to lower barriers to understanding and mitigating existing complications

Logistics and Compliance

- **[C17 - Crosscutting] Chain-of-Identity / Chain-of-Custody Recording:** Establish consistent product handling practices and digital information documentation for tracking products
- **[C18 - Crosscutting] Labeling Standards Specific to Regenerative Medicine Products:** Create a universal labeling system that accounts for different processing systems, technology, and local languages
- **[C19 - Crosscutting] Data Acquisition:** Create protocols to increase data quality, make data easier to share, and establish mechanisms to safeguard intellectual property and patient privacy
- **[C20 - Crosscutting] Cryopreservation Methods:** Establish best practices and a flexible framework for decision-making for cryopreservation methods and processes
- **[C21 - Crosscutting] Regenerative Medicine Product Packaging:** Define acceptable packaging materials and practices to prevent post-packaging contamination and ensure product sterility, stability, and safety
- **[C22 Crosscutting] - Transportation Standards for Regenerative Medicine Products:** Establish parameters for the control and consistency of packaging, handling, storage, and tracking of regenerative medicine therapies
- **[C23 Crosscutting] - Regenerative Medicine Terminology:** In consultation with major organizations in the fields of regenerative medicine research and development, create a document providing standard definitions for basic regenerative medicine terminology

Preclinical Studies

- **[G9] Methodology for Collecting and Evaluating Biodistribution Data:** Ensure techniques are consistently implemented for the appropriate procedures so that data can be compared
- **[G10] Development of Consistent Validation Methodology for Gene Therapy Manufacturing Processes:** Create broadly applicable validation guidelines by identifying potential commonalities across manufacturing processes

- **[C24 - Crosscutting] Animal Models for Safety Testing and Product Activity Evaluation:** Increase access to animal model data to enable cross-comparisons of, and confidence in, testing results

Clinical Trials

- **[G11] Evaluating Pre-existing Immunity to Adeno-associated Virus (AAV) Vectors:** Develop shared language and consistent methodology for evaluating pre-existing immunity to AAV vectors to better understand the role AAV immunity plays in clinical trial outcomes
- **[C25 - Crosscutting] Clinical Trial Interpretation with Unknown Cell-Specific Doses:** Broaden understanding of cell activity and variation over time
- **[C26 - Crosscutting] Safety Training and Education for Clinicians Administering Therapies:** Establish comprehensive training requirements to equip clinicians with skills needed to administer products safely and effectively
- **[C27 - Crosscutting] Patient Data Security:** Establish a standardized guide for HIPAA compliance during the cell and gene therapy manufacturing and administration process to increase patient safety and reduce the cost and time associated with product development

Tissue Engineering

Tissue engineering uses **scaffolds, cells, and/or biologically active molecules to create new, functional tissue or whole organs.** The potential to assemble functional constructs that restore, maintain, or improve damaged tissues or organs offers exciting prospects for changing traditional approaches to clinical treatment but also presents a number of unique challenges. The tissue engineering sector must overcome challenges with defining and **assessing cell attributes and functions to promote the proliferation of cells *in vivo* or *in vitro*, selecting and characterizing biocompatible materials, and ensuring long-term product safety.**

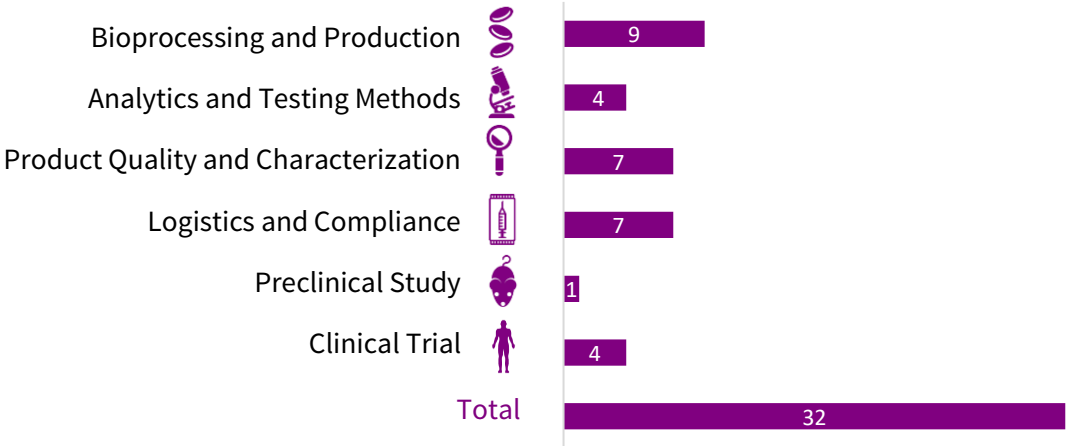
KEY THEMES:

- Researchers and product developers are working to create tissue engineering scaffolds with consistent properties and long-term integrity. Standards can help with this challenge.
- The tissue engineering sector currently lacks specific standards to define optimal testing methods and fit-for-purpose measurements, particularly in the Bioprocessing and Production and Clinical Trials functional areas.

POTENTIAL AREAS TO STANDARDIZE:

- Scaffold measurement techniques
- Criteria for scaffold materials selection
- Bioink material testing (e.g., printability, viscosity, tensile strength)
- Acceptable packaging materials properties, design, and storage
- Common testing methods (e.g., assays) to ensure long-term tissue engineering product safety
- Methods for defining critical quality attributes (CQAs)

TISSUE ENGINEERING STANDARDS NEEDS BY FUNCTIONAL AREA



RELATED EFFORTS

- SCB is coordinating standards advancement projects on fiber-based scaffolds and bioinks.
- ASTM is active in this area; they have convened in-person workshops and have a number of published standards.
- Existing standards for medical devices could provide a basis for tissue engineering-specific standards.

SUMMARY OF PRIORITIZED STANDARDS NEEDS – TISSUE ENGINEERING SECTOR

This section provides a brief description of each of the tissue engineering sector standards needs prioritized by the regenerative medicine community. **Each need listed below links to a detailed description** of the challenge, standardization opportunity, and efforts related to the standards need.

Bioprocessing and Production

- **[T1] Characterization of Scaffold Materials:** Establish measurement techniques and core characteristics to measure to ensure scaffolds consistency
- **[T2] Donor Tissue Sterilization:** Identify methods for sterilizing tissue products in batches to improve manufacturing efficiency
- **[T3] Bioprinting Specifications:** Establish guidelines for bioink printing parameters and variables like viscosity and tensile strength for more consistent outcomes
- **[C1 - Crosscutting] Ancillary Materials:** Create guidelines for evaluating ancillary materials to reduce the burden of fit-for-use studies and ensure lot-to-lot consistency
- **[C2 - Crosscutting] Cell Collection Procedures:** Establish streamlined cell collection requirements that ensure consistency, safety, and comparability in final cell therapy products
- **[C3 - Crosscutting] Cell and Tissue Therapy Manufacturing Equipment Requirements:** Set defined minimum requirements, enabling reduced manufacturing costs and increased production outputs
- **[C4 - Crosscutting] Knowledge Standard for Cell Types Used in Therapeutic Products:** Increase understanding of how to mitigate/respond to the effects of cell morphology
- **[C5 - Crosscutting] Methods and Processes for Cell Identity and Cell Line Authentication:** Establish consistent reporting practices to increase confidence in published data
- **[C6 - Crosscutting] Establishing Consistency in the Management System for Processing and Handling of Cells for Regenerative Medicine:** Create guidelines for the implementation of processing systems for cells for regenerative medicine to assist manufacturers in ensuring product quality and consistency across the industry

Analytics and Testing Methods

- **[T4] Correlation of Decellularization Measurements and Clinical Outcomes for Tissue Engineered Products:** Establish common analytical methods to evaluate the success of decellularization to assess decellularization methods and clinical outcomes
- **[C7 - Crosscutting] Cell Counting Methods for Regenerative Medicine Therapies:** Provide clearly defined criteria for use across cell-counting assays to improve comparability
- **[C8 - Crosscutting] Determining and Interpreting Cell Viability:** Enable researchers to design and use cost-effective assays that yield accurate and precise cell viability results
- **[C9 - Crosscutting] Defining Aspects of a Certificate of Analysis for Ancillary Materials:** Establish consistent analytical testing methods and COA formats for various ancillary materials that allow manufacturers to compare materials from different sources

Product Quality and Characterization

- **[T5] Biological Evaluation of Tissues and Extracellular Matrices Used in Tissue Engineering for in Vivo Studies:** Establish standard approaches to characterizing tissue-derived materials and their performance for in vivo applications
- **[C10 - Crosscutting] Human Cell Characterization:** Set guidelines for defining a cell's critical quality attributes (CQAs) and how to measure these CQAs to assess that the cell is fit-for-purpose
- **[C11 - Crosscutting] Product Potency Measurement Methods:** Establish guidelines for measuring potency and developing appropriate potency assays for different products
- **[C12 - Crosscutting] Test Methods to Measure Sterility, Mycoplasma, and Other Adventitious Agents:** Clarify when to use different test methods and how to interpret results
- **[C13 - Crosscutting] Acceptable Particulates in Regenerative Medicine Products:** Increase knowledge of potential particulate types, acceptable thresholds, particulate effects, and mitigation strategies
- **[C14 - Crosscutting] Release Criteria for Regenerative Medicine Products:** Define minimal appropriate release criteria to allow researchers to reliably demonstrate product quality and safety compliance
- **[C15 - Crosscutting] Consistent Language and Testing Practices for Sterility Testing Methods:** Clarify appropriate use cases for different methods and set consistent terminology

Logistics and Compliance

- **[C17 - Crosscutting] Chain-of-Identity / Chain-of-Custody Recording:** Establish consistent product handling practices and digital information documentation for tracking products
- **[C18 - Crosscutting] Labeling Standards Specific to Regenerative Medicine Products:** Create a universal labeling system that accounts for different processing systems, technology, and local languages
- **[C19 - Crosscutting] Data Acquisition:** Create protocols to increase data quality, make data easier to share, and establish mechanisms to safeguard intellectual property and patient privacy
- **[C20 - Crosscutting] Cryopreservation Methods:** Establish best practices and a flexible framework for decision-making for cryopreservation methods and processes
- **[C21 - Crosscutting] Regenerative Medicine Product Packaging:** Define acceptable packaging materials and practices to prevent post-packaging contamination and ensure product sterility, stability, and safety
- **[C22 Crosscutting] - Transportation Standards for Regenerative Medicine Products:** Establish parameters for the control and consistency of packaging, handling, storage, and tracking of regenerative medicine therapies
- **[C23 Crosscutting] - Regenerative Medicine Terminology:** In consultation with major organizations in the fields of regenerative medicine research and development, create a document providing standard definitions for basic regenerative medicine terminology

Preclinical Studies

- **[C24 - Crosscutting] Animal Models for Safety Testing and Product Activity Evaluation:** Increase access to animal model data to enable cross-comparisons of, and confidence in, testing results

Clinical Trials

- **[T6] Product Integrity Testing Methods:** Identify and codify common ways to test tissue engineering product integrity, including tensile strength and suture retention
- **[C25 - Crosscutting] Clinical Trial Interpretation with Unknown Cell-Specific Doses:** Broaden understanding of cell activity and variation over time
- **[C26 - Crosscutting] Safety Training and Education for Clinicians Administering Therapies:** Establish comprehensive training requirements to equip clinicians with skills needed to administer products safely and effectively
- **[C27 - Crosscutting] Patient Data Security:** Establish a standardized guide for HIPAA compliance during the cell and gene therapy manufacturing and administration process to increase patient safety and reduce the cost and time associated with product development

DETAILED STANDARDS NEEDS BY FUNCTIONAL AREA

Bioprocessing and Production

C1 ANCILLARY MATERIALS

Cell Therapy | Gene Therapy | Tissue Engineering

Ancillary materials—including growth factors, nutrients, reagents, and other raw materials—are introduced during the creation of a therapy but are not intended to be part of the product itself.

CHALLENGE: Ancillary materials often make it into the end product in residual amounts that can have unintentional impacts on product safety. The quality of ancillary materials can also have a dramatic impact on the potency and quality of the final product. Evaluating ancillary materials independently is time- and resource-intensive for both ancillary material suppliers and product manufacturers. In addition, not all manufacturers test ancillary materials the same way; this can create confusion about whether a product has been thoroughly vetted for clinical use.

FUNCTIONAL AREAS

- **Bioprocessing and Production Standards**
- Analytics & Testing Methods Standards
- Product Quality and Characterization Standards
- Logistics and Compliance Criteria Standards
- Preclinical Study Standards
- Clinical Trial Standards

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Create **guidelines for safety and quality evaluation of ancillary materials** to reduce the burden of ancillary materials fit-for-use studies and ensure lot-to-lot consistency.
POSSIBLE AREAS TO STANDARDIZE	• Knowledge standard on ancillary materials that may be present in biologics and their impacts • Controls and documentation of ancillary materials packaging, manufacturing, and storage • Characterization considerations • Safety and quality evaluation criteria for ancillary materials • Risk mitigation processes for selecting ancillary materials suppliers and products • Ancillary material testing methods and acceptable ranges

C1 ANCILLARY MATERIALS

RELATED EFFORTS

- A three-part U.S. documentary ISO standard (ISO/TS 20399) published in November 2018 addresses the ancillary materials needs discussed in this section from the perspective of users and suppliers (Part 1, Part 2, Part 3). Efforts are under way to combine and elevate these into a single international standard, ISO 20399 (in development).
- USP Chapter <1043>, Ancillary Materials For Cell, Gene, And Tissue-Engineered Products, offers general guidance on development of appropriate ancillary material qualification programs.

NEXT STEPS

- Solicit input from ancillary material providers on their processes to determine best practices for improved quality control.
- Conduct a gap analysis on existing standards.
- Solicit input from product developers to assess how they select ancillary materials providers.
- Research the potential side effects of residual ancillary materials in administered regenerative medicine products.
- Poll providers/suppliers and end users for risk-specific ranges of ancillary materials to achieve maximum standard specification.
- Determine what data should be provided with ancillary materials when given to end users.

C2 CELL COLLECTION PROCEDURES

Cell Therapy | Gene Therapy | Tissue Engineering

FUNCTIONAL AREAS

- **Bioprocessing and Production Standards**
- Analytics & Testing Methods Standards
- Product Quality and Characterization Standards
- Logistics and Compliance Criteria Standards
- Preclinical Study Standards
- Clinical Trial Standards

Cells are harvested from donors' organs, blood, and other parts of the body to use as the starting material for different types of regenerative medicine therapies, including those for targeted drug delivery, tissue repair, and immunotherapy.

CHALLENGE: Staff at collection centers often have difficulty switching between varied collection requirements for different manufacturers, potentially leading to errors in recordkeeping or the loss of usable starting material. Additionally, inconsistent cell collection practices both across and within centers can result in decreased efficacy of treatments due to unpredictable cell quality.

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Establish cell collection requirements that ensure **consistency, safety, and comparability in final products** and reduced loss of cell material.
POSSIBLE AREAS TO STANDARDIZE	• Collection protocols • Stabilization processes • Metadata to chart cell-collection process (timeline of when cells are collected, stabilized, and stored) • Methodologies and criteria for shelf life testing • Microcarriers for cell expansion • Specifications for inspection and receiving • Best practices for optimal cell viability and quality (e.g., temperature between collection and processing) • Packaging (vials, bags, etc.) • Shipping/handling protocols • Expiration dates • Clarification of use of anticoagulants and additives in cell collection/harvesting • Donor qualification and testing

RELATED EFFORTS

- SCB is coordinating a project to develop a documentary standard on cell collection documentation, record retention, collection protocols, disposables, transportation, and collection equipment.
- FACT has standards for consistent quality starting material collection practices, including operating procedures, training, process controls, and quality oversight. Such standards allow for flexibility for different cellular therapy products but also promote efficiency in collection practices.
- The World Marrow Donor Association (WMDA) has a standard for stem cell donor registries that includes cell collection best practices.

C2 CELL COLLECTION PROCEDURES

NEXT STEPS

- Solicit input from collection facilities and companies on existing collection protocols.
- Examine potential for radio-frequency identification (RFID) labeling.
- Increase hospital and collection center engagement to assess process limitations that lead to inconsistencies.

C3 CELL AND TISSUE THERAPY MANUFACTURING EQUIPMENT REQUIREMENTS

Cell Therapy | Gene Therapy | Tissue Engineering

FUNCTIONAL AREAS

- Bioprocessing and Production Standards
- Analytics & Testing Methods Standards
- Product Quality and Characterization Standards
- Logistics and Compliance Criteria Standards
- Preclinical Study Standards
- Clinical Trial Standards

Cell production platform technologies include hardware, software, and consumable materials that are used during the creation of cell therapies, or that come into contact with the product in development, including during processing at a clinical site.

CHALLENGE: Inconsistencies and unknown factors in cell therapy processing techniques and manufacturing equipment—even minor variations—can make it difficult to evaluate and ensure product quality and safety.

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Define minimum equipment requirements and general considerations for equipment involved in cell therapy manufacturing, enabling **reduced manufacturing costs and increased production outputs**.
POSSIBLE AREAS TO STANDARDIZE	• Hardware qualification, validation, and calibration methods • Software validation requirements • Container material and sizing • Methods to ensure safety and reduce potential impacts of consumables • Monitoring for equipment used in tissue engineering • Sterile connectors, including tubing sizes and materials • Real-time monitoring (e.g., sensors) and data documentation • System integration best practices • Terminology for consumables (open vs. closed process) • Requirements for supplier qualification

RELATED EFFORTS

- SCB is coordinating a project to develop an ISO documentary standard(ISO TS 23565) which will address cell therapy manufacturing terms, equipment requirements, and general considerations.
- Documentary standards related to this area have been published by:
  - ISO: ISO 9000, ISO 9001, ISO 13485, and the ISO 10993 series
  - ICH: ICH Q8 (R2) Pharmaceutical Development and ICH Q10 Pharmaceutical Quality System
- The FDA published related guidance documents:
  - Guidance for Industry: Class II Special Controls Guidance Document: Cord Blood Processing System and Storage Container
  - Guidance for Industry: Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

C3 CELL AND TISSUE THERAPY MANUFACTURING EQUIPMENT REQUIREMENTS

NEXT STEPS

- Solicit input from manufacturers on current processing techniques and manufacturing equipment to identify best practices.
- Research potential impacts of common processing variables.

C4 KNOWLEDGE STANDARD FOR CELL TYPES USED IN THERAPEUTIC PRODUCTS

Cell Therapy | Gene Therapy | **Tissue Engineering**

Cell behavior and performance is determined by cell morphology—its shape, form, structure, and size—and its environment (e.g., *ex vivo, in vitro, in vivo*).

CHALLENGE: Limited knowledge of cell morphology (for different cell types), how best to measure it for a given application, and how it connects to cell behavior and performance inhibits progress toward researching and developing new therapies for use in patients.

FUNCTIONAL AREAS

- **Bioprocessing and Production Standards**
- Analytics & Testing Methods Standards
- Product Quality and Characterization Standards
- Logistics and Compliance Criteria Standards
- Preclinical Study Standards
- Clinical Trial Standards

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Promote increased understanding of **how to mitigate/respond to the effects of morphology and environment** during cell therapy product development.
POSSIBLE AREAS TO STANDARDIZE	• Variables related to cell morphology • Biological mechanisms and how they affect cell behavior and performance • Measurement controls and calibration techniques for assessing morphology and measuring properties • Critical measurements for acceptance criteria

RELATED EFFORTS

- The National Center for Biotechnology Information (NCBI) published the Entrez Gene Database with information on cytokine interactions, pathways, and gene ontology.
- The Cytokines & Cells Online Pathfinder Encyclopedia focuses on the interactions between different cell types through cytokines.
- The National Heart, Lung, and Blood Institute (NHLBI) has labs dedicated to the study of Cell and Tissue Morphodynamics, Cell Biology, and Cellular Physiology, and regularly releases published research on these topics.
- A 2014 scientific paper explores different ways to measure cell properties, such as using image-based analysis to analyze cells' morphologic potentials for osteogenesis.

NEXT STEPS

- Solicit input from researchers on current morphology assessment techniques.
- Research the effects that cell morphologies and environments have on cell therapy products.

C5 METHODS AND PROCESSES FOR CELL IDENTITY AND CELL LINE AUTHENTICATION

Cell Therapy | Gene Therapy | Tissue Engineering

FUNCTIONAL AREAS

- **Bioprocessing and Production Standards**
- Analytics & Testing Methods Standards
- Product Quality and Characterization Standards
- Logistics and Compliance Criteria Standards
- Preclinical Study Standards
- Clinical Trial Standards

Because cell therapy products are made up of living cells that can change over time or become contaminated with other biological materials, researchers and manufacturers must be able to confirm the identity and purity of cells to develop safe products.

CHALLENGE: Laboratories do not always perform and report results of cell identity and cell line authentication studies since such tests can be resource-intensive. Missing or poor authentication data can lead to misinformation and call study results into question.

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Increase **consistency in cell authentication reporting** to foster confidence in published data.
POSSIBLE AREAS TO STANDARDIZE	• Authentication data requirements • Authentication methods • Reporting methods • Cell attributes requiring testing, by cell line

RELATED EFFORTS

- The American Type Culture Collection (ATCC) published a standard on short tandem repeat (STR) profiling as a cell line authentication/identification method.
- The National Institutes of Health (NIH) revised guidelines on applications for research funding to require proof of authentication and purity of cell lines and held workshops in 2014 and 2015 on reproducibility in cell culture studies.
- As of 2013, *Nature* requires all study authors to report the status of the authentication of cell lines.
- The Global Biological Standards Institute (GBSI) initiated a campaign to encourage cell line authentication.
- The American Society for Histocompatibility & Immunogenics (ASHI) and European Federation for Immunogenics both have standards with guidance for human leukocyte antigen (HLA) typing.
- ISO has an in-development standard for cell line authentication, ISO 23511.

NEXT STEPS

- Solicit input from researchers on reasons why they might not be performing these studies and what would make it easier for them to do so.
- Determine which cell attributes must be authenticated.

C6 ESTABLISHING CONSISTENCY IN THE MANAGEMENT SYSTEM FOR PROCESSING AND HANDLING OF CELLS FOR REGENERATIVE MEDICINE

Cell Therapy | Gene Therapy | Tissue Engineering

Cell processing refers to the handling and preparation of cell products for downstream processes, including the manufacturing of regenerative medicine therapy products. These processing steps can include culturing, harvesting, and genetic manipulation of cells.

CHALLENGE: Because regenerative medicine products rely on emerging research and technology, manufacturers must continually reevaluate their processes to maximize product quality. The complex nature of cells and cell processing during manufacturing make it difficult to ensure effective quality management. A standardized approach to the implementation of cell processing systems could help address these challenges.

FUNCTIONAL AREAS

- **Bioprocessing and Production Standards**
- Analytics & Testing Methods Standards
- Product Quality and Characterization Standards
- Logistics and Compliance Criteria Standards
- Preclinical Study Standards
- Clinical Trial Standards

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Create guidelines for the **implementation of processing systems for cells for regenerative medicine** to assist manufacturers in ensuring product quality and consistency across the industry.
POSSIBLE AREAS TO STANDARDIZE	• Collection of donor cells • Cell isolation • Cell culture and harvesting • Preservation of cells • Genetic manipulation

RELATED EFFORTS

- A 2015 article in *Stem Cells Translational Medicine* discusses process development strategies for promoting safety and quality of regenerative medicine products.
- FACT has standards for consistent cell therapy processing practices addressing processing of cells for hematopoietic cellular therapy products.
  - ISO has a standard addressing best practices for cell processing, ISO 13022, which was published in 2012.

C6 ESTABLISHING CONSISTENCY IN THE MANAGEMENT SYSTEM FOR PROCESSING AND HANDLING OF CELLS FOR REGENERATIVE MEDICINE

NEXT STEPS

- Solicit input from manufacturers on current processing techniques and manufacturing equipment to identify best practices.
- Develop guidelines for major steps in regenerative medicine cell processing.
- Identify manufacturing platforms appropriate for clinical trial application which are amenable to scaling.

G1 FRAMEWORK FOR GENE DELIVERY METHODS AND GENE EDITING TOOLS

Cell Therapy | **Gene Therapy** | Tissue Engineering

FUNCTIONAL AREAS

- **Bioprocessing and Production Standards**
- Analytics & Testing Methods Standards
- Product Quality and Characterization Standards
- Logistics and Compliance Criteria Standards
- Preclinical Study Standards
- Clinical Trial Standards

Gene editing involves the use of a viral vector or other delivery vehicle to insert a new nucleotide sequence into patients' cells to correct or compensate for a deficient version. There are currently a variety of approaches for gene editing and delivery.

CHALLENGE: Because gene therapy is a relatively new and constantly evolving subsector in the field of regenerative medicine, there is a lack of 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.

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	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.
POSSIBLE AREAS TO STANDARDIZE	• Appropriate uses of gene editing technology • Methods for gene editing tool selection • Best practices for different gene editing tools and delivery mechanisms • Approach for identifying off-target modification and acceptable levels of detection • Criteria for quality of reagents • Database that captures minimum information needed to allow cross-comparisons and understand nominal similarities, with ability to capture additional information as a resource

RELATED EFFORTS

- The National Institute of Standards and Technology (NIST) Genome Editing Consortium seeks to create appropriate standards for gene editing technologies.
- The National Institutes of Health (NIH) Somatic Gene Editing Program was created to accelerate somatic cell gene therapy.

NEXT STEPS

- Catalog current gene delivery methods and gene delivery tools.
- Develop guidelines for each type of gene delivery: insertion, removal, and replacement.
- Survey/interview researchers and product manufacturers on strengths and weaknesses of common gene editing tools and methods.

G2 STANDARDS REGARDING ETHICAL CONSIDERATIONS OF GENE THERAPY

Cell Therapy | **Gene Therapy** | Tissue Engineering

FUNCTIONAL AREAS

- **Bioprocessing and Production Standards**
- Analytics & Testing Methods Standards
- Product Quality and Characterization Standards
- Logistics and Compliance Criteria Standards
- Preclinical Study Standards
- Clinical Trial Standards

Ethical concerns in gene therapy include who has the authority to decide which genetic traits are undesirable, whether gene therapy should be used for non-therapeutic enhancement, and whether gene modifications should be made inheritable or performed on patients who are too young to consent. Various countries, as well as commercial and private enterprises, have dealt with these concerns in different ways.

CHALLENGE: The absence of a current code of conduct, together with some concrete examples of misuse of gene editing technology, have made clear the need for a community-wide ethics agreement. In addition, the global scope of this field means there is no universal governing body to enforce any guidelines.

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Define and create **consensus-based guidelines for ethical gene therapy practices** reflecting the perspectives of a broad and diverse collection of stakeholders in the gene therapy field.
POSSIBLE AREAS TO STANDARDIZE	• Preclinical, clinical, and post-clinical protocols • Guidelines for treatments by age and application area • Considerations for inheritable gene modifications (e.g., germline therapy) • Clarity on the difference between scientific ethics and broader opinion/considerations

RELATED EFFORTS

- The National Institutes of Health (NIH) National Human Genome Research Institute has ethical guidance for gene editing.
- The American Society of Human Genetics (ASHG) has a Code of Ethics.
- The Canadian Commission on Ethics in Science and Technology (CEST) has issued a position statement on germline (heritable) gene editing (English summary – PDF).
- The National Academies of Sciences Engineering Medicine released a consensus study report on heritable human genome editing.
- The World Health Organization (WHO) established an expert panel to develop global ethical standards and oversight of gene editing.
- The Alliance for Regenerative Medicine (ARM) has published commentary and offers resources published by other organizations related to ethical considerations of gene editing for somatic (non-heritable) versus germline cells.

G2 STANDARDS REGARDING ETHICAL CONSIDERATIONS OF GENE THERAPY

NEXT STEPS

- Solicit input from the gene therapy community to gather perspectives and assess points of agreement and disagreement.
- Consider which potential guidelines might be most broadly/internationally applicable.

T1 CHARACTERIZATION OF SCAFFOLD MATERIALS

Cell Therapy | Gene Therapy | **Tissue Engineering**

FUNCTIONAL AREAS

- **Bioprocessing and Production Standards**
- Analytics & Testing Methods Standards
- Product Quality and Characterization Standards
- Logistics and Compliance Criteria Standards
- Preclinical Study Standards
- Clinical Trial Standards

Scaffolds mimic the natural extracellular matrix to provide the support, structure, and necessary template for proliferation of cells in tissue engineering products. Scaffolds may be seeded with cells and cultured *in vitro* to generate tissues that will be implanted into a patient, or the scaffold itself may be implanted directly into the patient for *in vivo* tissue development. Scaffolds can be made from a variety of materials, including collagen, ceramics, polymer, or fibers.

CHALLENGE: The interaction between scaffold materials and cells is complex, and there is currently no consensus on the most relevant measurements and best measurement techniques for assessing scaffold properties. Equally importantly, scaffolds containing alien DNA remnants can cause adverse physical reactions in patients. The ability to accurately measure and reliably reproduce new scaffolds with the same properties is crucial for enabling the large-scale manufacturing of tissue engineering treatments for a broader base of patients who need them.

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Establish measurement techniques and core characteristics to measure to ensure the **consistency of the structural, mechanical, and biological properties of scaffolds**, improving the quality of tissue engineered products.
POSSIBLE AREAS TO STANDARDIZE	• Characterization of scaffolds • Measurement techniques • Criteria for materials selection • Implementation of photoacoustic tomography (PAT) • Core attributes and characteristics to be measured • Application-specific considerations

RELATED EFFORTS

- SCB is coordinating a standards advancement project to draft an ASTM standard (ASTM WK65476) on fiber-based scaffolds, as well as leading discussions around the potential for reference standards.
- ASTM convened an in-person workshop on standards and measurement needs for scaffolds and has published various standards related to scaffold measurement, characterization, and testing.

NEXT STEPS

- Develop a model scaffold system upon which to base a standard.
- Promote greater community engagement, especially from academia.

T2 DONOR TISSUE STERILIZATION

Cell Therapy | Gene Therapy | **Tissue Engineering**

FUNCTIONAL AREAS

- **Bioprocessing and Production Standards**
- Analytics & Testing Methods Standards
- Product Quality and Characterization Standards
- Logistics and Compliance Criteria Standards
- Preclinical Study Standards
- Clinical Trial Standards

Tissues like bone, skin, cartilage, and valves obtained from human donors can be used for repair or reconstruction of an injured part of the body. To reduce the risk of infectious disease transmission, donor tissue needs be sterilized whenever possible to make it safe for clinical use.

CHALLENGE: The living nature of tissue engineered products makes it difficult to sterilize material without impacting the molecular integrity of the tissue. Donor tissue is currently processed individually, which can be time- and resource-intensive, particularly in terms of space and equipment sterilization requirements.

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Identify **methods for sterilizing tissue products in batches to improve manufacturing efficiency,** especially in cases where sterilization is done to prevent cross-contamination. The industry could potentially model tissue engineering sterilization standards after blood bank standards for plasma and platelets.
POSSIBLE AREAS TO STANDARDIZE	• Sterilization methods for tissue allografts • Requirements for "aseptic" versus "terminal" sterilization • Required Sterility Assurance Level (SAL) for biologics • Product quality and characterization

RELATED EFFORTS

- ISO 11137 (Part 1, Part 2, and Part 3) is used for allografts that use terminal sterilization.

NEXT STEPS

- Expand outreach and communication about current standards in this area.
- Research blood bank sterilization standards and determine if they can serve as a baseline for creating donor tissue sterilization standards.
- Assess current knowledge landscape of sterilization (e.g., current methods, barriers to sterilization, time and resource challenges).

T3 BIOPRINTING SPECIFICATIONS

Cell Therapy | Gene Therapy | **Tissue Engineering**

FUNCTIONAL AREAS

- **Bioprocessing and Production Standards**
- Analytics & Testing Methods Standards
- Product Quality and Characterization Standards
- Logistics and Compliance Criteria Standards
- Preclinical Study Standards
- Clinical Trial Standards

Bioprinting—a method that uses 3D printing techniques to synthesize living tissues—is a rapidly expanding field within regenerative medicine with the potential to accelerate the testing timeline for new biopharmaceuticals that can treat a variety of conditions. Bioinks are used in bioprinting to mimic the extracellular matrix that supports cells in three dimensions.

CHALLENGE: As an emerging field with many different manufacturers and academic researchers independently developing products, the bioprinting field currently lacks measures to ensure product consistency. For example, inconsistent bioink properties make it difficult to reproduce test results and control product quality. Bioinks lack standards for properties such as printability and for printing parameters such as the distance between the nozzle and printing space.

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Establish **common best practices for bioprinting, including bioink properties and printing parameters,** to allow product developers to more easily characterize products, reproduce test results, and control product quality.
POSSIBLE	• Material properties (e.g., printability, viscosity, tensile strength) • Bioprinter variables (e.g., machinery, equipment specifications) • Electrical components of the printer (e.g., voltage) • Data management of patient information associated with printed materials

RELATED EFFORTS

- SCB is coordinating a project to develop an ASTM standard (ASTM WK72274) on desirable properties of bioinks. As a complement to these efforts, SCB is also working with the American Society of Mechanical Engineers (ASME) and the Institute of Electrical and Electronics Engineers (IEEE) to coordinate the development of potential standards around the validation of bioprinting hardware and bioprinter software and data governance.
- ISO/ASTM 52921, published in 2013, is a standard terminology guide for additive manufacturing that includes terminology relevant to bioprinting.

NEXT STEPS

- Assess likelihood for community adoption of a bioink standard.
- Consider three different standards: one about bioprinting materials, one focused on the hardware of the bioprinters, and one about bioprinting software and data management.

Analytics and Testing Methods

C7 CELL COUNTING METHODS FOR REGENERATIVE MEDICINE THERAPIES

Cell Therapy | Gene Therapy | Tissue Engineering

FUNCTIONAL AREAS

- Bioprocessing and Production Standards
- **Analytics & Testing Methods Standards**
- Product Quality and Characterization Standards
- Logistics and Compliance Criteria Standards
- Preclinical Study Standards
- Clinical Trial Standards

The ability to count the number of cells in a test sample is crucial to understanding a therayy's potency and making decisions about effective product dosing.

CHALLENGE: Imprecise and inconsistent measurements prevent researchers and product developers from using cell counts as a quality assurance metric and can delay research and development into new therapies. In addition, improper culturing due to counting errors can negatively affect final cell counts, result in lost sample material, and reduce therapy effectiveness.

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Create a **clearly defined set of criteria that can be used across cell-counting assays**, allowing for easier cross-comparisons and improved product quality assurance.
POSSIBLE AREAS TO STANDARDIZE	• Measurement controls, protocols, and standard operating procedures • Counting method qualification and validation • Cell-counting modalities (e.g., microscopy, imaging, flow cytometry) • Counting-dependent measurements (e.g., proliferation, metabolic activity) • Data analysis and reporting

RELATED EFFORTS

- SCB coordinated a standards advancement project to develop a two-part ISO documentary standard on cell counting.
  - Part 1, ISO 20391-1, was published in 2018
  - Part 2, ISO 20391-2, was published in 2019
- USP offers the CD34+ Cell Enumeration System Suitability Reference Standard.
- ASTM published ASTM F2739-19, a guide for quantifying cell viability within scaffolds.
- A National Institute of Standards and Technology (NIST) cell counting approach combines experimental design and statistical analysis to allow the user to evaluate the confidence of his/her cell counting measurement process through a statistical performance metric for cell counting.

NEXT STEPS

- Assess different modalities of cell counting (image-based and flow-based).
- Assess potential to develop a reference material that can be used to calibrate cell counting methods.

C8 DETERMINING AND INTERPRETING CELL VIABILITY

Cell Therapy | Gene Therapy | **Tissue Engineering**

FUNCTIONAL AREAS

- Bioprocessing and Production Standards
- **Analytics & Testing Methods Standards**
- Product Quality and Characterization Standards
- Logistics and Compliance Criteria Standards
- Preclinical Study Standards
- Clinical Trial Standards

Researchers must be able to measure cell health and responses to different stimuli to understand a therapy's effectiveness and identify any quality and safety risks.

CHALLENGE: It is difficult for researchers to identify the most appropriate method (e.g., assay) for assessing cell viability within a given therapy or cell type. In addition, test methods can be difficult to interpret due to a lack of understanding of what assays measure and how measured parameters correlate with cell viability.

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Enable researchers to **design and use cost-effective assays** that yield accurate and precise cell viability results.
POSSIBLE AREAS TO STANDARDIZE	• Data type to measure with assays (e.g., the number of living/dead cells) • Assay parameters (e.g., incubation time) • Stock cultures and testing environments • Needed supplies/equipment • Criteria for method selection (i.e., which assay to use and when to use it) • Time during process at which sample is collected • Data recording and documentation • Assessing impact of patient variability

RELATED EFFORTS

- ASTM F2739-19, a standard published in 2016 and updated in 2019, is a guide for quantifying cell viability within biomaterial scaffolds.
- The International Society of Cell & Gene Therapy (ISCT) publishes research on the scientific challenges of mesenchymal stromal cell (MSC) manufacturing, including assays relevant to viability.
- Researchers have published guides on choosing proper viability assays for different research projects.

NEXT STEPS

- Solicit input from researchers to determine their biggest pain points in interpreting cell viability.
- Assess whether viability assays currently on the market fully meet researchers' needs and identify specific gaps.
- Research different parameters and data types to determine the best designs for assays.

C9 DEFINING ASPECTS OF A CERTIFICATE OF ANALYSIS FOR ANCILLARY MATERIALS

Cell Therapy | Gene Therapy | Tissue Engineering

FUNCTIONAL AREAS

- Bioprocessing and Production Standards
- **Analytics & Testing Methods Standards**
- Product Quality and Characterization Standards
- Logistics and Compliance Criteria Standards
- Preclinical Study Standards
- Clinical Trial Standards

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.

CHALLENGE: Achieving high efficiency and low waste during manufacturing requires consistency in the quality of ancillary materials to facilitate development of precision manufacturing processes. 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.

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Establish **consistent analytical testing methods and COA formats** for various ancillary materials that allow manufacturers to compare materials from different sources.
POSSIBLE AREAS TO STANDARDIZE	• Appropriate testing methods for different ancillary materials • Critical quality attributes (CQAs) relevant to manufacturing consistency • Acceptable product parameters for basic ancillary materials • COA presentation and formatting • Requirements for supplier qualification

RELATED EFFORTS

- A three-part U.S. documentary ISO standard (ISO/TS 20399) published in November 2018 addresses the ancillary materials needs discussed in this section from the perspective of users and suppliers (Part 1, Part 2, Part 3). Efforts are under way to combine and elevate these into a single international standard, ISO 20399.
- USP Chapter <1043>, Ancillary Materials for Cell, Gene, and Tissue-Engineered Products, offers general guidance on development of appropriate ancillary material qualification programs.
- Akron Biotechnology published a white paper in *Cytotherapy* proposing a risk-based framework for ancillary material qualification.

C9 DEFINING ASPECTS OF A CERTIFICATE OF ANALYSIS FOR ANCILLARY MATERIALS

NEXT STEPS

- Assess current industry COAs as a basis for future standards.
- Solicit input from regenerative medicine manufacturers to determine CQAs affecting product consistency.
- Solicit input from ancillary material providers on their processes to determine best practices for improved quality control.

G3 METHODS FOR THE EVALUATION OF ENDOGENOUS T-CELL THERAPIES

Cell Therapy | **Gene Therapy** | Tissue Engineering

FUNCTIONAL AREAS

- Bioprocessing and Production Standards
- **Analytics & Testing Methods Standards**
- Product Quality and Characterization Standards
- Logistics and Compliance Criteria Standards
- Preclinical Study Standards
- Clinical Trial Standards

T-cell therapies use modified T cells—white blood cells closely involved in regulating cell-mediated immunity—to recognize and eliminate cancer cells. Endogenous T-cell therapies use artificial receptors added to T cells that have been designed to recognize a specific cancer antigen.

CHALLENGE: T-cell therapies can lead to a variety of negative reactions, including neurotoxicity, incorrect targeting of non-cancerous cells, and anaphylaxis. The introduction of T-cell therapies can also trigger cytokine release syndrome (CRS), an influx of inflammatory cytokines that produces a potentially life-threatening immune response.

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Define acceptable evaluation **methods for monitoring and mitigating common complications** arising from T-cell therapy.
POSSIBLE AREAS TO STANDARDIZE	• Identification of factors that can cause negative reactions to T-cell therapies • Methods for mitigating these factors at all applicable stages of the production process (e.g., harvesting, processing, and re-introduction) • Selection of potency assays for determining safe dose • Biomarkers for early detection of complications

RELATED EFFORTS

- In 2016, the FDA proposed the creation of databases on T-cell therapy safety.
- In 2018, the National Comprehensive Cancer Network (NCCN) issued a report on T-cell therapy, which addressed safety concerns including neurotoxicity and CRS.
- In 2019, researchers from the Huazhong University of Science and Technology published a comparison of various potential strategies to address T-cell therapy safety concerns.
- The European Medicines Agency (EMA) is developing revised guidance for medicinal products containing genetically modified cells, which includes an annex that discusses clinical considerations for T-cell therapies.

NEXT STEPS

- Conduct studies of adverse T-cell therapy reactions, including longitudinal studies to track long-term effects.

G4 VIRAL VECTOR GENE QUANTIFICATION

Cell Therapy | **Gene Therapy** | Tissue Engineering

FUNCTIONAL AREAS

- Bioprocessing and Production Standards
- **Analytics & Testing Methods Standards**
- Product Quality and Characterization Standards
- Logistics and Compliance Criteria Standards
- Preclinical Study Standards
- Clinical Trial Standards

Viral vectors are viruses modified to transfer genetic material into cells to treat genetic disorders. To deliver an effective gene therapy treatment, viral vectors must be quantified to determine the number of viral particles present in a given therapy product.

CHALLENGE: The field lacks uniform requirements for viral vector gene quantification, which can result in imprecise or inaccurate viral vector counts or miscommunication due to differences in data reporting practices. This presents a significant safety risk to patients, who may experience no therapeutic effect if a dose is too low or have an adverse immune response if it is too high.

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Establish **consistent measurement procedures and reporting requirements** to ensure that quantification results are as accurate as possible and can be readily understood by different stakeholders.
POSSIBLE AREAS TO STANDARDIZE	• Test method selection criteria • Guidelines for interpreting test results • Recordkeeping and reporting requirements for data comparability • Delivery vehicles (e.g., full vs. empty capsids) • Appropriate dosing of transvecting units • Polymerase chain reaction (PCR) variables, including serotypes, titers, preparation • Reference materials, including vectors, plasmids, and reagents

RELATED EFFORTS

- IsBioTech, in collaboration with other working group partners, has developed adeno-associated virus (AAV) reference materials, including for Adenovirus Type 5. These reference materials are available through ATCC.
- The PCR MIQE standards offer minimum information for publication of quantitative real-time PCR experiments.
- ISO has a standard on gene quantification, ISO 20395.

NEXT STEPS

- Assess potential benefits of developing a central database for community stakeholders.
- Seek consensus from laboratories on viral vector gene testing and data analysis.

G5 ESTABLISHING COMPARABILITY BETWEEN ASSAYS FOR MEASURING HUMAN IMMUNE RESPONSE TO VIRAL VECTORS

Cell Therapy | **Gene Therapy** | Tissue Engineering

FUNCTIONAL AREAS

- Bioprocessing and Production Standards
- **Analytics & Testing Methods Standards**
- Product Quality and Characterization Standards
- Logistics and Compliance Criteria Standards
- Preclinical Study Standards
- Clinical Trial Standards

Many genetic therapies utilize viral vectors as a gene delivery vehicle. However, patients previously exposed to the virus used as a vector or another with a similar serotype may have pre-existing immunity and produce neutralizing antibodies (NAbs) that interfere with the function of the therapeutic vector. In addition to reducing clinical outcomes for patients, the presence and activity of NAbs can confound the results of clinical trials. Due to these factors, there is a need for accurate and reliable testing for pre-existing immunity.

CHALLENGE: While cell-based neutralizing assays are considered ideal for detecting pre-existing immunity because they most closely reflect the *in vivo* activity of NAbs, these assays are complex in both design and interpretation and may not be feasible for every product. Enzyme-linked immunosorbent assays (ELISAs) present an alternative, but because not all antibodies are neutralizing, these assays are more prone to false positives and do not always correlate with results from cell-based assays.

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Develop a **standard approach to pre-existing immunity assay development, selection, and evaluation** to enhance patient safety, quality of clinical trial data, and ultimately efforts to circumvent the impact of pre-existing immunity.
POSSIBLE AREAS TO STANDARDIZE	• Validation framework for assays • Selection of cell lines for cell-based assays • Selection of antibodies for ELISA • Selection of quality measures for cell-based assays • Metrics for reading and interpreting test results • Clinical trial patient selection criteria

RELATED EFFORTS

- SCB is coordinating a standard advancement project for evaluating pre-existing immunity to AAVs.
- NIH-NCATS held a workshop on central nervous system (CNS) immunogenicity concerns for AAV-mediated gene therapy in June 2019.

G5 ESTABLISHING COMPARABILITY BETWEEN ASSAYS FOR MEASURING HUMAN IMMUNE RESPONSE TO VIRAL VECTORS

NEXT STEPS

- Analyze current best practices in evaluating patients for pre-existing immunity.
- Establish standard cell lines and controls for use in cell-based neutralizing assays.
- Establish consistent monitoring and reporting metrics to facilitate comparisons between products and clinical trial outcomes.
- Examine existing standards for measuring NAb response to protein therapeutics to assess their applicability to viral vectors.
- Consult with manufacturers over intellectual property concerns which could impede data sharing.

G6 BEST PRACTICES FOR CONDUCTING OFF-TARGET ANALYSES FOR GENE EDITING PRODUCTS

Cell Therapy | **Gene Therapy** | Tissue Engineering

FUNCTIONAL AREAS

- Bioprocessing and Production Standards
- **Analytics & Testing Methods Standards**
- Product Quality and Characterization Standards
- Logistics and Compliance Criteria Standards
- Preclinical Study Standards
- Clinical Trial Standards

Genome-editing technology seeks to treat genetic disorders by modifying or replacing genetic material in a subset of a patient's cells. A major concern in genetic therapy development is off-target effects, or alterations to genetic material (mutations) outside of the region of interest. Off-target disruption of healthy gene function has the potential to cause a wide variety of unintended side effects of variable severity, many of which might not manifest until well after the administration of therapy. In some FDA approvals, observation periods for off-target effects can be as long as ten years.

CHALLENGE: Although many *in silico* and *in vitro* methods exist to screen for potential off-target sites, the novelty of gene-editing therapies and the potentially long-lasting impact of off-target effects mean that the predictive power of these models and the actual *in vivo* impact of these effects remain poorly understood. Off-target assessments are expensive and time consuming, but the success of gene-editing technology relies on them to maintain the confidence of clinicians and the public.

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Establish **standards for monitoring off-target mutation effects** in gene therapy patients to improve patient safety and the development of predictive off-target screening methods.
POSSIBLE AREAS TO STANDARDIZE	• Screening methods and frequency • Methods for identifying potential off-target sites • Methods for mitigating off-target effects • Biomarkers for detection of off-target effects

RELATED EFFORTS

- An article in *Cell* provides considerations and discusses analysis for on- and off-target editing when using CRISPR technologies.
- An article in *Nature Communications* discusses the high success rate of using the CRISPR amplification method to detect off-target mutations.

G6 BEST PRACTICES FOR CONDUCTING OFF-TARGET ANALYSES FOR GENE EDITING PRODUCTS

NEXT STEPS

- Conduct longitudinal studies of gene therapy side effects.
- Consult with clinicians and patient advocates to determine acceptable use of novel gene-editing therapies.
- Consult with researchers to determine potential ways to mitigate off-target effects.
- Develop cost- and time-efficient methods for off-target mutation screening.

T4 CORRELATION OF DECELLULARIZATION MEASUREMENTS AND CLINICAL OUTCOMES FOR TISSUE ENGINEERED PRODUCTS

Cell Therapy | Gene Therapy | **Tissue Engineering**

FUNCTIONAL AREAS

- Bioprocessing and Production Standards
- **Analytics & Testing Methods Standards**
- Product Quality and Characterization Standards
- Logistics and Compliance Criteria Standards
- Preclinical Study Standards
- Clinical Trial Standards

Decellularization is the process by which the extracellular matrix (ECM) is isolated from the cellular component of a tissue or organ. This provides a natural scaffold for tissue regeneration that ideally retains the necessary structural and biochemical cues to direct cellular differentiation and allow a patient's own progenitor cells to regenerate into functional tissue for transplantation.

CHALLENGE: Decellularization is typically carried out through a combination of physical, chemical, and enzymatic processes, with methods and effectiveness varying based on the properties of the original tissue. All decellularization processes alter the physical or chemical nature of the ECM to some degree, and there is currently minimal standardization of methods for assessing the success of these processes in maintaining ECM composition or correlating it with clinical outcomes.

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Establish **common analytical methods to evaluate the success of decellularization** to assess decellularization methods and clinical outcomes.
POSSIBLE AREAS TO STANDARDIZE	• Evaluation of ECM geometric and biological properties • Decellularization method selection • Assessment of residual cellular material • Measurement of transplant or regeneration success and clinical outcomes

RELATED EFFORTS

- A 2017 article in *BioMed Research International* compares the advantages and disadvantages of multiple decellularization methods, including chemical and enzymatic, physical, and combinative approaches.
- ASTM WK57514, New Guide for Evaluating Extracellular Matrix Decellularization Processes, is an in-development standard intended to give recommendations on characterization of decellularization processes.

NEXT STEPS

- Define appropriate decellularization techniques based on source tissue and desired scaffold attributes.
- Standardize analytical methods to evaluate success of decellularization.
- Determine decellularized ECM qualities which best correspond to improved clinical outcomes.

Product Quality and Characterization

C10 HUMAN CELL CHARACTERIZATION

Cell Therapy | Gene Therapy | Tissue Engineering

FUNCTIONAL AREAS

- Bioprocessing and Production Standards
- Analytics & Testing Methods Standards
- **Product Quality and Characterization Standards**
- Logistics and Compliance Criteria Standards
- Preclinical Study Standards
- Clinical Trial Standards

Characterization of cells is the measurement and evaluation of their critical quality attributes (CQAs)—including purity, potency, identity, stability, and viability—to ensure product quality remains within acceptable limits. These attributes define the safety and effectiveness of therapeutic products made from these cells.

CHALLENGE: Many of the tests and tools necessary to evaluate CQAs exist, but product attributes are not consistently or thoroughly defined across the regenerative medicine community. Processes and measurement selection criteria also vary among researchers and product developers since products and applications differ significantly, making it difficult to compare measurement outcomes.

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Establish **guidelines for defining and consistently measuring and evaluating a cell's CQAs** to ensure a cell is fit-for-purpose.
POSSIBLE AREAS TO STANDARDIZE	• Cell characterization terms • Methods for determining appropriate CQAs based on application • Guidelines for stability considerations for different cell types and modalities • Guidance for cell-based imaging • Fit-for-purpose measurement design methods aligned with unique product properties, modes of action, composition, and processing • Microbial testing • Minimum characterization requirements across cell populations • Single-cell analysis standards

RELATED EFFORTS

- SCB is coordinating a standards advancement project to develop an ISO documentary standard (ISO 23033) on characterization of human cells.
- British Standards Institution (BSI) published PAS 93:2011 in 2011, a documentary standard on human cell characterization.
- ISO has a published standard ISO 21709 and in-development standards ISO/TS 22859, ISO 24603, and ISO 24651 for biobanking of cells, which have sections focused on cell characterization.
- These workshop proceedings at the 2017 Forum on Regenerative Medicine discuss measurement methodologies and approaches that produce accurate and reproducible cell measurements.

C10 HUMAN CELL CHARACTERIZATION

NEXT STEPS

- Compile a complete list of potential CQAs to consider for individual standards development.
- Conduct a gap analysis on current cell characterization standards.
- Establish a basic level of comparability/traceability of methods such as microscopy and imaging.

C11 PRODUCT POTENCY MEASUREMENT METHODS

Cell Therapy | Gene Therapy | Tissue Engineering

FUNCTIONAL AREAS

- Bioprocessing and Production Standards
- Analytics & Testing Methods Standards
- **Product Quality and Characterization Standards**
- Logistics and Compliance Criteria Standards
- Preclinical Study Standards
- Clinical Trial Standards

Potency is a quantitative measure of a product's ability to affect a desired therapeutic result in patients. Identity, purity, and stability of therapy component cells all contribute to a product's potency.

CHALLENGE: Due to the complexity and varying mechanisms of action of regenerative medicine products, researchers have difficulty identifying and developing consistent and effective methods for measuring product potency, leading to uncertainty about effective dosing. Currently, there is also a lack of specific regulatory guidance for assessing potency and limited sharing of potency test results.

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Increase understanding of how to measure potency in complex regenerative medicine products and **establish guidelines for how to develop appropriate potency assays** for different products.
POSSIBLE AREAS TO STANDARDIZE	• Consistent terminology for potency testing • Metrics for measuring potency • Model systems potency measurement methods • Varying potency considerations for different therapy products • Reference materials • Validation of potency assays

RELATED EFFORTS

- FDA published guidance on potency tests for cellular and gene therapy products in 2011. This guidance explains approaches for meeting the potency regulation (21 CFR 600.3(s)), which mandates product-specific testing.
- The European Medicines Agency (EMA) published guidance on potency testing of cell-based immunotherapy medicine products intended to treat cancer.
- The International Society of Cell and Gene Therapy (ISCT) published several research articles discussing considerations for developing a potency assay for cell therapy products.
- Health Canada (Canadian regulatory agency) published a presentation in 2016 on the challenges of potency assays for cell therapy products .
- ASTM published ASTM F3368, Standard Guide for Potency Assays for Cell Therapy and Tissue Engineered Products.

NEXT STEPS

- Solicit input from product developers about their potency testing strategies to gain insight into real-world examples and best practices.
- Assess current regulations to determine where gaps exist and where additional clarification would be beneficial.

C12 TEST METHODS TO MEASURE STERILITY, MYCOPLASMA, AND ADVENTITIOUS AGENTS

Cell Therapy | Gene Therapy | Tissue Engineering

FUNCTIONAL AREAS

- Bioprocessing and Production Standards
- Analytics & Testing Methods Standards
- **Product Quality and Characterization Standards**
- Logistics and Compliance Criteria Standards
- Preclinical Study Standards
- Clinical Trial Standards

To ensure safety and efficacy, product developers must test for infectious agents (e.g., microbes) in biological therapeutic products before administering them to patients.

CHALLENGE: There is a lack of published data and guidance on how to interpret the results of some infectious agent test methods, and cell therapy manufacturers lack support for validating and qualifying new testing methods. These challenges can prevent developers from conducting these tests or limit the usefulness of test results.

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Increase understanding of **how to interpret infectious agent test results**, leading to easier tests that are conducted more consistently and produce more accurate and reliable results.
POSSIBLE AREAS TO STANDARDIZE	• Rapid microbial testing methodology (RMTM) design and validation framework • Fluorescence *in situ* hybridization (FISH) and luminescence test methods (currently lacking published data on sensitivity, specificity, and accuracy) • Microbial reference materials to validate/calibrate equipment Guidance on residual impurities and proper antibiotic use • List of microbes or infectious agents that could be present in different environments • Disposal methods for contaminated cells

RELATED EFFORTS

- SCB is coordinating development of ASTM and ISO documentary standards on RMTMs: ISO 24190 (under development) and ASTM WK70143 (under development)
- The National Institute of Standards and Technology (NIST) launched an RMTM consortium.
- Published documentary standards on sterility testing and microbial test methods:
  - USP: USP General Chapter <60>, <61>, <62>, <63>, <71>, <1071>, and <1223>
  - Parenteral Drug Association (PDA): PDA TR 33
  - European Pharmacopoeia: Ph Eur 5.1.6 and Ph Eur 2.6.27
- AOAC International published *Presidential Task Force on Best Practices in Microbiological Methodology*.
- Published studies discuss sterility testing in cord blood (2013) and ways to eliminate infection in human and animal stem cells (2017).

C12 TEST METHODS TO MEASURE STERILITY, MYCOPLASMA, AND ADVENTITIOUS AGENTS

NEXT STEPS

- Conduct research into infectious agents (e.g., relative size and appearance, common environments).
- Conduct Round Robin testing to determine consistency of current methods
- Assess the strengths and weaknesses of current test methods.

C13 ACCEPTABLE PARTICULATES IN REGENERATIVE MEDICINE PRODUCTS

Cell Therapy | Gene Therapy | Tissue Engineering

FUNCTIONAL AREAS

- Bioprocessing and Production Standards
- Analytics & Testing Methods Standards
- **Product Quality and Characterization Standards**
- Logistics and Compliance Criteria Standards
- Preclinical Study Standards
- Clinical Trial Standards

Particulates (e.g., cell clumps, pieces of glass or metal, fibers) are undesirable foreign agents that can be introduced into cell therapy products through the external environment, from manufacturing or packaging materials, and from cell/protein degradation.

CHALLENGE: Researchers and product developers may have difficulty identifying the particulates that remain in a final product or may not know which ones could have toxic effects *in vivo*. Additionally, cell therapy products do not undergo final filtration steps like other biologic products because cells would be removed along with the particulates. As a result, particulate contamination is currently an unavoidable challenge in the field.

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Increase knowledge of potential **particulate types, acceptable thresholds, particulate effects, and mitigation strategies**.
POSSIBLE AREAS TO STANDARDIZE	• Types of particulates that could be present in a therapy and methods to detect them • List of known particulate effects and how they differ based on mode of administration (e.g., IV versus local injection) • Risk-based assessments for different particulates and amounts • Mitigation/sterilization processes

RELATED EFFORTS

- USP held a 2017 workshop on particulate control and determination in biologic drugs.
- ASTM WK43742, initiated in October 2013, is an in-progress standard that discusses characterizing the particulate burden for single-use manufacturing systems for biopharmaceuticals.
- The International Society of Cell & Gene Therapy (ISCT) Process and Product Development Subcommittee has published articles providing guidance and recommendations to product sponsors and suppliers about particulate sources, testing, monitoring, and controls.

NEXT STEPS

- Solicit input from regenerative medicine product developers and researchers to assess their level of particulate knowledge and methods used for detection.
- Research common particulates and their potential effects.

C14 RELEASE CRITERIA FOR REGENERATIVE MEDICINE PRODUCTS

Cell Therapy | Gene Therapy | Tissue Engineering

Release criteria are basic requirements related to product quality and safety that should be met or exceeded to demonstrate that a regenerative medicine product is ready to administer to patients. As the field of regenerative medicine grows at an exponential rate, it is increasingly important to establish common release criteria for new products to ensure safety, reliability, and effectiveness.

CHALLENGE: It can be difficult to adequately test whether a product meets all its release criteria due to short product shelf lives, lack of sensitivity in rapid test methods, constraints on test sample sizes, and varying test requirements due to differences in release criteria for different products and patients.

FUNCTIONAL AREAS

- Bioprocessing and Production Standards
- Analytics & Testing Methods Standards
- **Product Quality and Characterization Standards**
- Logistics and Compliance Criteria Standards
- Preclinical Study Standards
- Clinical Trial Standards

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Establish appropriate release criteria that account for the unique challenges of regenerative medicine products and **allow researchers to reliably demonstrate product safety, efficacy, and quality compliance**.
POSSIBLE AREAS TO STANDARDIZE	• Language and terminology • Product quality attributes • Cell types and states • Quality measurement methods throughout production • Validation of release tests • Risk assessment methods • Timeframe for performing release criteria testing • Final product reference materials and transduction • Clinical release and public safety data • Preclinical models • Appropriate ranges for plasmids used in cell and gene therapies

RELATED EFFORTS

- FACT includes requirements for processing facility directors to measure cell therapy products to assure safety, viability, and integrity, and document that products meet predetermined release specifications in their FACT-JACIE International Standards for Hematopoietic Cellular Therapy.
- ICH published guidelines on stability testing of new drugs and evaluation of stability data.
- FDA has relevant regulations:
  - 21 CFR Part 1271 provides donor eligibility requirements for human stem cells as release criteria.
  - 21 CFR Part 210 provides cell good manufacturing processes, including conformance specifications and sterility testing.

NEXT STEPS

- Solicit input from researchers and product developers to determine the issues they face when adhering to release criteria.
- Assess most relevant release criteria and test timing for product safety, reliability, and effectiveness.
- Establish working group of gene editing industry members, academic researchers, regulators, medical researchers, and patient advocacy groups.

C15 CONSISTENT LANGUAGE AND TESTING PRACTICES FOR STERILITY TESTING METHODS

Cell Therapy | Gene Therapy | Tissue Engineering

FUNCTIONAL AREAS

- Bioprocessing and Production Standards
- Analytics & Testing Methods Standards
- **Product Quality and Characterization Standards**
- Logistics and Compliance Criteria Standards
- Preclinical Study Standards
- Clinical Trial Standards

Researchers and product developers must test their therapeutic products to determine whether they are contaminated by infectious agents (e.g., microbes) before administering the product to a patient.

CHALLENGE: Guidelines for sterility testing of therapeutic products are not standardized or clearly defined across regulatory bodies or countries and thus are not implemented consistently by the broad regenerative medicine community. Additionally, there are inconsistent definitions of sterility as it applies to biological products.

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Establish **greater clarity on the different sterility testing methods and appropriate use cases,** as well as language that sets a consistent understanding of sterility.
POSSIBLE AREAS TO STANDARDIZE	• Terminology for test methods and sterility concepts • Appropriate sterility thresholds by application • Method selection • List of microbes/agents • Results criteria and documentation • Disposal methods for contaminated cells • Proper antibiotic use • Lab certification across countries

RELATED EFFORTS

- The FDA amended sterility testing requirements for biological products in 2012 to allow greater flexibility.
- Published documentary standards on sterility testing and microbial test methods:
  - USP: USP General Chapter <60>, <61>, <62>, <63>, <71>, <1071>, and <1223>
  - Parenteral Drug Association (PDA): PDA TR 33
  - European Pharmacopoeia: Ph. Eur. 5.1.6 and Ph. Eur. 2.6.27
  - Therapeutic Goods Administration (TGA): TGA guidelines for sterility testing of therapeutic goods
- USP published the article, Stimuli to the Revision Process: The Development of Compendial Rapid Sterility Tests.
- The American Society of Mechanical Engineers (ASME) has developed standard terminology for the tissue engineering community.

C15 CONSISTENT LANGUAGE AND TESTING PRACTICES FOR STERILITY TESTING METHODS

NEXT STEPS

- Assess current sterility testing standard language as a basis for future standards.
- Solicit community inputs on the safety and efficacy of existing test methods.
- Clarify appropriate tests and results criteria.
- Determine if international standards harmonization would be possible.

C16 GUIDELINES FOR VECTOR CHARACTERIZATION, DESIGN, AND VALIDATION FOR USE IN CELL AND GENE THERAPY PRODUCTS

Cell Therapy | Gene Therapy | Tissue Engineering

Prior to use in cell and gene therapy applications, viral vectors must first be designed, characterized, and validated for their safety and efficacy. Homogeneity (empty, full, oligomer); purity; viral particle load; genetic payload; and product consistency must be known and within safe ranges. Precise and dependable quantification of integrated vector copy number per cell is essential to establishing biological potency, which directly impacts therapeutic efficacy as well as the inherent risk of genotoxicity of viral vectors.

CHALLENGE: Researchers and manufacturers employ a variety of methods to quantify viral vector critical quality attributes (CQAs), but final metrics may vary based on the individual technique used, creating uncertainty around data reliability in an already complex biological system. Manufacturers are often protective of their methods and materials, making it difficult to identify specific areas of concern.

FUNCTIONAL AREAS

- Bioprocessing and Production Standards
- Analytics & Testing Methods Standards
- **Product Quality and Characterization Standards**
- Logistics and Compliance Criteria Standards
- Preclinical Study Standards
- Clinical Trial Standards

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Establish **guidelines to harmonize manufacturers' characterization, design, and validation processes** to lower barriers to understanding and mitigating existing complications.
POSSIBLE AREAS TO STANDARDIZE	• Methods for determining appropriate CQAs based on application • Guidelines for viral load and safety considerations • Reporting for safety, identity, purity, and efficacy to facilitate comparability studies • Standards and controls for assay development

RELATED EFFORTS

- The European Medicines Agency (EMA) published guidance on the design, manufacturing, characterization, and testing of vectors for gene therapy products in 2018.
- The European Pharmacopoeia (Ph. Eur.) 10th Edition contains a framework for assuring the quality and safety of raw materials used in the production of cell and gene therapy products, including vectors.
- USP Chapter <1047> summarizes the issues and best current practices in the manufacturing, testing, and administration of gene therapy products, including guidance for vector design.

C16 GUIDELINES FOR VECTOR CHARACTERIZATION, DESIGN, AND VALIDATION FOR USE IN CELL AND GENE THERAPY PRODUCTS

NEXT STEPS

- Establish basic reporting guidelines to allow for comparability of methods.
- Consult with researchers and manufacturers to determine best practices for analytical assay development.
- Develop analytical tools to assess safety and efficacy of viral vectors produced at scale.
- Identify sources of variation in viral vector production and monitoring.

G7 REVISITING APPLICABILITY OF STANDARDS FOR REPLICATION-COMPETENT RETROVIRUS TESTING

Cell Therapy | **Gene Therapy** | Tissue Engineering

Retroviruses are used as vectors to treat genetic diseases by mapping a modified, healthy genome onto the DNA structure of a host's cells. Lentiviruses, a subset of retroviruses, are unique in their ability to integrate into non-dividing cells. These vectors are designed to be self-limiting and must be tested for replication-competent retrovirus (RCR), a marker of uncontrolled replication ability, before therapeutic use.

CHALLENGE: Uncontrolled viral replication can lead to adverse outcomes such as the development of tumors. Though general principles for RCR testing do exist, they are not adequately tested to be sufficient to guarantee long-term safety.

FUNCTIONAL AREAS

- Bioprocessing and Production Standards
- Analytics & Testing Methods Standards
- **Product Quality and Characterization Standards**
- Logistics and Compliance Criteria Standards
- Preclinical Study Standards
- Clinical Trial Standards

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Expand on existing foundations to create a robust yet flexible set of **guidelines for safe and efficient RCR/RCL testing** and provide a framework for incorporating new test methods.
POSSIBLE AREAS TO STANDARDIZE	• Testing needs specific to lentiviruses and other common vectors (e.g., adeno-associated viruses [AAVs]) • Specific testing requirements at each production process step • Test method selection and validation framework • Protocol for patient monitoring after infusion

RELATED EFFORTS

- In 2020, the FDA released final guidance on testing of retroviral vector-based human gene therapy products.

NEXT STEPS

- Determine challenges faced by each type of virus to identify commonalities and differences.
- Evaluate factors needed to allow the standard to be adaptable to rapid changes in technology.

G8 METHODS FOR ASSESSING PRODUCT ACTIVITY AND COMPARABILITY

Cell Therapy | **Gene Therapy** | Tissue Engineering

FUNCTIONAL AREAS

- Bioprocessing and Production Standards
- Analytics & Testing Methods Standards
- **Product Quality and Characterization Standards**
- Logistics and Compliance Criteria Standards
- Preclinical Study Standards
- Clinical Trial Standards

The rapid proliferation of gene therapies has spurred development of a wide array of products—such as CRISPR-Cas9 genome-editing technology. Currently there is no agreed-upon framework in place for assessing product performance.

CHALLENGE: Lack of consistent methods for assessing product performance makes it difficult to compare products, slowing the progress of innovation and leading to confusion among patients and clinicians in making treatment decisions.

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Establish a **set of criteria for assessing product performance** that can be applied consistently across products in the gene therapy field.
POSSIBLE AREAS TO STANDARDIZE	• Identification of factors affecting product performance • Appropriate thresholds for performance data • Guidelines for sample preparation • Product performance test selection and requirements • Critical quality attributes (CQAs) with standard assays applied both early and late in development

RELATED EFFORTS

- The Alliance for Regenerative Medicine (ARM) launched an A-gene project with a chapter on comparability. The Standards Coordinating Body is supporting this effort.
- FDA published guidance in 2005 based on an International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) standard for assessing comparability for biological products before and after changes in their manufacturing process.
- ARM and USP cohosted workshop on comparability for cell and gene therapies in May 2019.

NEXT STEPS

- Create a preliminary performance assessment rubric to be expanded as new treatments are generated.
- Reach out to community stakeholders early in the process to ensure maximum engagement.

T5 BIOLOGICAL EVALUATION OF TISSUES AND EXTRACELLULAR MATRICES USED IN TISSUE ENGINEERING FOR IN VIVO STUDIES

Cell Therapy | Gene Therapy | **Tissue Engineering**

FUNCTIONAL AREAS

- Bioprocessing and Production Standards
- Analytics & Testing Methods Standards
- **Product Quality and Characterization Standards**
- Logistics and Compliance Criteria Standards
- Preclinical Study Standards
- Clinical Trial Standards

Proteins derived from the extracellular matrix (ECM), a network of macromolecules that support the cellular component of tissues, have become an object of increasing interest from regenerative medicine researchers based on the hypothesis that natural, tissue-derived materials will integrate better with host tissues during transplantation relative to synthetic biomaterials.

CHALLENGE: The benefits of naturally derived ECM proteins in tissue engineering remain mostly hypothetical due in large part to a lack of standard approaches to the assessment of these materials and their performance after transplantation. Current analytical methods are limited in scope based on specific applications, preventing a comparative assessment of various tissue-engineered products.

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Establish **standard approaches to characterizing tissue-derived materials and their performance** for *in vivo* applications.
POSSIBLE AREAS TO STANDARDIZE	• Definitions for ECM composition • Metrics for successful integration with host tissue • Preclinical *in vivo* models • Appropriate characterization methods based on ECM sources and properties

RELATED EFFORTS

- A 2016 article in *Biomaterials* reviews current ECM-derived biomaterials characterization methods and compares the advantages and limitations of relevant preclinical *in vivo* models.
- A 2016 article in *Tissue Engineering Part B: Reviews* discusses different types of cell-derived ECM products for orthopedic tissue engineering and advises on potential future directions for study.

NEXT STEPS

- Assess current understanding of ECM qualities relevant to successful transplant integration and identify gaps in knowledge.
- Solicit input from researchers on the most effective methods to characterize critical ECM qualities.
- Establish a standard system for characterizing ECM materials and reporting material integration metrics to facilitate comparative studies.

Logistics and Compliance

C17 CHAIN-OF-IDENTITY / CHAIN-OF-CUSTODY RECORDING

Cell Therapy | Gene Therapy | Tissue Engineering

FUNCTIONAL AREAS

- Bioprocessing and Production Standards
- Analytics & Testing Methods Standards
- Product Quality and Characterization Standards
- **Logistics and Compliance Criteria Standards**
- Preclinical Study Standards
- Clinical Trial Standards

Chain of identity is a record associated with a single patient, including their health records both before and after treatment. Chain-of-custody records all points of transfer and control for a product, including product starting material and all in-process manipulations through the point of delivery. A patient may receive multiple doses of a therapy, each of which would have its own chain of custody.

CHALLENGE: Inaccurate records or incompatible recordkeeping systems can cause delays when transferring products. This can potentially risk administering the wrong product to a patient or the inability to administer a product due to delays.

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Establish **consistent product handling and digital information documentation practices** to allow patients and clinicians to easily trace chain-of-identity and chain-of-custody information about a product.
POSSIBLE AREAS TO STANDARDIZE	• Data requirements • Labeling requirements • Recordkeeping system requirements • Documentation procedures • Electronic tracking methods (e.g., radio-frequency identification [RFID]) • Therapy-specific chains of custody and identification (allogeneic vs. autologous)

RELATED EFFORTS

- ISBT 128 (Donor Label Standards), approved in 1994, is a global standard for identification, labeling, tracking, and data transfer regarding medical products of human origin, set out by the International Council of Commonality in Blood Banking Automation (ICCBBA).
  - An SCB-coordinated project culminated in the publication of ST-018 ISBT-128, Standard Labeling of Collection Products for Cellular Therapy, which addresses information necessary for apheresis products used in cell therapy manufacturing.
- The European Commission (EC) issued Directive 2006/17/EC, which requires all therapies to be traceable to the original donor of the starting material.
- The Center for International Blood and Marrow Transplant Research (CIBMTR):
  - Maintains a data registry for cell transplantation and a Cell Therapy Registry for data collection for non-blood and marrow transplant (BMT) cellular therapies.
  - The Cellular Immunotherapy Data Resource (CIDR) hosts the Cell Therapy Registry for regenerative medicine in response to an unmet need for a centralized data repository for research.

C17 CHAIN-OF-IDENTITY / CHAIN-OF-CUSTODY RECORDING

NEXT STEPS

- Solicit input from stakeholders to determine pain points in their current recordkeeping systems and requirements between companies.
- Develop basic regulatory guidance that addresses chain-of-identity and chain-of-custody requirements.

C18 LABELING STANDARDS SPECIFIC TO REGENERATIVE MEDICINE PRODUCTS

Cell Therapy | Gene Therapy | Tissue Engineering

FUNCTIONAL AREAS

- Bioprocessing and Production Standards
- Analytics & Testing Methods Standards
- Product Quality and Characterization Standards
- **Logistics and Compliance Criteria Standards**
- Preclinical Study Standards
- Clinical Trial Standards

Product labels ensure that a cell therapy product can be efficiently identified and followed throughout the collection, production, and delivery process so it can be safely administered to the correct patient.

CHALLENGE: Labels can vary between companies and facilities because existing labeling standards are not universally adopted and do not always apply consistently at each step in the cell therapy supply chain. Inconsistent labels can cause confusion and mistakes, leading to delays with transferring products across the supply chain and posing a safety risk if healthcare providers cannot confirm that a patient is receiving the correct treatment.

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Update existing standards to create a universal labeling system that accounts for companies' **unique processing systems, technology differences, employee roles, and local languages**, and is flexible for use along the complete cell therapy supply chain.
POSSIBLE AREAS TO STANDARDIZE	• Data management of unique IDs used in multiple locations (e.g., collection facilities, hospitals, donation centers) • Multi-language translations • Protocol for tracking multiple lots from the same donor • Integration of chain of identity (COI) into electronic medical record systems

RELATED EFFORTS

- ISBT 128 (Donor Label Standards), approved in 1994, is a global standard for identification, labeling, tracking, and data transfer regarding medical products of human origin, set out by the International Council of Commonality in Blood Banking Automation (ICCBBA).
  - An SCB-coordinated project culminated in the publication of ST-018 ISBT-128, Standard Labeling of Collection Products for Cellular Therapy, which addresses information necessary for apheresis products used in cell therapy manufacturing.
- Single European Code (SEC) Commission Directive (EU) 2015/565, issued in 2015, intends to improve the traceability of human tissue and cells in the EU from procurement to application.
- FDA has relevant regulations:
  - 21 CFR Part 1271.90, Human Cells, Tissues, and Cellular and Tissue-Based Products provides labeling requirements for donor eligibility
  - 21 CFR Part 210 Subparts A & B provide requirements for good manufacturing practice (GMP) drug processing, packing, or holding

C18 LABELING STANDARDS SPECIFIC TO REGENERATIVE MEDICINE PRODUCTS

NEXT STEPS

- Examine current labeling systems to identify elements for standardization.
- Solicit input from product developers and storage facilities to identify difficulties with current labeling systems.
- Determine how labeling practices differ and what their intended purpose is at each point in the value chain.
- Assess labeling in other global industries to determine if any best practices could be applied to regenerative medicine.

C19 DATA ACQUISITION

Cell Therapy | Gene Therapy | Tissue Engineering

FUNCTIONAL AREAS

- Bioprocessing and Production Standards
- Analytics & Testing Methods Standards
- Product Quality and Characterization Standards
- **Logistics and Compliance Criteria Standards**
- Preclinical Study Standards
- Clinical Trial Standards

The data generated throughout the research, development, and application of regenerative medicine therapies can inform efficient innovation of therapeutic products and help demonstrate the efficacy, safety, or regulatory compliance of a product.

CHALLENGE: The quality, accuracy, and completeness of the existing body of data varies. Formats exist for acquiring and recording data, but there is no standard to encourage their use, which makes it difficult to compare like data. Additionally, companies do not have a streamlined method to share their data while retaining their intellectual property (IP) and maintaining patient/donor privacy.

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Implement **protocols to increase data quality**, make data easier to share, and establish mechanisms to safeguard IP and patient privacy.
POSSIBLE AREAS TO STANDARDIZE	• Patient/donor privacy considerations • Data management and storage plans • Data registry/database characteristics • Data security considerations • Data elements (form fields) • Application programming interfaces (APIs) and integration • Methods to study long-term effects of therapies in patients • Management of metadata

RELATED EFFORTS

- In 2016, the FDA announced a pilot program to create databases of safety and manufacturing information on T-cell therapies.
- The European Medicines Agency (EMA) published scientific guidelines on good pharmacovigilance practices and post-authorization efficacy studies to help establish a framework for dialogue among pharmaceutical companies, registry holders, and regulators on study designs.
- The American Society of Clinical Oncology (ASCO) developed a big-data project, CancerLinQ, to share real-world cancer patient data.
- The International Committee of Medical Journal Editors (ICMJE) requires researchers to share de-identified patient data for possible publication in the major medical journals under their jurisdiction.
- The Center for International Blood and Marrow Transplant Research (CIBMTR):
  - Maintains a data registry for cell transplantation and a Cell Therapy Registry for data collection for non-blood and marrow transplant (BMT) cellular therapies.
  - Is also creating a registry for regenerative medicine in response to an unmet need for a centralized data repository for research.

C19 DATA ACQUISITION

NEXT STEPS

- Solicit input from companies to identify their most common concerns around data sharing.
- Develop a plan to address these concerns and safeguard against IP and patient privacy issues.
- Identify strengths and weaknesses of existing data recording formats to use as the basis of a potential standard.

C20 CRYOPRESERVATION METHODS

Cell Therapy | Gene Therapy | Tissue Engineering

FUNCTIONAL AREAS

- Bioprocessing and Production Standards
- Analytics & Testing Methods Standards
- Product Quality and Characterization Standards
- **Logistics and Compliance Criteria Standards**
- Preclinical Study Standards
- Clinical Trial Standards

Cryopreservation is a controlled freezing process used to help extend the life of a cell therapy product during sterility testing, storage, and transportation.

CHALLENGE: Cryopreservation can alter cells and introduces additional operational steps (with associated costs and risks) to the manufacturing process. Stakeholders are addressing these issues independently, which can lead to inconsistencies in products from different manufacturers.

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Establish **best practices and a framework for decision-making** for cryopreservation methods and processes.
POSSIBLE AREAS TO STANDARDIZE	• Framework for selecting and validating cryopreservation methods • Methods for evaluating effect of cryopreservation methods on critical quality attributes • Shipping and transportation requirements, including storage containers and temperatures • Specifications of cryopreservation equipment • Cryopreservation site requirements

RELATED EFFORTS

- The Parenteral Drug Association (PDA) is leading the development of a consensus-based standard that will provide a common framework for selecting cryopreservation methods. SCB is supporting this PDA-led effort.
- FACT Standards for Immune Effector Cells contains specifications on cryopreservation, including recordkeeping and storage requirements.
- USP developed USP General Chapter <1044> on best practices for cryopreservation, maintenance, and use of a wide range of cells, therapy products, and cell banks.
- In 2018, the International Society for Biological and Environmental Repositories (ISBER) released a revised document on best practices for biobanks, which includes considerations for freezing and thawing biological specimens.
- The American Type Culture Collection (ATCC) developed a technical manual for cryopreservation of biological materials in cooperation with Thermo Fisher Scientific.

NEXT STEPS

- Solicit input from hospitals and manufacturers about their current cryopreservation processes.
- Interview subject matter experts on best practices and basic safety considerations for cryopreservation.

C21 REGENERATIVE MEDICINE PRODUCT PACKAGING

Cell Therapy | Gene Therapy | Tissue Engineering

Due to the complexity and unique properties of regenerative medicine products, they have packaging needs that differ from those of traditional pharmaceutical products, particularly for establishing and maintaining sterility up to the point of administration.

CHALLENGE: There is a lack of common sterility requirements across the supply chain for the packaging of biological material, and the packaging used by vendors is not interchangeable, which leads to increased costs since suppliers must make different packaging for each vendor. Additionally, regenerative medicine product packaging must control for temperature, liquids, and other factors. There is no clear roadmap for how to develop these packages.

FUNCTIONAL AREAS

- Bioprocessing and Production Standards
- Analytics & Testing Methods Standards
- Product Quality and Characterization Standards
- **Logistics and Compliance Criteria Standards**
- Preclinical Study Standards
- Clinical Trial Standards

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Define **acceptable packaging materials and practices to prevent post-packaging contamination** and ensure product sterility, stability, and safety when administered to patients.
POSSIBLE AREAS TO STANDARDIZE	• Acceptable packaging materials properties, design, and storage • Manufacturing conditions of packaging materials • Labeling requirements • Suite of packaging sizes and dimensions (like FedEx) • Barrier properties testing • Packaging and labeling test methods applicable to cryogenic shipments

RELATED EFFORTS

- Current standards for medical devices could potentially be leveraged to develop standards specific to tissue engineering product packaging:
  - ASTM F1608, Standard Test Method for Microbial Ranking of Porous Packaging Materials (Exposure Chamber Method)
  - ASTM F2475, Standard Guide for Biocompatibility Evaluation of Medical Device Packaging Materials
  - ASTM F3039, Standard Test Method for Detecting Leaks in Nonporous Packaging or Flexible Barrier Materials by Dye Penetration
- ISO 11607 has been used to validate packaging needs, but only for dry products.
- In-development standard ISO 20404 addresses packaging of cells for therapeutic use.
- AATB has a tissue packaging standards guidance document.

C21 REGENERATIVE MEDICINE PRODUCT PACKAGING

NEXT STEPS

- Assess packaging standards for medical devices and how they may apply to regenerative medicine products.
- Identify and conduct research to address knowledge gaps for packaging needs.
- Research shipping and logistical partners that have the capability to work in the regenerative medicine space.

C22 TRANSPORTATION STANDARDS FOR REGENERATIVE MEDICINE PRODUCTS

Cell Therapy | Gene Therapy | Tissue Engineering

FUNCTIONAL AREAS

- Bioprocessing and Production Standards
- Analytics & Testing Methods Standards
- Product Quality and Characterization Standards
- **Logistics and Compliance Criteria Standards**
- Preclinical Study Standards
- Clinical Trial Standards

Because regenerative medicine therapies are made of living components, they have unique transportation needs. Appropriate practices for packaging, handling, storage, and tracking must ensure product quality and protect associated data.

CHALLENGE: Different transportation providers—particularly across geographic regions—often have varying protocols that may not account for the sensitivity of regenerative medicine products to transport conditions such as temperature and vibration. Additionally, transportation solutions used at small scales (e.g., use of a courier) may not work for a mass-produced commercial product.

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Establish parameters for the **control and consistency of packaging, handling, storage, and tracking** of regenerative medicine therapies that can be applied widely across transportation providers.
POSSIBLE AREAS TO STANDARDIZE	• Labeling and tracking procedures • Handling precautions • Transport scheduling best practices • Recordkeeping protocols • Therapy-specific minimum transport environmental control and monitoring requirements (e.g., temperature, vibration, etc.) • Packaging best practices for transit

RELATED EFFORTS

- ISO 21973, which was developed with coordination support from SCB, addresses transportation of cells for therapeutic use.
- WHO has published guidance on regulations for transport of infectious substances, such as bacteria, offering best practices that can be built on to safeguard cells during transport.
- The IATA Dangerous Goods Regulations reference provides guidelines for preparation and handling of dangerous goods shipments by air, including considerations for ensuring that microorganisms survive during transit.
- FDA has relevant regulations:
  - 21 CFR Part 600 Subpart B provides requirements for transport temperatures and recordkeeping for biological products.
  - 21 CFR Part 610 Subpart G provides biological product labeling requirements.

C22 TRANSPORTATION STANDARDS FOR REGENERATIVE MEDICINE PRODUCTS

NEXT STEPS

- Identify common transportation pain points and logistical challenges.
- Solicit input from transportation providers and product manufacturers on lessons learned during scale-up of operations to transport higher product volumes.
- Collect data on transport environmental conditions needed to maintain optimal safety and quality of specific regenerative medicine products.
- Assess potential conflicts between regulatory requirements and safety needs (e.g., customs package inspections).

C23 REGENERATIVE MEDICINE TERMINOLOGY

Cell Therapy | Gene Therapy | Tissue Engineering

FUNCTIONAL AREAS

- Bioprocessing and Production Standards
- Analytics & Testing Methods Standards
- Product Quality and Characterization Standards
- **Logistics and Compliance Criteria Standards**
- Preclinical Study Standards
- Clinical Trial Standards

Lexicons defining specific words and phrases relevant to the regenerative medicine field are often inconsistent across standard documents developed at different times or by different standards development organizations (SDOs). Researchers in many sub-fields within regenerative medicine may also have their own terminology specific to their area of expertise that does not translate across disciplines.

CHALLENGE: The highly interdisciplinary nature of regenerative medicine research and development creates a need for common terminology despite shared terms often carrying different meanings or connotations across subject areas or organizations. A basic lexicon of fundamental terms in regenerative medicine would facilitate collaboration and make the field more accessible to new stakeholders.

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	In consultation with major organizations in the fields of regenerative medicine research and development, **create a document providing standard definitions for basic regenerative medicine terminology**.
POSSIBLE AREAS TO STANDARDIZE	• Harmonization of basic research and manufacturing terminology • Harmonization of therapeutic nomenclature across SDOs • Clarification of areas of overlap • Processes for defining new terms for emerging knowledge, technology, and processes

RELATED EFFORTS

- The British Standards Institution (BSI) published a Publicly Available Specification (PAS) on the definitions of more than 200 terms used in regenerative medicine to establish consensus for industry, government, and academia stakeholders in the United Kingdom.
- The International Council for Commonality in Blood Banking Automation (ICCBBA) published ST-002 ISBT 128, Standard Terminology for Medical Products of Human Origin, which defines terminology used for transfusion and transplantation products to ensure standard labeling of products and establish a common international understanding of the terms.
- A guide for the terminology and diagnostic applications of leucocyte monoclonal antibodies is available in *Histopathology* and aims to allow for comparison and quality across the field.
- ASTM F2312-11, Standard Terminology Relating to Tissue Engineered Medical Products, defines basic terms and presents the relationships of the scientific fields related to tissue engineered medical products (TEMPs). An SCB-coordinated effort is under way to update this standard.

C23 REGENERATIVE MEDICINE TERMINOLOGY

NEXT STEPS

- Identify relevant SDOs and other bodies to consult on establishing a common lexicon.
- Assess the regenerative medicine literature to determine the most prevalent, cross-cutting terminology.
- Solicit input from researchers, manufacturers, and clinicians on the areas of greatest confusion or ambiguity regarding terminology.

Preclinical Studies

C24 ANIMAL MODELS FOR SAFETY TESTING AND PRODUCT ACTIVITY EVALUATION

Cell Therapy | Gene Therapy | Tissue Engineering

FUNCTIONAL AREAS

- Bioprocessing and Production Standards
- Analytics & Testing Methods Standards
- Product Quality and Characterization Standards
- Logistics and Compliance Criteria Standards
- **Preclinical Study Standards**
- Clinical Trial Standards

Animal models, or model organisms, are non-human animals used to test therapies and treatments before they are administered to humans. These models have verified genetic characteristics to allow for controlled testing and may have been bred or genetically modified to have traits relevant to the testing application.

CHALLENGE: Some animal models used in the development of therapies are proprietary or limited to a single laboratory due to their focus on a specific rare disease. Additionally, while mice and rats are commonly used animal models, they are not as predictive of human results as tests using larger animals like primates, dogs, or pigs; however, larger animals have not yet been fully characterized and developed as models for regenerative medicine applications.

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Increase **access to animal model data to enable cross-comparisons** of, and confidence in, testing results across the regenerative medicine community.
POSSIBLE AREAS TO STANDARDIZE	• Guidance for characterizing and validating genetically modified animal models • Best practices for testing of human-based products in animal models • Study design and data reporting requirements • Cell delivery systems

RELATED EFFORTS

- The National Institutes of Health (NIH) convened a workshop to discuss standards for animal study design and reporting in 2012.
- ICH S6(R1) covers the preclinical safety testing requirements for biotechnological products, including guidelines for the use of animal models.
- A CBER guidance document, *Product Development Under the Animal Rule*, provides information and recommendations on drug and biological product development when human efficacy studies are not ethical or feasible.

NEXT STEPS

- Conduct studies on cell delivery systems in animals.
- Catalog existing academic animal models to determine how they could be used in industry and preclinical trials.

G9 METHODOLOGY FOR COLLECTING AND EVALUATING BIODISTRIBUTION DATA

Cell Therapy | **Gene Therapy** | Tissue Engineering

FUNCTIONAL AREAS

- Bioprocessing and Production Standards
- Analytics & Testing Methods Standards
- Product Quality and Characterization Standards
- Logistics and Compliance Criteria Standards
- **Preclinical Study Standards**
- Clinical Trial Standards

Biodistribution is a method of tracking the movements of specific compounds in a living subject. The biodistribution data of gene editing vehicles such as viral vectors can be measured either by their particle distribution or by their transduction pattern.

CHALLENGE: While particle distribution and transduction pattern techniques are garnering widespread support from the gene therapy community, the field lacks definitive guidelines for collecting and evaluating this data that could allow cross comparisons between the work of different researchers and clinicians.

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Ensure biodistribution **data techniques are consistently implemented for the appropriate procedures** so that data can be compared and used for the development of improved gene therapy products.
POSSIBLE AREAS TO STANDARDIZE	• Consensus on which biodistribution approaches are most applicable for different procedures or animal models • Factors for selection of biodistribution methods • Biodistribution testing requirements and timing • Data quality criteria • Quantitative polymerase chain reaction (qPCR) assay • Transgene assessment in animal models

RELATED EFFORTS

- The FDA has guidance on Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events, which addresses preclinical study design to assess vector biodistribution.
- The International Pharmaceutical Regulators Forum (IPRF) published a reflection paper on biodistribution.

NEXT STEPS

- Solicit input from industry to determine which biodistribution approaches are currently used for which applications.
- Research factors affecting success of biodistribution methods.

G10 DEVELOPMENT OF CONSISTENT VALIDATION METHODOLOGY FOR GENE THERAPY MANUFACTURING PROCESSES

Cell Therapy | **Gene Therapy** | Tissue Engineering

Validation of gene therapies is the process of demonstrating to regulators that a new gene therapy product or production process is safe and effective for its intended use.

CHALLENGE: Gene therapy manufacturers often work independently to validate common operational steps for their production systems, which results in duplication of work and lengthy, resource-intensive approval processes.

FUNCTIONAL AREAS

- Bioprocessing and Production Standards
- Analytics & Testing Methods Standards
- Product Quality and Characterization Standards
- Logistics and Compliance Criteria Standards
- **Preclinical Study Standards**
- Clinical Trial Standards

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Create **broadly applicable validation guidelines** by identifying potential commonalities across gene therapy manufacturing processes.
POSSIBLE AREAS TO STANDARDIZE	• Framework for selection of validation methods by process step or application area • Criteria for determining acceptable test outcomes • Risk assessment framework • Personnel training to minimize lab-to-lab variability • Sample requirements for quality control assays

RELATED EFFORTS

- The Cambridge Healthtech Institute (CHI)'s 12th annual bioprocessing summit focused on gene therapy Chemistry, Manufacturing, and Control (CMC) and analytics.

NEXT STEPS

- Solicit input from industry to assess current widely used gene editing approaches and evaluate consistency/efficacy/safety of those approaches.
- Identify potential areas of overlap and consider steps that might be safely eliminated.

Clinical Trials

C25 CLINICAL TRIAL INTERPRETATION WITH UNKNOWN CELL-SPECIFIC DOSES

Cell Therapy | Gene Therapy | Tissue Engineering

FUNCTIONAL AREAS

- Bioprocessing and Production Standards
- Analytics & Testing Methods Standards
- Product Quality and Characterization Standards
- Logistics and Compliance Criteria Standards
- Preclinical Study Standards
- **Clinical Trial Standards**

Cell dose is a measure of the viable cells present in a given treatment, which can vary within a trial and across trials for different therapies.

CHALLENGE: The mechanisms for cell activity are complex and poorly understood, and cell counts may vary over time, which makes it difficult to count cells and establish standard, effective doses and routes of administration (ROA) in clinical trials. This leads to inconsistent trial results that are hard to interpret and replicate and may not be sufficiently reliable to progress to the next phase of clinical trials.

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Broaden **understanding of cell activity and variation over time** to establish guidelines to identify reliable mechanisms for administering safe, efficacious doses.
POSSIBLE AREAS TO STANDARDIZE	• Cell counting methods/technologies • Optimal timing for dose assessment • Qualifying ROAs • Dose preparation methods

RELATED EFFORTS

- Efforts around cell counting (including an SCB standard advancement project) can ensure accurate counts are measured when comparing doses across trials.
- USP published a CD34+ Cell Enumeration System Suitability Reference Standard, as well as USP chapter <127>, Flow Cytometric Enumeration of CD34+ Cells.

NEXT STEPS

- Conduct comparative ROA and dosage studies.
- Assess common causes of inconsistent doses.

C26 SAFETY TRAINING AND EDUCATION FOR CLINICIANS ADMINISTERING THERAPIES

Cell Therapy | Gene Therapy | Tissue Engineering

Clinicians need specialized knowledge to be able to administer therapeutic products and inspire patient confidence in new cell, gene, and tissue engineering therapies.

CHALLENGE: The newness of the regenerative medicine field and constant innovation in therapies require clinicians of all experience levels to continuously update their knowledge on a wide number of new treatments to administer them safely and efficiently. There is currently no broad agreement on essential knowledge and skills for regenerative medicine or effective measures of those skills that can be applied consistently across the field.

FUNCTIONAL AREAS

- Bioprocessing and Production Standards
- Analytics & Testing Methods Standards
- Product Quality and Characterization Standards
- Logistics and Compliance Criteria Standards
- Preclinical Study Standards
- **Clinical Trial Standards**

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Establish **clear and comprehensive training requirements** to equip clinicians with the skills needed to administer products safely and effectively.
POSSIBLE AREAS TO STANDARDIZE	• Required knowledge areas • Education program accreditation • Testing criteria

RELATED EFFORTS

- FACT's Standards for Immune Effector Cells contains general guidance on training for clinical program directors and attending physicians.
- The Advanced Regenerative Manufacturing Institute (ARMI) is training clinicians in multiple disciplines on the use of stem cells and allograft tissues to treat musculoskeletal issues like osteoarthritis and sports injuries.
- AABB offers an online certificate program for biomedical healthcare professionals to learn about cell therapies.
- It may be possible to leverage the workforce education efforts of ASTM Committee E56 on Nanotechnology to develop a baseline for tissue engineering certification programs.

NEXT STEPS

- Solicit input from manufacturers to identify topics to include in training.
- Assess current training programs to build a basis for a tissue engineering certification/training program and the most appropriate entity (e.g., professional society) to administer it.

C27 PATIENT DATA SECURITY

Cell Therapy | Gene Therapy | Tissue Engineering

FUNCTIONAL AREAS

- Bioprocessing and Production Standards
- Analytics & Testing Methods Standards
- Product Quality and Characterization Standards
- Logistics and Compliance Criteria Standards
- Preclinical Study Standards
- **Clinical Trial Standards**

The Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule, enforced by the U.S. Department of Health and Human Services (HHS), protects patient privacy by requiring appropriate safeguards for the storage and transmission of personal health information and limiting the ways in which such information can be used or disclosed without patient consent.

Manufacturers and clinical facilities generating and using regenerative medicine products derived from patient cells or other biological samples must ensure that proper procedures are in place for HIPAA compliance.

CHALLENGE: Regenerative therapy manufacturers working outside the traditional healthcare system often require guidance for maintaining HIPAA compliance. In addition, many emerging therapies using patient-derived cells and other raw materials present novel considerations for ensuring compliance throughout the manufacturing process and product deployment.

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Establish a **standardized guide for HIPAA compliance** during the cell and gene therapy manufacturing and administration process to increase patient safety and reduce the cost and time associated with product development.
POSSIBLE AREAS TO STANDARDIZE	• HIPAA guidelines for regenerative therapy manufacturing • Personal data associated with patient-derived materials • International standards for data handling • Security safeguards for the storage and transmission of data during manufacturing • Privacy guidance for patients and healthcare providers

RELATED EFFORTS

- A 2014 article in *BMC Medical Ethics* offered an assessment of risks and made policy recommendations for the privacy challenges specific to cell-based research and interventions.
- An article published in *Cell Stem Cell* in 2016 proposed a data-sharing framework aimed at striking a balance between the need for high-quality data and the importance of protecting patient privacy in pluripotent stem cell research.
- The European Union (EU) established the European General Data Protection Regulations in 2018, which include provisions specific to genetic and biometric data that are relevant to biobanks and researchers working with induced pluripotent stem cells (iPSCs).

C27 PATIENT DATA SECURITY

NEXT STEPS

- Solicit input from regenerative medicine manufacturers on the challenges of HIPAA compliance and needs for guidance.
- Consult with HHS officials on concerns for emerging therapies.
- Assess potential data security barriers to international deployment of regenerative medicine products.

G11 EVALUATING PRE-EXISTING IMMUNITY TO AAV VECTORS

Cell Therapy | **Gene Therapy** | Tissue Engineering

FUNCTIONAL AREAS

- Bioprocessing and Production Standards
- Analytics & Testing Methods Standards
- Product Quality and Characterization Standards
- Logistics and Compliance Criteria Standards
- Preclinical Study Standards
- **Clinical Trial Standards**

Adeno-associated viruses (AAVs) are one of the most promising vectors for the delivery of gene therapy products because they are non-pathogenic and rarely produce an immune response. Some patients, however, have a pre-existing immunity to AAVs that can limit the efficacy and safety of gene therapy treatments.

CHALLENGE: There is currently no common approach for assessing patients for pre-existing immunity to AAVs prior to clinical trials, leading to safety risks for patients with immunity and making it difficult to assess whether an unsuccessful clinical trial outcome is due to ineffective gene therapy products or whether AAV immunity is a factor.

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Develop **shared language and consistent methodology for evaluating pre-existing immunity to AAV vectors** to better understand the role AAV immunity plays in clinical trial outcomes and prevent patient exclusion from or resistance to trial participation.
POSSIBLE AREAS TO STANDARDIZE	• Language and terminology • Validation framework for assays • Antibody reference materials • AAV serotype-specific considerations • Limit of detection/antibody titer threshold • Knowledge standard on basic virology/immunology and cross-reaction antibody effects • Identifying safety concerns related to AAV vector immunity • AAV immunity testing variables (tools, reagents, controls) • Metrics for reading and interpreting test results • Methods for evaluating safety related to dose (e.g., potential toxicity) • Measurement techniques for cellular immune response

RELATED EFFORTS

- SCB is coordinating a standard advancement project for evaluating pre-existing immunity to AAVs.
- NIH-NCATS held a workshop on central nervous system (CNS) immunogenicity concerns for AAV-mediated gene therapy in June 2019.

NEXT STEPS

- Analyze current best practices for evaluating patients for AAV vector immunity.
- Discuss promising future areas for research into immunity to AAV vectors.

T6 PRODUCT INTEGRITY TESTING METHODS

Cell Therapy | Gene Therapy | **Tissue Engineering**

Tissue engineering products require adequate structural properties to function correctly inside the human body and need to be tested to ensure long-term product safety.

CHALLENGE: Tissue engineering products are more complex than traditional medical devices, and have unique testing needs that are not fully understood. With the field still in its infancy, it is difficult to ascertain what the testing needs are and how to determine when those tests have been satisfied. There is also no broad consensus on acceptable product lifespan, specifically on a product-by-product basis.

FUNCTIONAL AREAS

- Bioprocessing and Production Standards
- Analytics & Testing Methods Standards
- Product Quality and Characterization Standards
- Logistics and Compliance Criteria Standards
- Preclinical Study Standards
- **Clinical Trial Standards**

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Identify and codify **common ways to test tissue engineering product integrity**, including tensile strength and suture retention, to ensure tissue engineering products meet safety thresholds for use in clinical environments.
POSSIBLE AREAS TO STANDARDIZE	• Common testing methods (e.g., assays) to ensure long-term product safety • Level of tensile strength needed for integrity • Methods for defining critical quality attributes (CQAs) • Sample preparation • *In vitro* tissue engineering models • *In vivo* product integrity test methods

RELATED EFFORTS

- Numerous existing standards for *in vivo* medical devices (e.g., pacemakers) could be leveraged to frame new standards in this area.

NEXT STEPS

- Assess product integrity testing methods for medical devices and address knowledge gaps when applied to tissue engineering products.
- Solicit input from researchers and manufacturers to identify current tissue engineering product integrity testing best practices.

APPENDIX A. METHODOLOGY

Data Gathering Approach

The regenerative medicine community is composed of diverse stakeholders—including manufacturers and industry organizations, product developers, tool and service providers, professional and scientific societies, government entities, standards developing organizations (SDOs), clinicians, academic centers, and research entities—across the fields of cell therapy, gene therapy, and tissue engineering. This appendix outlines Nexight Group and The Standards Coordinating Body for Gene, Cell, and Regenerative Medicines and Cell-Based Drug Discovery's (SCB) process and methodology for soliciting this expertise in developing this report.

Nexight Group and SCB completed three stakeholder surveys on needed standards in regenerative medicine, conducted interviews with subject matter experts, facilitated a mini-workshop on gene therapy standards with regenerative medicine experts, and hosted a two-day workshop highlighting the benefits of participating in the standards development process. This data collection was followed by a technical review of the synthesized information by SCB leadership and its Cell Therapy, Gene Therapy, and Tissue Engineering Sector co-chairs.

Summary of Data Collection Sources

	STAKEHOLDER POLLING	INTERVIEWS	SECTOR WORKING GROUPS	REPORT DEVELOPMENT	TECHNICAL REVIEW
Method	Structured surveys	Semi-structured interviews	Facilitated workshops	Data processing, cleaning, and triangulation	Data cleaning and triangulation
Objectives	Identify and prioritize gaps in current standards as well as the potential opportunities, challenges, and benefits of additional standards	Validate the areas of greatest opportunity and need for standards, clarify the opportunities and challenges for these standards, and capture the climate for advancing standards	Add to, validate, clarify, and prioritize the list of needed standards within sector-specific working groups of community stakeholders	Add to, validate, and clarify list of existing standards and potential opportunities for standards development. Synthesize and summarize key themes and needs by sector	Ensure technical accuracy and identify and address gaps through review and validation of report
Participants and Data Sources	Poll distributed to more than 600 experts worldwide, with 120 responses	21 interviews with experts	Breakout sessions during the *Realizing the Benefit of 21st Century Cures Through Standards Development* workshop, March 18-19, 2019 Workshop on standards at the Gene Therapy for Rare Disorders Conference, March 26, 2019	Synthesis of documents, interviews, polls, and other inputs	Review by SCB Executive Committee; SCB Board of Directors; and Cell Therapy, Gene Therapy, and Tissue Engineering sector co-chairs

About Nexight Group and the Standards Coordinating Body

In 2017, the U.S. Food and Drug Administration awarded a 1.5-year contract to Nexight Group and The Standards Coordinating Body for Gene, Cell, and Regenerative Medicines and Cell-Based Drug Discovery to engage with experts to recommend processes and outline a plan for identifying, prioritizing, and assessing promising standards in regenerative medicine and advanced therapies; develop outreach and educational material on standards development; support projects to advance needed standards; and engage the community to prioritize needed standards.

Nexight Group is a small business based in Silver Spring, Maryland, with extensive experience engaging diverse experts in discussions about gaps and needed solutions to advance scientific fields, establishing new collaborative organizations, developing roadmaps and strategic plans, establishing new business processes, and supporting technical education and outreach efforts. In collaboration with the Georgia Institute of Technology and the Georgia Research Alliance, Nexight Group led the coordination and development of *Achieving Large-Scale, Cost-Effective, Reproducible Manufacturing of High-Quality Cells: A Technology Roadmap to 2025*, a roadmap that aims to facilitate widespread access to life-changing cell therapies, engineered tissues, medical devices, and drug discovery and testing platforms through collaborative research and development. In 2018, Nexight Group and SCB co-authored *The Regenerative Medicine Standards Landscape* report with funding from the U.S. Food and Drug Administration (FDA). This report provides a snapshot of the current landscape for regenerative medicine standards. It outlines existing and in-development standards, providing a reference that individual organizations can use to identify available standards to improve their operations. An updated version of the report is currently available for public review on the SCB website.

The Standards Coordinating Body (SCB) is a non-profit organization with a mission to **coordinate the accelerated advancement and improved awareness of standards and best practices that address the rapidly evolving needs of the global regenerative medicine advanced therapy community**. To accomplish its mission, SCB operates through public-private partnerships with government agencies, regulatory bodies, and other government organizations involved in establishing consensus standards for regenerative medicine and other advanced therapy products. With members from industry, professional societies, and government and academic entities, SCB occupies a unique niche within the regenerative medicine ecosystem and has no vested interests in a particular scientific, commercial, clinical, or policy approach. SCB is focused on **facilitating the use and development of standards in response to demonstrated need expressed by a range of stakeholders**.

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