STANDARDS DEVELOPMENT FOR
REGENERATIVE MEDICINE THERAPIES

REALIZING *THE* BENEFIT *OF* 21st CENTURY CURES *THROUGH* STANDARDS DEVELOPMENT

A WORKSHOP CONVENED BY FDA, NIST, SCB, AND NEXIGHT GROUP

WORKSHOP REPORT • MARCH 2019

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INTRODUCTION AND SUMMARY

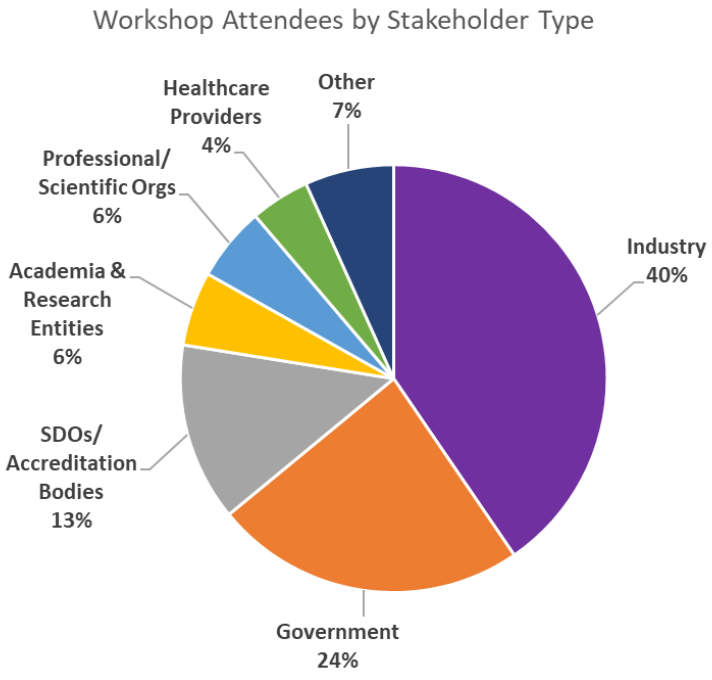
On March 18–19, 2019, nearly 100 stakeholders from across the regenerative medicine community participated in the *Realizing the Benefit of 21st Century Cures through Standards Development* workshop—co-convened by the U.S. Food and Drug Administration (FDA), National Institute of Standards and Technology (NIST), the Standards Coordinating Body (SCB), and Nexight Group, and held at the National Cybersecurity Center of Excellence (NCCoE) in Rockville, MD.

Through a series of presentations and interactive Q&A panels with experts, the workshop covered the **standards development process, how to participate, and how standards help improve the quality and safety of regenerative medicine.** The workshop also included a number of case studies that provided a real-world picture of how standards development works and the value of taking part in the process.

A key goal of the workshop was to provide a chance for members of the regenerative medicine community to actively participate in prioritizing and advancing needed standards. Through break-out sessions, participants identified and explored four high-priority standards needs: **cell viability, chain of identity and chain of custody, characterization of scaffold materials, and viral vector gene quantification.** These topics, in addition to many more that participants helped prioritize, will inform SCB's future work in coordinating the development of specific standards topics and will be incorporated into SCB's *Report on Needed Standards* (scheduled for release in late April), which will inform additional standards advancement efforts across the community.

Workshop attendees also participated in break-out sessions to provide input into two SCB-coordinated standards advancement projects: Characterization of Human Cells for Therapeutic Use and Rapid Microbial Testing Methods. The real-time discussion across a wide range of stakeholder groups generated highly valuable feedback for these projects—the rapid microbial testing methods ASTM standard effort was accelerated by about six months through a single hour of facilitated discussion.

This report provides summaries of the presentations, case studies, panel discussions, and break-out sessions throughout the workshop. Full presentations are available on the SCB website.



WELCOME AND KEYNOTE PRESENTATIONS

WELCOME PRESENTATION: Collaborations on Standards for Regenerative Medicine Therapies

Celia Witten, Ph.D., M.D., Deputy Director, FDA Center for Biologics Evaluation and Research (CBER)

The *21st Century Cures Act*—signed into law in 2016—included many provisions for accelerating medical product development through collaboration among stakeholders. The Center for Biologics Evaluation and Research (CBER) is responsible for implementing the provisions related to regenerative medicine under Section 3036: Standards for Regenerative Medicine and Regenerative Advanced Therapies. That role includes consulting with stakeholders to advance standards, identifying opportunities to advance the development of new therapies and laboratory research, and developing and updating guidance and regulations related to standards for biologics.

CBER works in partnership with the National Institute of Standards and Technology (NIST) due to the complementary expertise of the two organizations: CBER has a deep understanding of standards needs in the regenerative medicine community and can ensure that new standards do not conflict with FDA regulations, while NIST provides expertise in specific analytical challenges.

CBER and NIST have worked together to co-sponsor workshops in support of standards development. The two organizations also support ASTM and ISO standards, and laboratory collaborations on flow cytometry, cell counting, and cell viability. They currently work together to provide technical support to the Nexight Group/SCB contract to coordinate community efforts toward the development of standards for regenerative medicine therapies.

Key Takeaways

- **The *21st Century Cures Act*** called for increased focus on standards to support the accelerated development of regenerative medicine therapies.
- **Collaboration between FDA and NIST** provides well-rounded standards development support to the regenerative medicine community.
- **Standards development is a community effort** that requires coordination among regulators, SDOs, industry, and other stakeholders.

KEYNOTE PRESENTATION: Changing the Course of Human Health through Bold Pursuits in Science

Chris Wiwi, Ph.D., CAR-T Technical Commercialization Lead, Celgene Corporation

As the number of regenerative medicine therapies—such as the Celgene bb2121 CAR-T product—poised for commercialization increases, the link between standards and efficiencies in production is becoming more apparent. Standards can help to enable and accelerate the challenging process of scaling therapies from Phase 1 proof-of-concept clinical trials to commercially viable products.

To commercialize regenerative medicine therapies successfully, companies must be able to establish processes that are reliable, scalable, accessible, affordable, and reproducible. Reproducibility is key, because these products are expensive to produce and needed urgently by patients, and manufacturers can't afford inconsistencies that can lead to safety or quality concerns.

As new therapies proceed to Phase 2 clinical trials, product developers face challenges with limited access to translational and clinical data, particularly data related to long-term safety and product critical quality attributes. This key information needed to establish a fixed commercial process and complete a Biologics License Application (BLA) package is often still in flux or under development. The lessons learned during the creation of these early commercial products could feed into standards and best practices that could support the development of higher-quality products.

Standards development can help the field move forward by providing increased access to publicly available data and consistent best practices in support of process automation, improved potency assays, better raw material control, increased supply chain reliability, and development of electronic systems and analytics to improve needle-to-needle times. Standards can also support facility optimization and reduce manufacturing costs by helping manufacturers better manage resources and limit idle time.

Key Takeaways

- CAR-T therapies are among the **many regenerative medicine products beginning to move from Phase 1 clinical trials toward commercialization**, which brings unique challenges.
- Manufacturers addressing these challenges can **share their growing clinical and translational knowledge to inform the development of new standards** that can benefit the whole industry.
- Standards efforts related to **assay validation, manufacturing process automation, product characterization, control strategies, and supply chain consistency** could help to accelerate commercialization of regenerative medicine products.

KEYNOTE PRESENTATION: Why Standards are Critical for the Transfer of Novel Technologies from Academia to Clinical Use

Barbara Boyan, Ph.D., Dean, College of Engineering, Virginia Commonwealth University (VCU)

One major reason that it can be challenging to translate new technologies from academia to clinical use is that the guiding principles and objectives of academia differ from those in industry. **University scientists are not typically incentivized to transfer technology**, and so it is rare for them to prioritize these activities over others like knowledge development, publication, and obtaining peer-reviewed extramural funding. For those scientists who decide to dedicate time and energy to translation, **an understanding of standards is a key component of developing safe and high-quality products**.

Tissue engineering products are highly complex, using varied cell types, scaffold designs and materials, and preclinical testing models. Small variations in materials or procedures can make the difference between the success and failure of a product. However, it is **common for individual scientists to create their own approach to address common problems**, and they often overlook opportunities to share their knowledge or benefit from the knowledge of others. To address this challenge, **academia needs support from industry to better understand the value and application of standards**.

Developing a successful product often requires knowledge sharing between different stakeholders throughout the product lifecycle, including academics developing the new technology and surgeons who will put it into practice. For example, an implant that does not consider the proximity of osteoblasts to blood vessels and nerves would not be successful after implantation in the body. **Standards could support this knowledge sharing, but there are currently few standards in the biomedical engineering field, and little awareness within the field of the standards that exist.** An important step in addressing this challenge is to **encourage universities to place greater emphasis on standards**, particularly reference materials.

Key Takeaways

- **Standards are critically important** for translating academic inventions to clinical practice.
- **Academics must be educated** to use standards.
- **A multi-pronged approach,** involving buy-in from academics, surgeons, and industry, is necessary.

OVERVIEW OF STANDARDS DEVELOPMENT FOR REGENERATIVE MEDICINE PRODUCTS

PRESENTATION: Building the Foundation for Regenerative Medicine Innovation through Standards

Judith Arcidiacono, M.S., International Regulatory Expert, Standards Liaison, Office of Tissues and Advanced Therapies, FDA/CBER

This presentation: 1) reviewed common standards terminology, 2) outlined the benefits of standards in regenerative medicine, and 3) provided an overview of the standards development process.

Key Takeaways

- **What is a standard?** Standards are voluntary guidelines, while regulations have the force and effect of law and are generally mandatory, setting out specific requirements that regulated products and entities must meet. Standards can take the form of documents that set forth performance characteristics, testing methodology, manufacturing practices, scientific protocols, specifications, data guidelines, or terminology; or can be physical reference materials that are sufficiently homogenous and stable for use in measurement processes.
- **What are the benefits of using standards?** Standards help facilitate consistent and predictable product manufacturing and assessment, field testing, clinical trial data exchange, and product labeling. Standards can also help to streamline premarket review and facilitate market entry for safe and effective products, including products from emerging technology areas.
- The **standards development process** includes:
  - **Upstream activities:** Identify needed standards, conduct feasibility assessments, and draft an outline of the standard with interested parties
  - **Standards development within a standards developing organization (SDO):** Submit a proposal to an SDO, drafting and commenting by stakeholders, approval at working group and technical committee levels, and standard publication
  - **Downstream activities:** Standards are reviewed every five years and are either revised or withdrawn at that time

PRESENTATION: The Standards Evolution of Regenerative Medicine

Sheng Lin-Gibson, Ph.D., Chief Biosystems and Biomaterials Division, NIST

This presentation provided an overview of the historic landscape of regenerative medicine standards development, including:

- interagency coordination through the Multi-Agency Tissue Engineering Science (MATES) Interagency Working Group, resulting Manufacturing USA institutes, and NIST-FDA collaboration
- passing of the *21st Century Cures Act*
- continued involvement of ISO and ASTM
- championing of standards development by select industry organizations and the Alliance for Regenerative Medicine
- publication of key reports relevant to the field
- the formation of the Standards Coordinating Body (SCB) to fill a critical gap in coordinating experts and standards advancement projects, assessing needs, developing education materials, and promoting standards use

The presentation also detailed the "who, what, when, where, and why" of standards development.

What: Standards serve many, and often multiple, purposes. They establish common understanding, practices, procedures, methods, requirements, operational and management systems, or reference materials.

Why: Standards can help ensure consistent manufacturing and testing of products. Overall, a standard is designed to ensure that there is an agreed-upon process, but does not dictate what the process is.

Who and Where: Many U.S. and international standards developing organizations (SDOs) and stakeholders from throughout the community work to develop relevant standards. Collaboration and communication among these organizations is key to avoid duplicative or contradictory standards.

When: When deciding whether to develop a standard, it is critical to assess scope, audience, requirements, consequences, and potential duplication. Requirements to assess include the maturity of the field or technology area this standard addresses, the level of consensus within the field, and the urgency of the standard need. The feasibility assessment must also consider potential unintended consequences, such as stifling innovation or creating an undue regulatory burden, as well as the availability of similar standards to avoid confusion and wasting resources.

How: There are many ways to contribute to the standards development process, including reaching out to colleagues to discuss standards needs, participating in an SCB-coordinated working group, or joining an SDO technical committee.

Key Takeaways

- **The purpose of a standard is to create commonality in a field** to help improve consistency in product and process development, testing, and implementation.
- **SDOs and other organizations across the U.S. and around the world work to create standards.** Collaboration and communication is key to avoid duplicative development.

- Before the standards development process can start, it is important to **define the potential standard's scope, audience, requirements, consequences, and possible duplicative efforts.**
- The **Standards Coordinating Body (SCB) can fill a critical gap in regenerative medicine standards advancement** by coordinating experts and standards advancement projects, assessing needs, developing education materials, and promoting standards use.

PANEL DISCUSSION: "Fireside Chat" – Documentary Standards and Reference Materials

Gordon Gillerman, NIST; Malcolm Moos, FDA; Scott Colburn, FDA; John Elliott, NIST (moderator)

Question: What are the biggest misconceptions in standards development?

People may assume that standards *must* be met to get a product to market. In fact, standards are not mandatory, and the standards development process is open to everyone to help shape standards that are most useful and applicable across the field. Standards help ensure product consistency in the market and reduce some of the burden when applying for regulatory approval. In addition, some people may think that international standards are developed only by Geneva-based organizations, when any SDO could develop a standard that gains international acceptance.

Question: What are the differences between the different types of standards?

Standard guides are the simplest type of documentary standard and are essentially literature reviews. Test methods and standard practices are a bit more involved, with test methods sometimes appearing as appendices in broader documentary standards. Reference materials are well-characterized, homogeneous materials used for measurement and test method quality assurance.

Question: How do we qualify using animals as a standard?

The challenge for animal models is to develop ones that model a human environment as closely as possible (e.g., a disease model). Certain assays already exist, including an animal model for osteoinductive activity *in vivo*, and a quadruped model for repairing the surface of the knee. That said, most animal models are unique to the disease or condition being treated, making animal models difficult to standardize.

Question: Do guidances ever become the origin of a new standard, and does the FDA ever include non-standards in their guidances?

The FDA does include certain non-standards in guidances. Guidances focus more on what should be done rather than how to do it, so standards can elaborate on the "how" for a guidance.

Question: How can standards development teams avoid partial FDA recognition of standards?

It is important to get to know and keep in touch with FDA liaisons early in the development process to ensure the standard will be recognized by FDA. The FDA and other agencies—including the International Medical Device Regulators Forum (IMDRF)—developed their own guidelines on what they look for in standards.

PANEL DISCUSSION: Common Questions About Standards, Demystified

Anne Caldas, ANSI; Malcolm Moos, FDA; Wen Bo Wang, Fate Therapeutics; Barbara Boyan, VCU College of Engineering (moderator)

Question: Is CBER going to encourage the use of specific standards?

It is possible CBER will adopt a formal standards recognition process in the future as more standards relevant to products with biological components become available. It is already possible and encouraged to include applicable standards in a submission package to CBER.

Question: How can people navigate the complex standards landscape?

As an overview, the standards landscape includes more than 200 ANSI-accredited SDOs, which produce U.S.-specific standards and may also carry out international standards work, often through participation in ISO Technical Advisory Groups (TAGs). People can participate by serving on technical committees, voting on these standards, or if they are more time-constrained, contributing feedback when the standards go out for public comment. Outside of ANSI-accredited SDOs and ISO, there are consortia that may not need the same level of due process. Government, consumers, and other interested parties also have a seat at this table and can inform development of standards and best practices.

Question: Incorporating induced pluripotent stem (IPS) cells into a product is an incredible challenge. How do you think about standards in this work?

It is possible to look to related, more established fields for existing guidance on issues like assay and process development. Experts in the industry need to voice their needs and collaborate with academia to influence the development of more focused standards. We are looking for guidance and standards to de-risk and speed up the process of delivery to patients and save time in assay development overall.

We also need to publish standards in a way that helps people understand they're being given a tool. There's a surgeon who publishes videos of animal surgeries so people can see how it's done. We need to give instruction on optimal ways of doing things.

Discussion (Audience and Panel): A lot of excitement in the field is outside the United States. How can the United States leverage this international energy in standard and product development?

Some domestic standards developers are also ISO TAG administrators, so work in the United States can become the basis for an ISO document. That's why you need good representation on the TAGs to attend international meetings—it's hard and costs money, but if you're not at the table, other members will make decisions on your behalf. Joining a TAG, reviewing documents, and taking a leadership role are all ways to influence the process.

It's helpful to pull in individuals in different countries who work in the industry early in the process so when you have the standard and are ready to move, it's a much smoother transition.

Fate Therapeutics: We are working with ISO groups and NIST, taking steps to influence standard development for biotechnology, and participating in relevant workshops. We have been participating and calling on colleagues in the industry to participate.

Discussion (Audience and Panel): How can we encourage standards adoption in academia?

- Industry could help bring standards training programs to academia at larger scale. Some free resources exist as well. ANSI has a university outreach program, and there is a free resource about standards at the Standards Boost Business website.
- The best way to get these messages across is to attend lab meetings and get on the Ph.D. committee of a student. Work directly with students and help them understand the differences between working on a product in an academic lab and making a product in the real world.
- Communicate the need for and value of standards to promotion and tenure committees.
- Incentivize academics to convert their published work to a potential standard, encouraging publication of papers in parallel with academic discovery.
- Industry should put a separate part of their budgets toward funding standards efforts in academia. If not, we will keep asking academia to do something we haven't incentivized.

STARTING WITH SUCCESS IN MIND

CASE STUDY: Counting Colony Forming Units

George Muschler, M.D., Orthopedic Surgeon, Cleveland Clinic

Summary of Standards Development Effort

- The Cleveland Clinic laboratory identified a need for **automated colony counting for stem cells in tissue** to account for variability in samples in different surfaces, in different media, or even within the same person.
- **Automated image acquisition** proved useful for scanning slides, providing nearly 900 individual image tiles per chamber to allow for faster processing.
- Dr. Muschler and his colleagues developed an **ASTM standard** detailing how to use a microscope with a motorized stage to perform **automated colony forming unit (CFU) assays**.

Best Practices and Lessons Learned

- Dr. Muschler's team sought **community confirmation** that the potential standard would be useful.
- The team **ensured the standard would be valid for many types of cells** by performing different tests and considering a range of dialogue and definitions.
- Had SCB existed at that point**, SCB would have helped to increase the efficiency and speed of the development process**.

CASE STUDY: Osteoinductivity

Alyce Linthurst Jones, Ph.D., Director of Cardiovascular Product Development, LifeNet Health

Summary of Standards Development Effort

- Dr. Jones helped develop an **ASTM standard** on *in vivo* evaluation of osteoinductive potential for materials containing demineralized bone (DBM).
- Her team needed to find a way to develop a standard **without duplicating existing assay methods,** recognizing that many **companies had already developed their own unique methods**.
- The new standard's goals were to **increase uniformity in results reporting** among different laboratories and to **provide the FDA with a consensus standard** to use for sponsors of 510(k) submissions.

Best Practices and Lessons Learned

- Dr. Jones's team **avoided using words like "should" and "must"** to help minimize dissent and encourage compromise.
- **Diversity in leadership and committee membership** was integral to maintaining an energized team.
- The team may have **developed the standard in less time** if they had let go of the desire to create an "absolutely perfect" standard.

Panel Discussion

Alyce Linthurst Jones, LifeNet Health; George Muschler, Cleveland Clinic; Claudia Zylberberg, Akron Biotech; Chris Wiwi, Celgene (moderator)

Question: What are the main hurdles for getting the field to buy into a standard?

- Some standards require access to cost-prohibitive technologies that may not work well with existing software. The cost to implement the standard and train people to use it can inhibit its use in the field as well.
- Global consensus groups may face a language/terminology barrier when working together on standards.
- In certain cases, regulatory requirements will increase community buy-in to standards that function as a user-friendly guide that helps break down the requirement.

Question: What can be done early in development to help ease a standard's adoption for a broad audience?

- It is important to begin the development process with an idea of what the scope will be.
- After developing an outline, assigning parts to different authors can help ensure the standard has input from people across the community and save time during balloting.
- Holding regular phone or video calls with team members (coordinating across different time zones) helps to address any challenges in real time.
- Group leads can also make sure that any action items are followed up on promptly, and that revisions are made as early as possible.

Question: Is it necessary to create a new standard when attempting to expand one to other applications?

Ideally, standards developing groups will anticipate different applications as the standard is written. Voluntary standards allow companies to adapt the standard as needed. If enough companies modify the standard in the same way, the standard may be officially revised, or a new standard may be developed.

Question: How is standard development and research paid for?

- Team members volunteer their personal time and contribute existing material (e.g., slides) from their own organizations to help reduce costs.
- Other organizations may provide samples to help with testing and validation.
- Some members may be able to use research grant money or fold standard development costs into their existing research and development budget.

Question: Were there any parts of the standards development process that were easier than expected?

Stakeholders were eager to get involved and worked together to overcome any challenges. SDO staff were also very helpful when team members had questions or needed supplementary information.

MOVING FROM IDEA TO INNOVATION

CASE STUDY: Viability of Cryopreserved Therapies

Brian J. Hawkins, Ph.D., Chief Technology Officer, Pluristyx

- Cell therapy manufacturers must ensure 70% viability of cryopreserved cell therapies to meet Health and Human Services critical quality attribute requirements**.** However, manufacturers **repeatedly work in isolation** to identify and develop their cryopreservation approaches. This **demonstrates a need for standardized procedures** to avoid duplicate work and enhance viability outcomes.
- Cryopreservation techniques are **highly complex**, and therapies' **post-thaw cell viability is both assay- and process-dependent.** To develop a guidance document, there was a need for basic understanding of the **impact of different cryopreservation techniques and process parameters** (e.g., thaw rate, freezing rate, and cryopreservation media) on viability outcomes.
- In addition, it was important to **define the point at which to measure viability** (e.g., immediately post-thaw, or 24 hours later) to better understand a therapy's viability at the time it reaches the patient.
- Equipped with deep technical understanding of the complexity of cryopreservation techniques and their impact on viability outcomes, Pluristyx is **working with the Parenteral Drug Association (PDA)**—an ANSI-accredited standards developer—**to develop a cryopreservation best practices framework.** The proposed standard aims to ensure manufacturers consider all variables to optimize the end viability of their therapies, without prescribing rigid procedures.

CASE STUDY: Microscopy Fluorescence Intensity

Michael Halter, Ph.D., Biosystems & Biomaterials Division, NIST

Summary of Standards Development Effort

- Several standards for cell-based assays rely on imaging measurement approaches, without specifying how to acquire images or recognizing that different approaches could impact measurement results**.** There was a **need to support imaging measurement execution** and **a large number of stakeholders who would potentially be interested** in receiving that support. Enhanced standards on imaging measurements could also **potentially drive adoption of more sophisticated imaging technologies**.
- Dr. Halter served as technical lead on an **ASTM committee** to develop **guidance on microscopy imaging approaches,** relying on foundational imaging principles to inform diverse approaches, rather than outlining a specific test method.

Best Practices

- The committee initially **studied existing standards** so they could leverage past work, reaching out to other members of the community and searching online to uncover standards they weren't already aware of.
- The team **focused on defining principles** that weren't tied to specific technology-types so that the standard would remain valuable into the long term.
- Dr. Halter engaged professional societies and experts/resources to **understand scientific paper writing** and the **consensus standards process.**
- They **circulated the standard to quality control experts** to gather their feedback before submitting it for final review and approval.

Lessons Learned

- **Solicit as much feedback** on draft standards **as possible,** as early as possible.
- **Engage people experienced in standards review/writing** from the beginning to build materials that align with reporting needs and best practices.

Panel Discussion

Clare Allocca, NIST; Michael Halter, NIST; Brian Hawkins, Pluristyx; Jessica Carmen, Pullan Consulting (moderator)

Question: How do you know that you have an idea for a standard?

Even though a standard idea may arise from specific needs in your own work, it's important to build standards that will have broad impact (i.e., are applicable beyond one specific assay).

- **Microscopy Fluorescence Intensity Case Study:** They opted to develop a guide focused on principles foundational to imaging, rather than design a specific test method.
- **Viability of Cryopreserved Therapies:** This standard offered a framework to build different cryopreservation approaches, rather than mandate a specific process.

It's also important to consider whether there are other technical experts available and willing to support the standard's development.

Question: What do you do after you get your standard published?

Continue to raise awareness about the standard, train stakeholders on its implementation, provide education on its technical details (if necessary), and gather feedback on additional standards needs. This can include attending meetings and conferences to discuss the standard, hosting webinars, and leveraging existing networks with key stakeholders to share information about the standard and gather their feedback.

Question: How do you keep up with the pace of technology changes when developing a standard?

It can take years to develop a standard, meaning the standard can easily be outpaced by technological innovations. All approved standards are also regularly reevaluated to ensure they remain aligned with community needs. Thus, it's important to develop standards that will remain relevant throughout the development process and throughout the lifespan of the standard itself. For example, this could mean:

- **Focusing on performance attributes rather than design specifications,** articulating desired outcomes and different ways to ensure those outcomes.
- **Identifying core principles to a topic area** that aren't sensitive to technology changes.
- **Developing a quicker document than an international standard**, such as a technical specification or technical report, to conserve energy on guidance tied to specific technologies.

REFERENCE MATERIALS

PRESENTATION: The Importance of Reference Materials

John Elliott Jr., Ph.D., Cell Systems Science Group Leader, NIST

Reference materials (RMs)—which may be biologics (e.g., fixed cell samples) or non-biologics (e.g., equipment parts)—are **sufficiently homogeneous and stable** with respect to one or more specific properties. They can be **used to calibrate equipment, characterize variability, and validate and verify measurements**, providing definitive evidence that measurement systems are working as expected. In the future, NIST or other SDOs may develop documentary standards that outline considerations for developing RMs for use in-house or by the broad regenerative medicine field.

Examples of RMs used in different applications are as follows:

- **Flow cytometry**—RMs used to calibrate flow cytometers for clinical (lymphocyte) diagnostics include relative intensity (ERF) beads for fluorescent channels and freeze-dried peripheral blood mononuclear cells (PBMCs) with certain antibodies. These RMs help ensure that results within the same experiment are comparable and that flow cytometers will produce transferable results across laboratories.
- **DNA sequencing and RNA detection**—DNA plasmids with known abundance ratios help assess the technical performance of differential gene expression experiments. These materials help evaluate hardware and software performance, establish the limits of detection and linearity ranges, and determine system suitability for spike-in control.

- **Fluorescence microscopy**—A commercially available glass disk, manufactured by Schott, helps address variation in day-to-day microscope performance due to user changes, software settings, and hardware malfunctions. NIST developed a user guide, which includes videos, notes, and charting spreadsheets, to help users install the disk and learn how to use it to evaluate and benchmark their microscope's performance.

Key Takeaways

- Reference materials are biological or non-biological materials that are **sufficiently homogeneous** and **stable with respect to one or more specific properties**. They are used to validate measurements and calibrate equipment.
- Reference materials **ensure confidence** in the accuracy, value, and certainty of measurements with high variability (e.g., flow cytometry, DNA sequencing, fluorescence microscopy) and help **make those measurements instrument-independent**.
- SDOs may create **documentary standards** that outline techniques or best practices for developing reference materials.

CASE STUDY: Human Adenovirus 5 (Ad5)

Keith Carson, M.B.A., Founder and Content Chair, ISBiotech

Summary of Standards Development Effort

- Regulators needed a way to **compare viral vector submissions** to determine non-toxic dose amounts appropriate for use in clinical trials.
- A working group of experts from industry, academy, and FDA (non-voting members) convened to develop a **viral gene vector reference material** (RM).
- Group members **shared data and donated material,** including cell lines, viral seed stock, vectors, consumables, and characterization data, to develop the Ad5 RM.

Best Practices and Lessons Learned

- **Voluntary sharing of data and materials was critical** to developing the standard in a shorter timespan without incurring any costs.
- Companies should find a way to **share their data and methods** to keep a RM development process moving and lessen the effort required from team leads to obtain needed material and information.
- It took **10 years** for the first lot of Ad5 to be sold; close to 75% of the 5,000 vials have been used.

CASE STUDY: CD34+ Cell Enumeration Standard

Kevin Carrick, Ph.D., Director of Global Biologics, U.S. Pharmacopeia (USP)

Summary of Standards Development Effort

- The number of CD34+ cells mobilized in hematopoietic grafts is a good predictor of success of apheresis and engraftment potential. Through interactions with community stakeholders, USP **identified a need for a CD34+ cell enumeration standard** that could ensure consistent CD34+ counts across laboratories and clinical centers.

- USP **developed a reference standard** made from peripheral blood—containing human leukocytes, erythrocytes, and CD34+ cells that have been fixed and lyophilized—that can be used to assess reagents and ensure correct gating for data acquisition and analysis.

Best Practices and Lessons Learned

- USP conducted a **multi-laboratory collaborative study** to establish the mean and range for the number of CD34+ cells per vial.
- Collaborators used an **existing USP chapter on flow cytometry** when testing the material.

Panel Discussion

Kevin Carrick, USP; Keith Carson, ISBiotech; Jean Qiu, Nexcelom Bioscience LLC; John Elliott, NIST; Sowmya Viswanathan, University Health Network; Sumona Sarkar, NIST (moderator)

Question: What are the most useful applications for reference materials right now?
Reference materials help establish system suitability and ensure that laboratories can benchmark their test results to allow for cross-comparison. Reference materials can also help quantitate and compare biologics or different-sized particles in biological research.

Question: What are common barriers to developing reference materials?
It can be a challenge to find the right partner to provide raw materials, and knowing how to use the material and develop stable formulations can take a long time to learn. In addition, most technology manufacturers closely protect their data and methods. Stakeholders need to be willing to get involved in standards development efforts and work as a precompetitive team.

Question: How can we balance developing materials made for specific purposes with developing materials that have more flexibility across the field?
This is an ongoing challenge due to the limited amount of information available and the complexity of biological material. The focus should be on making sure that assays and measurement platforms work before attempting to work on more wide-reaching development efforts.

Follow-Up Question: What standards are available regarding clinical flow cytometry for cell biomanufacturing?
The Clinical & Laboratory Standards Institute (CLSI) offers documentary standards for using blood cells with flow cytometry.

Question: Who is using the USP CD34+ enumeration standard?
USP cannot tell yet, but they do not think they have hit the target audience for the standard yet due to more people viewing the standard versus actually purchasing it.

Question: Do reference materials come with standard protocols for their use?
USP reference materials link to a related USP chapter, and it is expected (though not mandatory) that users will refer to the chapter's protocol.

Follow-Up Question: Is a material's utility limited without a standard protocol for use?

Reference materials do not need a standard protocol for their use, and this may not be considered a need until there is some sort of crisis. Protocols are usually developed first, but this seems to be changing.

KICKING OFF AND ADVANCING DEVELOPMENT: BREAK-OUT SESSIONS

Cell Characterization

Two break-out groups discussed the biggest challenges and the most important techniques to standardize to increase the effectiveness of cell characterization. These findings will inform and accelerate the SCB-coordinated cell characterization standards advancement project.

Key points raised during the discussions included:

- Inconsistencies in terminology and the lack of guidance for defining critical quality attributes (CQAs)
- The breadth of this topic area, which will likely require multiple standards for the different characteristics or processes that contribute to cell quality, such as cell count
- The lack of knowledge in the field, and a need to better connect the dots between assays and clinical outcomes
- The need for relevant experimental controls, such as reference materials

The group found it most useful to consider cell characterization along three lines: cell attribute, type of test for measuring that attribute, and specific test method. In doing so, they found commonality between some of the assays—for example, membrane integrity, viability measurement, and cell count can all be assessed with flow cytometry. This could be a point of entry for standardization.

Common Techniques to Standardize

Group members identified seven major cell attributes important for cell characterization: safety, identity, purity, viability, potency, impurity profile, and stability. Within each of these attributes, they identified types of tests and in some cases specific test methods in need of standardization. Some group members questioned when during the product lifecycle cell characterization should take place; this is another topic that could be standardized in addition to test-specific standards.

Biggest Challenges in Standardization

A key challenge identified during discussion was a lack of information-sharing in the industry, particularly around potency, which typically requires proprietary measurement methods. Measuring potency is difficult because there is little confidence in measurement from person-to-person or lab-to-lab. Additionally, there is no consensus on whether potency sampling is adequate. Group members also expressed a need for support in validating and interpreting test results and improving understanding of how characterization needs change as a product moves toward commercialization.

Key Takeaways

- **Cell characterization should be split** into multiple, specific standards.
- **Selecting appropriate test methods and validating and interpreting test results** are major challenges in this topic area.
- CQAs vary for specific products, **so standardizing test methods common to multiple quality attributes** could be a useful entry point for standardization.

Rapid Microbial Test Methods - ISO Design and Validation Framework Standard

Two break-out groups convened to discuss current standards development efforts for rapid microbial test methods (RMTMs). The discussion in these groups will help support and accelerate the SCB-coordinated RMTM standards advancement projects with in-development ASTM International and ISO standards. The group focusing on the ISO standard regarding RMTM design and validation frameworks discussed the progress made so far and provided valuable inputs on scope and other aspects for consideration.

Risk Assessments

Group members questioned the scope of topics to include in risk assessments, noting certain missing parameters that people consider when conducting microbial tests. The members recommended adding employee training, sampling plans, understanding of raw materials, site capability for performing RMTMs, patient tolerance for testing time, detailed facility history, and culture duration.

User-Specific Requirements

The group suggested expanding the user-specific requirements part of the standard to include validatability (i.e., what can and cannot be validated), accuracy, costs, sample preparation, the availability of reference materials, identification and speciation, training, and quantitation (i.e., determining how many microorganisms are present).

Organisms to Test For

The current standard includes a suggested list of 52 microorganisms to test for. Group members questioned its inclusion, fearing that the list was too specific and could be interpreted as organisms that must be tested for in every situation, even when not applicable. The group recommended keeping the standard's focus on testing processes and how to determine what organisms to test for, and reorganizing the list based on organisms that could be present in different environments (e.g., hospitals, laboratories). The list could then function as examples of organisms that may be present in certain environments.

Key Takeaways

- More considerations need to be added to the **risk assessments** portion of the standard.
- The group identified **additional user-specific requirements** for inclusion in the standard.
- Members recommended using the list of organisms as examples of what to test for in certain environments, while keeping the standard focused on how to **determine appropriate test processes, parameters, and organisms to test for.**

Rapid Microbial Test Methods - ASTM Tissue Engineering Scaffold Standard

ASTM International is developing a **preliminary standard guide on rapid microbial test methods** (RMTM) for **Tissue Engineered Medical Products** (TEMP) involving scaffolds. The standard guide will focus on **sampling issues and techniques to manage sterility assurance** in TEMPs. During this break-out session, participants were provided with an overview of the content that will be included in the standard, brainstormed **other topics to add**, and identified **stakeholders to involve** in the standard's development.

Topics to Consider

Core sampling technique considerations that participants noted included **material type** (e.g., hard or soft), material **manufacturing process** (e.g., unique considerations for multilayer structures), types of **organism distributions**, sources of **sampling interference** that could cause false positives or negatives, the use of **surrogate tissues** for samples, and environmental **contaminants**.

Sampling issues that participants discussed included defining **representative sample sizes** for different types of TEMPs, **appropriate sampling location(s)** for heterogeneous products, and **when** to collect samples (e.g., in-process or at release). To inform these sampling decisions, group members noted that it's important to define the **source of contamination** for different products, and identified a **need to qualify the sensitivity** of different test systems. Participants also suggested **standardizing the way companies store their testing data** so that it can be shared between organizations.

Group members indicated that the document should focus on **standardizing sterility test methods** rather than assuring sterility outcomes. They noted that **multiple types of standards documents may be necessary** to address diverse sampling issues and techniques across TEMPs and contaminants (e.g., aerobic vs. anaerobic bacteria, cellular vs. acellular products, dry vs. hydrated products).

Stakeholders to Engage

Key **stakeholders** that participants suggested engaging included **regulatory bodies, standards developing organizations**, **subject matter experts** (e.g., toxicologists, bacteriologists, statisticians), product **manufacturers**, **raw material providers** (e.g., bioink producers), **testing laboratories**, and **patients**.

Key Takeaways

- TEMPs **sampling issues are complex and vary greatly** between product types.
- There is a **need for more data on RMTM TEMP testing methods** to qualify test sensitivities and guide standardization efforts.
- Standardization in this area may require **multiple types of documents** and will **focus on assuring test method processes** rather than test results.

PRIORITY STANDARDS ADVANCEMENT PROJECTS: BREAK-OUT SESSIONS

Cell Viability

Select workshop participants convened into a break-out group to discuss the scope of potential cell viability standards, identify key stakeholders who should be involved in their development, and brainstorm problems or challenges that cell viability standards could solve.

Scope of Viability

Group members questioned the scope of the term "viability," with one member noting that it is not a useful quality attribute for certain products. Other group members mentioned that viability and potency are related, and that **a potential standard might have to focus more on assays to avoid blurring the lines of different viability attributes**.

Problems Solved with Standards in This Area

Group members noted that standards would help **enable viability assay comparisons, clarify the best ones to use, and indicate when to use assays**. Standards would also allow SDOs to establish criteria for testing and would reduce the burden of FDA product reviews.

Stakeholders to Involve in Standards Development

The group identified many different stakeholders who should be involved in cell viability standards development, including cell banking organizations (or other companies routinely cryopreserving cells), professional societies, cell certifiers, cell product users, cell manufacturers, instrument manufacturers, biologics manufacturers, regulators, and (potentially) public health companies.

Chain of Custody and Chain of Identity

Participants discussed chain of custody (COC) and chain of identity (COI) standardization opportunities for regenerative therapies, defining the potential impact of standardization activities in this area, outlining the potential scope of standardization efforts, and identifying stakeholders to engage.

Impact

More reliable COC and COI processes would **help manufacturers quickly and precisely identify and resolve failures in the supply chain**, ensuring patients receive their intended therapies and that these therapies were developed and handled correctly. This would i**ncrease trust in the regenerative medicine industry**, allow providers to more precisely identify therapy parameters that impact patient outcomes, and afford researchers more time to study cell characterization.

Needs

There is a need for **simplified data formats**—that can be read by both humans and machines—to support information exchange and to automate verification systems, as well as for **consistent product labeling approaches, standardized terminology, and consolidated history documents** for all therapies a patient receives. There's also a need to rethink traditional privacy protocols that may compromise patient safety when using personalized therapies.

Ideas for Standardization

Participants' ideas around COC and COI standardization included incorporating **double verification measures** at every step of a therapy's development and transport, building out a framework for **automated COI and COC systems**, outlining overall processes for COC and COI to define **critical steps** and suggest appropriate controls for each one, and developing a **guidance document for creating patient COI and COC protocols**.

Stakeholders

Key stakeholders that participants recommended engaging included blood and tissue banks, supply chain managers, clinicians and pharmacists, manufacturers (including of shipping materials), information technology developers, and companies from industries with strong tracking systems (e.g., fish shippers).

Characterization of Scaffold Materials

This session covered the possible impacts of a standard in this area, key stakeholders that should be involved, and next steps for further standards development.

Impact on Research Areas/Organizations

Standards in this area could help provide guidance on **what to measure for characterization and why**, and could be used to **validate characterization test methods**. Ultimately, such standards could improve comparability of characterization results from person-to-person or lab-to-lab.

When developing a standard in this area, it will be critical to ensure that the standard is not so specific that it squashes innovation, or so rigid that it increases the regulatory burden.

Stakeholders

Stakeholders that should be involved in scaffold characterization efforts include:

- Regulatory bodies (e.g., FDA)
- Academics
- SDOs (e.g., ASTM, ISO)
- Testing companies
- Materials suppliers
- Equipment manufacturers and suppliers
- Manufacturing USA Institutes (e.g., ARMI)

Next Steps

Participants suggested that the regenerative medicine community convene additional workshops with the above stakeholders and that individual stakeholders get involved with SCB and encourage their colleagues' involvement in standards advancement efforts.

Viral Vector Gene Quantification

The group discussed feasibility questions related to viral vector gene quantification, one of the high-priority standards topics identified during the gene therapy prioritization break-out session. The discussion covered the ideal scope of a potential standard, how the standard may impact stakeholders, possible stakeholder roles, as well as next steps.

Scope

The group indicated that a potential viral vector gene quantification standard should account for full versus empty capsids, titers, genomes, testing methods, documentation, infectivity, and knowledge of dose. They noted that *in vivo* and *ex vivo* viral vector gene quantification processes may need separate standards with similar subcategories.

Impacts

The group assessed potential impact of the standard on different stakeholder groups, including both broad categories and specific organizations they felt would have a unique perspective. Some of the key impacts they identified included:

- **Industry:** Better consistency in dose-determining assays
- **Academia:** Improved scientific rigor and reproducibility
- **NIST:** Ability to produce an evidence-based transduction protocol

Stakeholder Roles

The group identified multiple potential standard advancement roles for each stakeholder group. Some examples from this discussion included:

- **FDA:** Publish guidance supporting product safety and effectiveness
- **Industry**: Contribute best practices for method development
- **Academia:** Build awareness of in-progress and recently published research that could inform standards development
- **NIST:** Support measurement and standardization of equipment used for characterization
- **Payors:** Raise concerns related to reimbursement and ensure they are addressed
- **SDOs:** In addition to their central role as developers of the standard, they could also smooth the process by being responsive to stakeholders

Next Steps

The group decided that the most valuable next steps toward the development of a standard would be to identify specific methods for standardization (e.g., quantitative polymerase chain reaction [qPCR] for AAVs) as well as needed standards materials. This could be supported by a stakeholder survey to select widely applicable projects for viral vector gene quantification standard development.