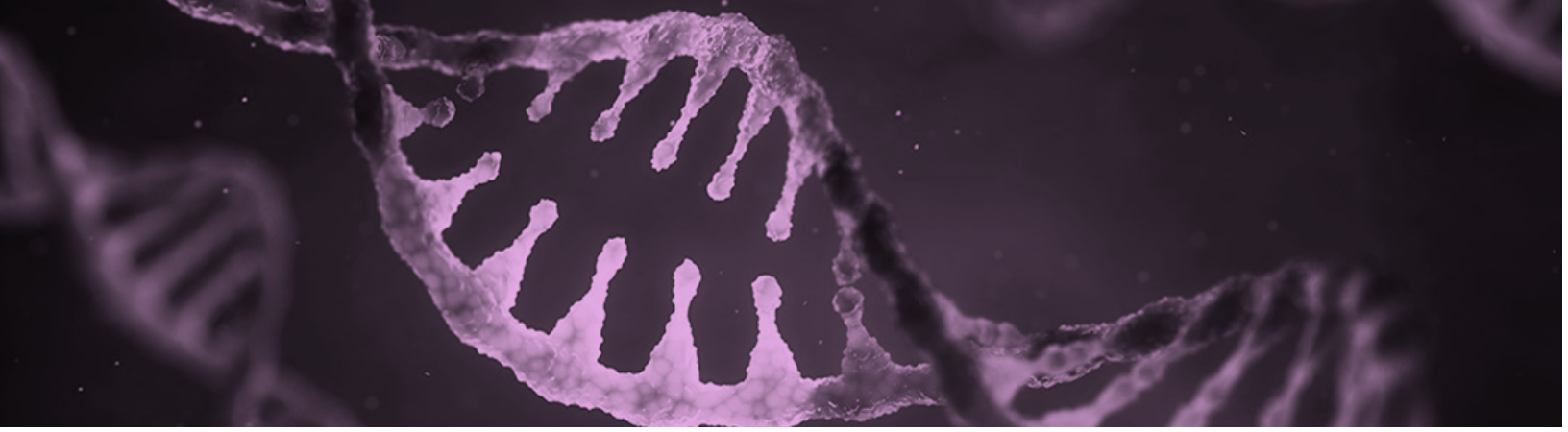

WORKSHOP FOR THE IDENTIFICATION AND STANDARDIZATION

of Methods for Assessing Gene Therapy Product Activity and Comparability and the Evaluation of T-Cell Therapies

WORKSHOP SUMMARY

December 2023

STANDARDS COORDINATING BODY
REGENERATIVE MEDICINE

FDA U.S. FOOD & DRUG ADMINISTRATION

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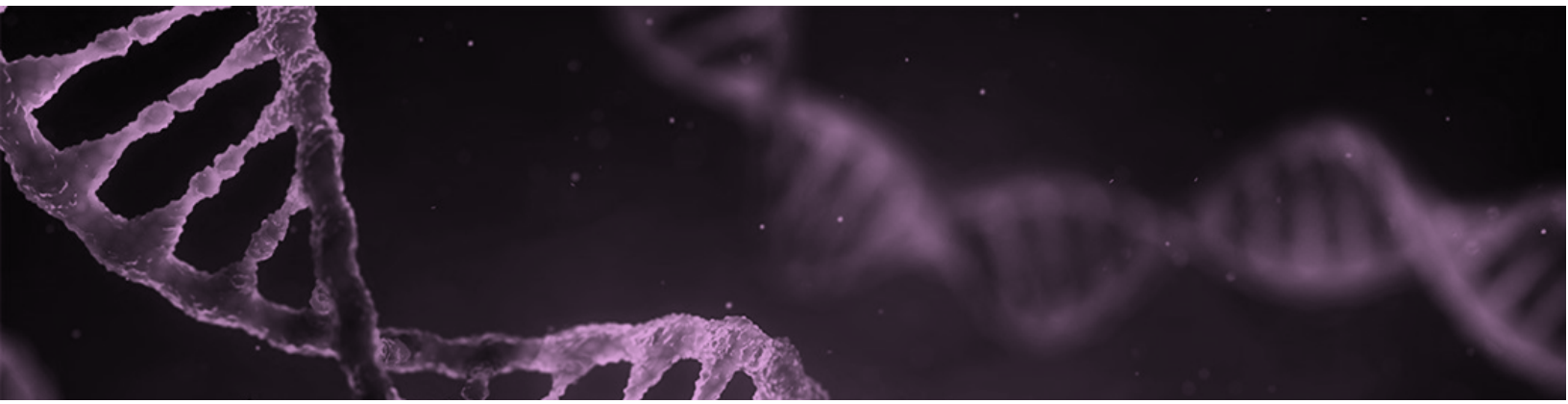
NEXIGHT GROUP



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INTRODUCTION AND SUMMARY

Since the *21st Century Cures Act* was signed into law in December 2016, the U.S. Food and Drug Administration (FDA) has been engaged in ongoing efforts to fulfill its provisions to accelerate medical product development through the advancement of standards. The Standards Coordinating Body for Regenerative Medicine (SCB) is supporting FDA's efforts by coordinating the activities of the regenerative medicine community to accelerate regenerative medicine standards development.

In December 2022, SCB conducted feasibility assessment meetings to assess the readiness of two high-priority areas of need for standards development:

- Methods for Assessing Gene Therapy Product Activity and Comparability
- Methods for the Evaluation of T-Cell Therapies

The assessment found that these broad topics would be feasible and beneficial to standardize. However, FDA identified a need to **further refine the scope of these standards needs with input from the community** about current challenges and gaps. To do so, FDA co-organized a workshop in November 2023 with SCB, FDA, and the United States Pharmacopeia (USP) to build on the results of the feasibility assessments and identify specific topics that are feasible to standardize and would make a significant positive impact on the regenerative medicine field.

The workshop was a hybrid two-day event held at USP headquarters in Rockville, MD. It was attended by more than 50 in-person stakeholders and 180 virtual stakeholders from industry, academia, standards development organizations (SDOs), and government agencies, among other regenerative medicine stakeholder groups.

The workshop included presentations by regulatory and industry representatives on the challenges and best practices in assessing cell and gene therapy products for quality, safety, and efficacy, and areas where it would be most valuable to focus attention for standardization, as well as information on standards and the standards development process.

Each day centered around a breakout session that offered participants a chance to engage in **detailed discussions of standards needs for gene and cell therapy product assessment.** After identifying needs, the groups voted on potential standards that would have the greatest positive impact in the field. The top four prioritized standards topics for each group included:

Gene Therapy

1. Empty/full/partial capsid characterization
2. Genome titer assays
3. Standardizing infectivity for adeno-associated viruses (AAVs), adenoviruses, and other viral vectors
4. Standards for impurities in the manufacturing process

T-Cell and Other Cell Therapies

1. Best practices for statistical approaches to comparability analyses
2. Phenotype - flow cytometry markers/antibodies/controls

3. Killing assays for CAR-T products
4. Assays to assess for presence of replicating viruses

Based on these discussions, SCB will **organize new working groups** to further assess the feasibility of the prioritized topics for standardization and potentially advance them to SDOs for development. Stakeholders interested in joining a working group can contact SCB.

DAY 1 PRESENTATIONS

WELCOME PRESENTATION

Dawn Henke, Ph.D., Senior Scientific Program Manager, Standards Coordinating Body

The key goals of the workshop include:

- **Identify specific standards needs** for assays for T-cell therapies and gene therapy product activity and comparability and gather information that will guide the future development of standards for advanced therapies
- **Share community challenges and best practices** related to the assessment of cell and gene therapy products
- **Learn about standards**, including their benefits, the standards development process, implementation of standards, and relevant existing regenerative medicine standards

Dr. Fouad Atouf, Ph.D., Senior Vice President, Global Biologics, USP

USP has been working in the standards space for more than 200 years, focused on addressing unmet needs for the quality of medicines, particularly in assay development. Regenerative medicine presents a unique challenge for standardization due to the fact that the **technology is constantly shifting** and the approaches established for small molecule therapies often do not translate to gene and cell-based therapies due to their innate variability.

Because the manufacturing and testing needs differ for each regenerative medicine product, it would be valuable to **shift away from a product focus in developing standards** and instead identify crosscutting issues and challenges. The workshop offers an opportunity to gather diverse perspectives from the community to identify these commonalities and needs.

Key Takeaways

- **The workshop's key goals** included sharing of community challenges and best practices, learning about standards and their benefits, and gathering input from the community to identify needed standards for assessment of gene and T-cell therapies.
- It is challenging to develop standards for regenerative medicine due to **ongoing shifts in technology and the variability of products.**
- Standards for regenerative medicine will typically focus on **common methodology rather than product-specific needs.**

STANDARDS COORDINATING BODY OVERVIEW

Dawn Henke, Ph.D., Senior Scientific Program Manager, Standards Coordinating Body

SCB is an independent 501(c)(3) organization that was established in 2016 to act as a communication vehicle for the multiple stakeholder groups involved in the development of standards. It serves to **engage, educate, and coordinate the regenerative medicine community** around standard advancement.

Among the resources offered by SCB is the Regenerative Medicine Standards Portal, a **searchable database of hundreds of regenerative medicine standards** across more than 25 organizations. The Portal also provides a snapshot of standards needs identified by the regenerative medicine community and their relative urgency and impact, which is informed by a semi-annual community survey. In addition, the Portal tracks opportunities to participate in standards development such as open ballots and working groups for in-development standards that are looking for experts.

Another key element of SCB's work is the **coordination of standards working groups**. SCB involvement in these working groups has served to reduce the time spent on pre-development activities such as prioritization and feasibility assessment, **accelerating the availability of these standards** for the community. As part of this coordination work, SCB supports two National Institute of Standards and Technology (NIST) consortia in developing standards, reference materials, and other resources for the topics of rapid microbial testing methods (RMTM) and flow cytometry.

SCB is currently **developing several resources to support standards education** for the regenerative medicine community. These include a pilot training program for the use of standards in manufacturing processes developed in partnership with ARMI | BioFabUSA, as well as a course on the implementation of ISO 20391, Cell Counting (part 1 and part 2), that will soon be available on the International Society for Cell & Gene Therapy (ISCT) learning platform. SCB is also developing a course on the implementation of ISO 20399, Ancillary Materials Present During the Production of Cellular Therapeutic Products and Gene Therapy Products.

Key Takeaways

- SCB's goal is to **engage, educate, and coordinate the regenerative medicine community** to accelerate the development of standards to support the creation of safe and effective therapies.
- The SCB **Regenerative Medicine Standards Portal provides a single, searchable repository** of published and in-development standards, standards needs identified by the community, and standards updates and participation opportunities.
- **Stakeholders can help support SCB's mission** by investing in one of its Focus Areas; current Focus Areas include Data Management and Standards Implementation Education and Workforce Development.

STANDARDS RECOGNITION PROGRAM FOR REGENERATIVE MEDICINE THERAPIES (SRP-RMT)

Judy Arcidiacono, M.S., International Regulatory Expert, Office of Tissues and Advanced Therapies, FDA Center for Biologics Evaluation and Research (CBER)

CBER recently finalized guidance describing its new Standards Recognition Program for Regenerative Medicine Therapies (SRP-RMT). The program aims to identify voluntary consensus standards (VCS) that can **facilitate the development and assessment of regenerative medicine products** regulated by CBER. The program is applicable to standards developed following principles of openness, balance, consensus, and due process; the American National Standards Institute (ANSI) accredits SDOs that adhere to these principles. The program will **not be applicable to non-voluntary consensus standards** (e.g., pharmacopoeia standards, accreditation standards, and standards created by institutions or societies), though the use of non-voluntary consensus standards can still be valuable to manufacturers in improving safety and consistency of products.

FDA anticipates that the SRP-RMT will help to **promote the development of standards** that can be used to streamline regenerative medicine product review. In addition, it can **assist product developers in identifying standards** that FDA has reviewed for scientific soundness and consistency with FDA regulations and policies. The program will also be valuable to reviewers by helping them **evaluate proper use of standards in regulatory submissions.**

There are several ways that standards can be identified for consideration in the recognition program.

- **FDA staff serving as liaisons to SDOs** can nominate standards for review**.**
- **Stakeholders in the regenerative medicine community** can also request recognition of specific standards via email at SRP-RMT@fda.hhs.gov. These requests should include the SDO name, standard designation, version and year published, and a brief rationale explaining why the standard should be recognized.

Standards recommended for inclusion will undergo review by FDA subject matter experts and may receive either **complete recognition or partial recognition** of certain sections. Evaluation criteria include:

- Whether the standard was developed by a VCS body
- Scientific soundness of the standard
- Absence of any conflict with existing FDA statute, regulations, or policy
- Ability of the standard to help a sponsor meet regulatory expectations
- Ability of the standard to assist FDA in regulatory assessment

The recognized standards will **be listed on the FDA Standards Development for Regenerative Medicine Therapies page** and accompanied by a Standard Recognition Sheet (SRS) with details of the recognition (e.g., standard information, recognition rationale, extent of recognition). Stakeholders may still use standards in regulatory submissions even if those standards are not recognized by the SRP-RMT.

Key Takeaways

- The SRP-RMT identifies voluntary consensus standards that can **help to facilitate FDA review of regulatory submissions for regenerative medicine products**; however, non-recognized standards may still be used in regulatory submissions.
- Stakeholders can **request the consideration of specific standards** for inclusion in the SRP-RMT by emailing SRP-RMT@fda.hhs.gov with the standard details and rationale for inclusion.
- Recognized standards will be **updated on the Standards Development for Regenerative Medicine Therapies page** of the FDA website twice per year.

COMPARABILITY AND THE MANAGEMENT OF MANUFACTURING CHANGES FOR CELLULAR AND GENE THERAPY PRODUCTS

Anurag Sharma, Ph.D., Gene Therapy Reviewer, FDA CBER

Comparability studies are performed to confirm that manufacturing process changes (e.g., to improve manufacturing efficiency or scale up operations) **do not have adverse effects on the safety or efficacy** of products. FDA recommends regenerative medicine therapy manufacturers **develop a formal risk management strategy** for manufacturing changes to determine when comparability studies are needed. The ICH Q9(R1) Quality Risk Management standard can aid in the development of such a strategy.

FDA **published two recent draft guidance documents** outlining the agency's expectations relevant to manufacturing changes for regenerative medicine therapy products. As of December 2023, these guidance documents are still being finalized.

- Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products describes how to manage and report manufacturing changes to FDA, as well as how to design and perform analytical comparability studies. The guidance covers topics including how to obtain advice on comparability studies, what to include in a comparability protocol and comparability report, the goals of the comparability report, and more.
- Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products gives advice on all aspects of manufacturing of vectors and CAR-T cells, including change management and comparability when manufacturing a CAR-T cell product at multiple facilities.

The extent of data needed for comparability studies will vary based on the phase of the product, with changes later in the product lifecycle typically requiring more rigorous studies. FDA encourages manufacturers to **plan ahead for changes**: This can include implementing significant changes to product manufacturing as early as possible (e.g., prior to beginning any pivotal studies), developing a thorough understanding of the impact of each manufacturing step on a product's critical quality attributes (CQAs), and producing and maintaining sufficient lots to support comparability studies.

Sponsors should notify FDA of planned manufacturing changes that could affect product quality well in advance by **submitting an amendment to the Investigational New Drug (IND) application or Biologics License Application (BLA)**, as well as including a summary of changes in the annual report for the

IND/BLA. If the change is significant enough to result in a fundamentally different product, FDA may require a sponsor to file a new application.

Key Takeaways

- Manufacturers should approach manufacturing changes and design of comparability studies with **risk management at the forefront.**
- Regenerative medicine product manufacturers should **plan ahead** for manufacturing changes and ensure they are prepared to conduct comparability studies as their operations change.
- Manufacturers are **responsible for notifying FDA of planned manufacturing changes** though their IND or BLA and can also receive advice through this process.

OPPORTUNITIES FOR STANDARDIZATION IN COMPARABILITY OF CELL AND GENE THERAPIES

Tal Salz, Ph.D., Consultant (Practice Expert), Dark Horse Consulting

When considering the development of standards for comparability, it is important to first ask whether standardization of this area **is desired** by industry, FDA, and other stakeholders; whether such standards would **reduce burdens** on these groups; and whether there is **common ground** among comparability practices that would lend itself to the development of standards.

Comparability studies are complex and can vary significantly from product to product, particularly for cell and gene therapies. However, there is an opportunity for **standardization of common elements** associated with comparability evaluation, such as:

- Risk assessment
- Side-by-side testing
- Study procedures, method equivalence
- Statistical approaches
- Qualification of scale-down models
- Qualification of retains
- Study reporting
- Terminology

Developing **flexible standards** for these shared elements could help stakeholders perform comparability assessments with less subjectivity and report more meaningful results to FDA.

As an example of how one of these areas might be standardized, an approach to standardization of risk assessment could include **the development of common evaluation criteria** that could be used to generate a "risk score" (e.g., severity, probability, and detectability). Similarly, a standard on side-by-side testing could potentially advise on how to **minimize variables** to ensure samples are tested under the same conditions, including use of the same testing facility, reagent lots, and operators and instruments. Companies could also benefit from the development of **standard templates** for presenting comparability studies and reports, which would help to prevent a common issue in which key information is missing during regulatory review.

Terminology is another key area within comparability testing that would benefit from standardization; there are many instances where **different organizations use the same terms to mean different things** (e.g., "split source" could mean two samples from the same donor taken at the same time, or months

apart). In other cases, terms are defined in guidance documents, but more detail would be valuable for the industry.

Key Takeaways

- Identifying opportunities to standardize elements of comparability assessment of cell and gene therapy products will be **challenging due to their variability but would be valuable** for industry and FDA.
- **Establishing comparability acceptance criteria** is a key challenge that may not be possible to standardize because these elements are unique to each product.
- Other significant challenges, such as **limited lots available for comparability testing**, may benefit from standards (e.g., standardization of principles for developing scaled-down models).

EVOLVING STANDARDS AND TOOLS TO MEET INDUSTRY NEEDS IN CELL AND GENE THERAPY

Dr. Diane McCarthy, Ph.D., Senior Scientific Director, Global Biologics, USP

The Value of Standards

According to FDA guidance for industry, "The use of standards can **facilitate product development** and **reduce the amount of documentation** needed in a regulatory submission, thus contributing to a more efficient submission evaluation and, ultimately, **improving time to market**."

The benefits of standards include:

- **Increasing consistency** in manufacturing processes and product testing
- **Supporting innovation** and adoption of new technologies
- **Making it easier to meet regulatory expectations** to facilitate market entry for safe and effective products

However, more alignment is needed around common standard needs, as there are currently a diverse range of product types, unique requirements for raw materials, and a lack of alignment on product quality attributes and test methods.

Challenges in Ensuring Quality of Raw Materials

A key challenge in producing cell and gene therapy products that are compliant with Good Manufacturing Practices (GMP) is that cell and gene therapy products are not amenable to extensive purification, filtration, or terminal sterilization. Using **GMP-compliant raw materials** could help address this problem. There are currently several standards under way that aim to guide sponsors in developing such materials.

For example, USP has recently recognized a gap in plasmid DNA best practices and began developing a USP chapter on plasmid DNA, which will cover manufacturing considerations, quality management, and DNA starting material quality. Similarly, USP is working on standards and tools for the enzymes used in cell and gene therapy processing and the cytokines and growth factors used in cell culture.

Product Quality Attributes

USP has two existing general practices chapters that support the manufacturing and quality control of cell and gene therapy products: <1046> Cell-based Advanced Therapies and Tissue-based Products, and <1047> Gene Therapy Products. These chapters cover a variety of different types of therapies, but there is **a need for more specific guidance on different modalities**.

For this reason, Chapter <1047> is being updated to split out some of the content into a **dedicated chapter on practices for AAV gene therapy manufacturing.** Additionally, USP, the National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL), and NIST have recently collaborated on an **interlaboratory study** to assess and harmonize methods for measuring the ratio of **full-to-empty viral capsids** for AAV products. Similar studies could contribute to the expansion of more specific standards for determining the product quality attributes of different cell and gene therapy products.

Impurities

Each manufacturing process comes with its own set of **process-related impurities**. For example, some common cell substrate-derived process impurities include residual DNA and host cell proteins (HCP). These impurities can lead to impacts on product quality, safety, and efficacy. For residual DNA, there are quantitative World Health Organization (WHO) and FDA guidelines on how much residual DNA is allowed in a final product dose. USP is working on standards that address residual impurities for polyethylenimine (PEI) and replication competent testing for AAVs as well as standard reference materials to support residual DNA analysis.

Key Takeaways

- Standards provide **consistency** in manufacturing processes and product testing, support **innovation** and adoption of new technologies, and make it easier to **meet regulatory expectations** to facilitate market entry for safe and effective products.
- Cell and gene therapy products are not amenable to extensive purification, filtration, or terminal sterilization. In order to develop GMP-compliant cell and gene therapy products, **GMP raw materials should be used**.
- Manufacturing processes come with **process-specific impurities**. USP has several standards under way to help assess these impurities.
- Stakeholders can review proposed revisions to USP standards by **subscribing to the Pharmacopeial Forum (PF).**

NIST GENOME EDITING CONSORTIUM OVERVIEW

Samantha Maragh, Ph.D., Leader, Genome Editing Program, NIST

NIST is a **nonregulatory Federal agency** within the U.S. Department of Commerce. Its mission is to promote U.S. innovation and industrial competitiveness by advancing measurement science, standards, and technology in ways that enhance economic security and improve our quality of life. NIST's collaborations with the FDA on standards development leverage NIST's expertise in measurement sciences and its ability to engage with industry and others on pre-competitive technologies; FDA

provides scientific and regulatory expertise to ensure that standards are relevant to regulatory challenges in the field and do not conflict with existing FDA regulation and policy.

NIST Genome Editing Program

Genome editing has applications in medicine (drug development, gene surgery), biotech (fuel, food, materials), and biology (animal models, epigenetic variation). **The NIST Genome Editing Program supports quality in measurements for translating genome edited products to market.**

The genome editing community has **identified standards needs** for various topics, including:

- Qualification of genome editing components considered critical for manufacturing
- Evaluation and comparison of delivery systems
- Identification of off-target activity areas
- Evaluation of assays for detecting genome variants
- Resources or practices for data and bioinformatics performance

The **NIST Genome Editing Consortium** **was launched in 2018** to convene experts across academia, industry, non-profits, and government to address the measurements and standards needed to increase confidence in utilizing genome editing technologies in research and commercial products. The consortium includes three working groups: Specificity Measurements, Data and Metadata, and Lexicon.

WG1, Specificity Measurements focuses on developing cell- and DNA-based control materials and testing analytical methods via interlab analysis. The working group recently conducted an interlab blinded study to test the capability of assays to accurately report variant size and frequency. Participants included technology users and technology makers. The working group has generated a set of Phase 1 DNA and cell-based control materials and is conducting final data analysis of its first interlab study. It is also currently working on developing additional engineered cell controls, with some clonal cell lines completed.

WG2, Data and Metadata has several areas of focus, including supporting the development of community norms for data formats and tools for benchmarking data analysis; identifying metadata that would need to be shared, housed, and interrogated from genome editing experiments; and developing tools to accelerate metadata sharing. The working group has completed Phase 1 development of metadata entries and a template, and is currently developing a metadata schema, testing use cases and user interfaces, and working toward interoperability of a metadata standard format and database(s) to house records.

WG3, Lexicon focuses on identifying terms and their definitions to form a common genome editing community lexicon. The working group has identified 42 key, high-level terms across categories. NIST interacts with various organizations to refine the terms and works to harmonize them internationally. The working group's efforts led to the development of an International Organization for Standardization (ISO) standard on genome editing vocabulary, ISO 5058, which was published in 2021 and updated in July 2022.

Key Takeaways

- **NIST collaborates with many stakeholder groups within the regenerative medicine community**, including FDA, USP, international organizations, and industry, to develop standards and technology.
- The genome editing community has identified **standards needs critical for genome editing components,** including qualification of genome editing components, evaluation and comparison of delivery systems, and identification of off-target activity areas, among others.
- The **NIST Genome Editing Consortium** convenes experts across three working groups to advance measurements and standards to support utilization of genome editing technologies in research and commercial products.

PANEL DISCUSSION: GAPS AND CHALLENGES IN THE REGULATORY/APPROVAL PROCESS

Judy Arcidiacono, M.S., FDA

Samantha Maragh, Ph.D., NIST

Diane McCarthy, Ph.D., USP

Tal Salz, Ph.D., Dark Horse Consulting

Anurag Sharma, Ph.D., FDA

Question: What key topics do you want to focus on in this discussion?

- **Maragh**: One of the biggest gaps is in documenting processes sufficiently for other operators to understand. If you fail to do this, you lose continuity.
- **Sharma**: We are seeing more complex manufacturing changes, which result in more complex comparability study designs. However, we don't often see standards used in comparability studies. Use of reference standards in analytical assays gives you control and reduces variability.
- **Arcidiacono**: I can't overstate how important standards are for cell and gene therapy. There are already relevant standards that could be used in these fields—cell or gene therapy may not be in the title of these standards, but there are ISO standards for measuring nucleic acids and for evaluating polymerase chain reaction (PCR) methods, for example.
- **McCarthy**: There are different considerations for the two types of standards. Documentary standards will continue to evolve quickly, so we need to work together to modify existing standards or develop new ones. Physical standards must be fit for purpose—what is needed to support a particular analytical test?
- **Salz**: When we think about standards, it always takes us to methods. Developing standards for methods can help us do a lot of things indirectly related to comparability. It can be harder to answer questions about practices: How do we do this? What is the framework?

Question: When commonly used potency readouts have not been shown to impact efficacy and safety, what is the rationale for using these readouts?

- **Sharma**: Our thinking is that potency is an attribute that is very sensitive to manufacturing changes. It's important to do a risk assessment. That's why we advise sponsors to develop a quantitative potency assay so differences can be detected.
- **Salz**: Some potency assays relate grossly to safety and efficacy, but it can be difficult to see safety and efficacy changes unless they are outside a certain range. For example, when the vector copy number is very low, you don't see efficacy anymore. There is a lot of potential for standardizing commonly used elements of potency assays. I'm not sure if there's development in that field, but it would be very powerful.
- **Arcidiacono**: Our approach is gathering experts and getting input on what everybody uses. We find there typically aren't that many differences. This has helped us publish standards in ISO and ASTM. The standards are often broad and generic and serve as an umbrella document, then more specific documents are developed that refer to them.

Question: What are standard sequencing methods required to detect on- and off target changes?

- **Maragh**: There are no required methods right now; people can use whatever they think is relevant. But you need to characterize changes to the best of your ability. We recognize that large structural rearrangements can happen, so you need to use technologies that identify those.

Question: Would standards for analytical methods need to be generated by the sponsor using their own product, or from commercial sources?

- **Arcidiacono**: There is no requirement to use standards, and standard methods could be anything. Anyone can come to ISO or ASTM with a proposal for a standard. Developing internal reference materials is up to the sponsor.
- **Sharma**: The sponsor can develop their own internal reference materials and doesn't need to calibrate against external reference materials, but there may be external materials available that are helpful for the community to understand and compare products for studies.
- **Maragh**: It is important to be clear about what a reference material can and can't tell you. It may tell you if your process or reagents are working, but not your serotype or product or cell type. You may need something more specific for your validation process: something internal that is more exactly like your sample.
- **McCarthy**: There is so much diversity in products that in many cases you have to develop something for a new product. You might need a combination of multiple standards to support assays.

Question: How should we decide what potency assays to include for the studies we do?

- **Sharma**: Start with several assays, and as you gain more experience and product development reaches later phases, drop some assays and focus on those that best meet your purpose.

- **Salz**: If you have several assays determining the same thing, use the one that is the most quantitative to assist with comparability. Use a method with low variance, related to the mechanism of action, that is able to detect meaningful change.

Question: What are your thoughts on managing a network of manufacturing sites, especially for autologous gene-modified cell therapies, and the comparability challenges of adding a new manufacturing site or lab to that network?

- **Salz**: If you come up with an equivalence range based on safety and efficacy data and have an understanding of what would constitute a biologically meaningful difference, you can compare data from facilities to that range, and your reference doesn't change across comparisons.

Question: We are forming a consortium to develop T-cell therapies for cancerous solid tumors. We need a plan for gathering data on various cell attributes to launch a clinical trial. Am I correct that the use of standards is not required in order to file an IND? Also, do you have advice on characterization of various cell attributes?

- **Salz**: Correct, you are not obligated to use standards. It's your choice.
- **Arcidiacono**: It's not a requirement, but standards would be helpful to ensure you are getting the same information from all consortium members. The advantage to using standards is that everyone does the same thing. FDA offers guidance for cell and gene therapy, including standards guidance.
- **Sharma**: Unfortunately, FDA does not have a mechanism to provide advice without a product.

DAY 2 PRESENTATIONS

Navigating Regulatory Milestones Throughout Development

Patrick Bedford, Co-Founder and Director, weCANdev Consulting Group, Inc.

Cell and gene therapy product developers face various **challenges with analytics** throughout the product lifecycle. Product developers typically develop analytical methods during the early discovery phase, when they have few resources and relatively high uncertainty about regulatory expectations. This can result in the **development of assays that will not adequately meet a product's needs** around aspects such as data quality as it moves toward commercialization.

Analytical methods must also be qualified and validated, which often occurs as research is nearing the translation stage. Many companies receive financial support at the onset of drug development but **struggle to get ongoing support as they near translation**, a situation referred to as the Valley of Death. As a result, supporting assay development during this stage is particularly important.

Even the products that successfully evade the Valley of Death and go to market suffer from the lack of funding that occurs during the later stages of product development. This scenario often leads to insufficient analytical development, a situation in which **assays are used that may work on a small scale but would not be cost effective** when the product achieves commercialization. **Standards could help**

organizations more efficiently develop, qualify, and validate assays and help prevent future issues such as low data quality or poor cost effectiveness.

Key Takeaways

- Many startups **struggle to develop assays commensurately with their products**. They often use less cost-effective assays until they need to scale up the product for commercialization. At this point, it is often too late in the process to transition to different assays.
- **Standards could help cell and gene therapy product developers develop, qualify, and validate analytical methods more efficiently,** which would be valuable for organizations facing resource constraints.

Navigating the Milestones in Developing Commercially-viable Cell and Gene Therapy Products

Krishna Panchalingam, Ph.D., Associate Director, Cell and Gene Therapy Global Technical Operations/Development Services, Lonza

Lonza is a contract development and manufacturing organization (CDMO) that offers support to cell and gene therapy developers across the analytical lifecycle. Through the course of its work with clients on topics such as assay optimization, qualification, and validation, Lonza has **identified several common challenges** that could potentially be addressed through the development of relevant standards. These include:

- Analytical quality concerns such as ensuring specificity, repeatability, and accuracy
- Ensuring data integrity compliance
- Using phase-appropriate assays that meet regulatory requirements
- Using adequate controls and references

To follow GMP requirements for cell and gene therapy products, product developers must **identify in-process checkpoints**—go or no-go points—to determine how well each process is going. At these checkpoints, products are evaluated on their therapeutic product profile and whether they are worth the money and effort to continue producing. If they are not, the product is dropped. **Analytics are key to this development approach**.

CQAs and the assays that test for them must be decided on early in the manufacturing process. By the time products transition from laboratory development to full-scale manufacturing, the process and assays should be well defined. **Many clients leave assay determination and evaluation until later in the development process.** For example, many do not even start using potency assays until their products are being made at scale, and without using these potency assays, researchers cannot fully understand the mechanism of action that the drug uses to produce its therapeutic effect.

Key Takeaways

- **In-process checkpoints exist throughout the manufacturing process** to determine whether each product should be discontinued or pushed on to the next step. Analytics are critical to these checkpoints.
- **CQAs and the assays that test for them must be decided early** in the manufacturing process so that manufacturers can understand how their therapies work on a molecular level. This improved understanding will make it easier to make adjustments when needed.

GENE THERAPY COMPARABILITY CHALLENGES AND PRACTICES: AN INDUSTRY PERSPECTIVE

David Litwack, Ph.D., Associate Vice President, Scientific Strategy and Communications, Prevail Therapeutics (a subsidiary of Eli Lilly)

Prevail Therapeutics is an Eli Lilly company that works on AAV gene therapy for neurodegenerative disorders. They face traditional manufacturing challenges, but also other **challenges related to rapid development within the gene therapy field.**

Gene therapy has developed at a remarkable speed. The first paper on CRISPR/Cas9 technology was published eleven years ago. On November 16, the first gene therapy treatment for sickle cell disease was approved in Britain. This rapidity presents several challenges: as organizations develop their products, **they may find that there is suddenly a new assay they need to consider**. Additionally, there are **no uniform, across-the-board practices**, which makes it difficult to compare experiences. Yet comparability is critical in this field: organizations must pool experiences to make safer and more efficacious medicines for patients.

The big question in the field is **how product quality affects safety and efficacy**. This is not yet well understood. Other challenges include the complex biology of cell and gene therapy products, uncertainty about the variables that lead to manufacturing inconsistencies, limited material for use in characterization and comparability studies, and the lack of standard cutoffs for CQAs.

Prevail Therapeutics **recently moved from the HEK293 to SF9 platform** for the greater scale available through SF9. They found that SF9 produced more full capsids and fewer empties and partials. They were also able to confirm that products developed with the new platform are highly similar, with no adverse impacts on quality, safety, or efficacy. There are, however, challenges with the SF9 platform. The company has less experience with the platform, so it is more expensive to set up. Contaminants and purification are different, requiring many changes when switching platforms. There was also limited material available for comparability studies. The switch was a big investment and it took time, but it was necessary in order to increase their scale of output for the future.

Developing well-written standards in a manner that encourages data sharing while protecting intellectual property (IP) is challenging, but possible and essential. None of the organizations in this field treat enough patients to produce sufficient data. If they can't compare information, they can't learn,

and the field will not progress. It is critical for patients and their safety that the industry shares information on acceptable parameters for these revolutionary therapies.

Key Takeaways

- **The gene therapy field has grown at remarkable speed,** presenting rich opportunities but several unique challenges.
- The big question in the field is **what effect product quality has on safety and efficacy**.
- **Switching from the HEK293 to SF9** platform presented several challenges, but Prevail Therapeutics has found it allows them **greater scale** with **no significant change in quality, safety, or efficacy**.
- **Standards are necessary to encourage data sharing** while protecting industry IP. Access to more data is critical for patient safety and advancement in this field.

Kite's Experience with CAR-T Manufacturing and the Role of Standards

Mehrshid Alai-Safar, Ph.D., Vice President of Regulatory CMC, Kite

Thilini Fernando, Ph.D., Senior Scientist, Kite

Kite is a cell therapy manufacturer primarily focused on the development of CAR-T cell treatments for cancer. CAR-T cell therapy manufacturing, which involves modifying T-cells to recognize and attack cancer cells, has **unique challenges compared with conventional pharmaceutical manufacturing**. Whereas conventional manufacturing can make thousands of the exact same product, CAR-T cell manufacturing **lots must be individualized**. In addition, the **inherent variability of starting material** and **complex manufacturing processes** involved in CAR-T product development can lead to difficulty maintaining consistent quality and safety across products.

Another challenge with CAR-T products is that by the time cancer patients are using CAR-T cells, they have typically already undergone many different treatments and are entering CAR-T treatment in a vulnerable state of health. As such, it is important for manufacturing sites to maintain **effective chain-of-custody** (records of the product starting material and any changes it has undergone) **and chain-of-identity** (health records on individual patients from before and after each treatment), so that they do not deliver the wrong cells to their patients. **Standards can be valuable tools** for harmonizing recordkeeping and other practices across organizations to ensure the safety and consistency of T-cell therapy products.

Implementation of Platform Technologies for Streamlining Analytical Life Cycle Management

Kite adopted the droplet digital polymerase chain reaction (ddPCR) platform as a means of streamlining and standardizing its practices around enumeration of vector copy numbers. Use of the ddPCR platform simplifies the analytical lifecycle through automation, while offering additional benefits to robustness, precision, accuracy, and throughput. The ddPCR platform utilizes common targets for product and reference genes, can help standardize measurement across programs, allows absolute quantification,

and has standardized qualification and validation approaches, which can support rapid technology transfer.

Key Takeaways

- CAR-T cell therapy lots **must be individualized to each patient**, which can lead to challenges with product variability.
- It is critical for CAR-T treatment centers to **maintain clear chain-of-custody and chain-of-identity records** to protect patient safety.
- The **ddPCR platform can be used to streamline and improve consistency** of vector copy number enumeration.

PERSPECTIVES ON PRECLINICAL SAFETY NEEDS FOR MODIFIED T-CELL THERAPIES

Yixiang (Sean) Xu, Ph.D., Senior Scientist, Bristol-Myers Squibb

Hui Ling, Ph.D., Senior Principal Scientist, Novartis

Cell Therapy - TRAcking, Circulation, Safety (CT-TRACS) is one of 18 committees at HESI, a nonprofit focused on resolving global health and environmental challenges. CT-TRACS aims to **address safety concerns in the clinical translation of cell-based therapies**, including tumorigenicity and the study of biodistribution questions such as where cells used in treatments go and how long they persist there. CT-TRACS is **conducting a multi-site study of an Interleukin-2 (IL-2) assay for assessing tumorigenic risk of CAR-T therapies**. The purpose of the study is to develop a standard approach for the assay to enable more robust and consistent results and give a better understanding of tumorigenicity risk.

The study achievements so far include the **establishment of a standardized assay protocol** with a defined format, culture media, readout, and assay length, as well as a defined sensitivity range. The study also **identified a positive control oncogene** and found a correlation between cells transformed using that oncogene (oncogene E) in vitro and the formation of cancer in a mouse model. CT-TRACS is seeking feedback from regulators on the efforts in terms of when and how to use this assay and the applicability of the assay to different types of CAR-T programs (e.g., autologous, allogenic, or with or without gene editing).

CT-TRACS is engaged in several other activities to support knowledge sharing to improve the safety of cell-based therapies. One of these activities is a **stakeholder survey on current practices in assays for genomic stability** of allogenic cell therapies that will culminate in a publication in a peer-reviewed journal. In addition, it is developing a **consensus white paper on assay formats for on-target, off-tumor, and off-disease edits** that focuses on points to consider and best practices for developing assays.

Key Takeaways

- CT-TRACS brings together international stakeholders in the regenerative medicine community to share scientific knowledge and **improve the safety of cell therapy products.**

- One of CT-TRACS' major efforts is to **establish standards and controls around an IL-2 assay for assessing tumorigenic risk of CAR-T therapies** to allow therapy developers to better understand and report these risks to FDA.
- CT-TRACS is also developing publications on **current practices in assays for genomic stability of allogenic cell therapies and assay formats for on-target, off-tumor, and off-disease edits.**

PANEL DISCUSSION: GAPS AND CHALLENGES IN THE PRODUCT DEVELOPMENT PROCESS

Mehrshid Alai-Safar, Ph.D., Kite

Patrick Bedford, weCANdev Consulting Group, Inc.

Thilini Fernando, Ph.D., Kite

Hui Ling, Ph.D., Novartis

David Litwack, Ph.D., Eli Lilly

Krishna Panchalingam, Ph.D., Lonza

Yixiang (Sean) Xu, Ph.D., Bristol-Myers Squibb

Question: You mentioned using non-GMP materials as an approach to mitigate comparability challenges from lack of materials. How would regulatory agencies validate comparability when the original process was produced using GMP materials?

- **Litwack:** We did not have this issue with our filing because we used a mixture of materials to demonstrate the bridge between the GMP and the non-GMP materials. This shows the importance of standards—comparability studies help address some of the uncertainty, but there are technical limits with them that standards could better address.
- **Panchalingam:** We created a risk assessment for the process to develop non-GMP materials, which assessed the difference between the non-GMP and the GMP materials in terms of comparability.

Comment: Host cell proteins can be immunogenic, and this presents an issue when patients (especially children) require multiple treatments. The presence of these proteins will continue provoking an immune response each time redosing occurs.

- **Litwack:** This is the biggest concern for the gene therapy field and reflects the challenge with pre-existing immunity to commonly used AAV vectors. Our product is a one-time treatment, so we haven't run into the issue of continued immune response, but we are trying to anticipate this issue by increasing the durability of the product. We are starting to see increased durability in clinical trials.

Question: For the comparison study that compared full, empty, and partial capsids, do you advocate for one method over others? Was the takeaway from this that the analytical ultracentrifugation (AUC) was preferred, or was it just the one with the most data?

- **Litwack:** It will depend on the situation, and this is an area where standards could help. I needed to try many different techniques to figure out what would work, and some would not allow us to see partials. The AUC worked well and did allow us to detect partials. However, we started this study in 2018/2019, so our choice might differ if we were to start it today. Although standards would help, it would remain a challenge to develop one that wouldn't get outdated by the rapid development of technology.

Question: Do analytical assays used for comparability studies need to be validated, or can we use R&D-based assays?

- **Fernando:** We do some comparability studies during development, but we do them more thoroughly after qualification.
- **Litwack:** We validate all the assays we use and do the same type of qualification, but a lot of them don't go to a regulatory body.
- **Panchalingam:** It depends on whether they are fit-for-purpose.

Question: Regarding cytokine-independent oncogene incorporated cells, given media with fetal calf serum (FCS) or some other growth factor in it, have you investigated what growth factors are involved and what the ranges are?

- **Xu:** We have not tested growth factors and are not sure how cytokines impact them. We did test some media, including the ones we used during the manufacturing process and others used in T-cell cultures. The R10 media gives us a positive outcome. We tested others that were more cytokine-enriched, but they didn't give us a positive result. FCS seems to work better than human serum, but that is not universal for other oncogenic events. IL-2 and IL-7 intend to give survival signals. There is a dormancy before an oncogene starts actual damage, around 21–28 days. Normal T-cells won't be able to survive long enough for the oncogene to do damage.

Question: Have you looked into whether you could clone vectors that have around 15–20 lentiviral insertions to see if they could generate a positive control with a different mechanism rather than inserting a gene? This would be another way to see what is going on and look at T-cell clone sites since you are trying to observe rare events. Also, is there evidence of changes in something to cause malignancy, or are those separate events? What assay could detect that?

- **Xu:** Regarding insertions, we have to follow patients for 10–15 years; so far, we haven't received any report from this tracking that indicate an issue from the CAR-T product detected in the patient. This is an indication that insertion into the genome is a theoretical risk, but not happening in most patients. Regarding malignancy, if the patient's immune system is weak, does that risk the T-cell becoming abnormal? Most CAR-T products so far are simple, with no additional gene editing. In vivo studies indicate there are not a lot of CAR-T cells remaining a few months after dosing, but we don't have an answer on longer-term effects yet.

- **Bedford:** It will be hard to develop an assay for these products due to the patient-to-patient variation. It also depends on how we define quality. This is an area where standards could help move more products to commercialization.

BREAK-OUT SESSIONS

Gene Therapy

The gene therapy breakout sessions included a broad discussion of challenges associated with gene therapy development. Some of the key challenges that emerged included:

- Difficulty ensuring clearance of helper viruses due to their similarity to adenoviruses and a need for reliable helper virus removal methods and common limits on levels of residual helper virus
- Variability in assays and methods for measuring full and empty capsids, including uncertainty around determining safe levels of empty capsids
- Difficulty defining partial capsids and a need for alignment on a consistent definition
- Lack of clear metrics to define viral vector quality
- Variability in the use of microphysiological systems (MPS) and cell-based assays to assess gene therapies (e.g., cell culture methods, cell sources, characterization approaches)

The group then examined the challenges they had identified and developed a list of potential standards that would address each challenge:

- Empty/full/partial capsid characterization
- Genome titer assays
- Standardizing infectivity for AAVs, adenoviruses, and other viral vectors
- Standards for impurities in the manufacturing process
- Potency assays
- Ultracentrifugation approaches
- Total AAV capsid particle concentration
- Post translational modifications in AAVs
- Standards on in-process testing, particularly focused on the vector stability profile
- MPS characterization
- Aggregation assessment

The group held a vote to prioritize the list of standards topics based on which would be most impactful if standardized in the near future. The top three topics included:

1. Empty/full/partial capsid characterization
2. Genome titer assays
3. Standardizing infectivity for AAVs, adenoviruses, and other viral vectors

For each of the priority topics, the group held a deeper discussion on what elements might be valuable to include in a standard on the topic.

Standards for Empty/Full/Partial Capsid Characterization

A standard on this topic could address:

- Definitions of full/empty or possibly partial capsids

- Guidance on how to obtain, use, and characterize reference materials
- How to report empty/full results
- How to assess and address genome truncation within capsids
- Method for measuring empty/full capsids
- Interpretation of varying results among different methods (e.g., AUC vs. charge detection mass spectrometry [CDMS])

The group also identified potential barriers to standard development:

- A need for new technologies or methods to apply the standard and training on how to use them
- Industry concerns about how specifications are defined and the implementation timeline
- Industry reluctance to change established practices
- Data integrity and compliance gaps for software packages used for new technologies
- Cost barriers and resource constraints in adopting the standard (e.g., obtaining new instrumentation)

Standards for Genome Titer Assays and Infectivity for Viral Vectors

For each of these topics, the group identified two similar standards that would be needed:

- A standard on the **use of reference materials** covering their availability, use, characterization, methodology, and creation
- A **methodology standard** covering terminology and best practices

The group also identified potential barriers to standard development:

- How the standard would age with current technology and revision cycles
- Developers who already have technology in place may be reluctant to make changes
- How to bridge/transition to the standard
- How to deviate appropriately
- Cost of implementation of new technologies into process
- Software required for data acquisition

T-Cell and Other Cell Therapies

The discussion on cell therapies touched on numerous challenges in the field; some of the major challenges included:

- The need for statistical methods to assist with analyzing complex data
- Limitations from the standpoint of sample validity and generating enough statistical power to allow meaningful comparisons
- Difficulty convening experts and encouraging information sharing
- Uncertainty around the right markers to evaluate for product quality and safety

Participants also discussed various action items that could support standardization, including identifying existing standards to leverage, characterizing existing kits, and improving communication to raise awareness across stakeholders about relevant standards development activities and existing standards resources.

Participants then identified standards that could address each of the challenges they had discussed. These standards topics included:

- Best practices for statistical approaches to comparability analyses
- Phenotype – flow cytometry markers/antibodies/controls
- Killing assays for CAR-T therapies
- Assays to detect the presence of replicating viruses
- Standard approach to IL-2 independent proliferation
- CAR expression assays for rapid CAR-T cell manufacturing
- Assays for oncogene mutation assessment at the induced pluripotent stem cell (iPSC) stage
- Standard cell line transduced with platform/universal targets for vector copy number assays
- Artificial intelligence/machine learning-based cell counting
- Specific functional assays and expected readouts for signaling domains commonly used in CARs

The group prioritized topics that would be valuable to standardize and engaged in a deeper discussion of the top two prioritized topics. The top two topics included:

- Best practices for statistical approaches to comparability analyses
- Phenotype – flow cytometry markers/antibodies/controls

For each of the priority topics, the group discussed the elements that the standards should include to be most impactful, as well as stakeholders to engage in the standard advancement effort.

Standards for Best Practices for Statistical Approaches to Comparability Analyses

A standard on this topic could address:

- Stimuli companion documents (e.g., via USP)
- Education (e.g., when equivalence evaluation is needed and when it is not)
- Prescriptive guidance on methods, including:
    - Testing pre- and post- change product in the same assay
    - Sample sizes on different risk score CQAs
    - Clinical study requirements for non-comparable products (patient safety)

Stakeholders to involve in the standard advancement effort could include statisticians, professional societies, industry, smaller manufacturers, and CDMOs.

Potential barriers to standard development include:

- Lack of available expertise
- Small sample sizes
- Too much variability among stakeholders in choice of assays

Standards for Phenotype – Flow Cytometry Markers/Antibodies/Controls

A standard on this topic could address:

- Quantitative understanding of mitochondrial strength
- Analysis of T-cell penetration and penetration of serological materials passing the blood-brain barrier and targeting neoplastic cells
- Gating strategy/data analysis

- Standard controls for assay performance and tracking
- Markers and impurity profiles for specific T-cell lineages/populations
- Qualified controls for each step of the most critical phenotypic assay
- Limits of dynamic range of assays
- Protocol for choosing parameters for titrated reagents
- Expectations for release vs. characterization assays, including:
    - Parameters for method qualification and validation
    - Gating controls
    - Method bridging

Stakeholders to involve in the standard advancement effort could include the International Society for Stem Cell Research (ISSCR), the NIST Flow Cytometry Consortium, American Society of Hematology (ASH), manufacturers, CDMOs, and end users.

Potential barriers to standard development include:

- Variability in reagents, instruments, and analysis approaches
- Rapid change in availability of new markers
- Difficulty aligning on phenotypes of interest
- Challenge with implementation if the standard is too complex or deviates too much from current industry practice

APPENDIX A: WORKSHOP AGENDA

Workshop Objectives

1. Educate participants on standards benefits, the standards development process, implementation of standards, and relevant existing regenerative medicine standards
2. Share community challenges and best practices related to Assays Used to Assess Cell and Gene Therapy Products
3. Identify specific standards needs for assays for T-Cell Therapies and Gene Therapy Product Activity and Comparability

Thursday, November 16, 2023

Time (Duration)	Session
8:30-9:00 am	**Networking and Registration**
9:00-9:15 am	**Introduction by Dr. Fouad Atouf, Ph.D. (USP) and Justin Barch (SCB)**
9:15-9:55 am	**Judy Arcidiacono (FDA)** • CBER Standards Recognition Program for Regenerative Medicine Therapies and the use of standards in the regulatory process • Types of standards (e.g., technical specification, decision-making guide)
9:55-10:20 am	**Anurag Sharma, Ph.D. (FDA)** • Comparability and the management of manufacturing changes for cellular and gene therapy products
10:20-10:45 am	**Tal Salz, Ph.D. (Dark Horse Consulting)** • Opportunities for standardization in comparability
10:45-10:55 am	*Break*
10:55-11:20 am	**Dr. Diane McCarthy, Ph.D. (USP)** • USP standards work on cell and gene therapies
11:20-11:45 am	**Samantha Maragh, Ph.D. (NIST)** • NIST Genome Editing Consortium Overview • Identifying and developing needed standards
11:45 am-12:15 pm	**Panel Discussion with Day 1 Speakers** • Gaps and challenges in the regulatory/approval process in gene therapy comparability and T-cell assessment
12:15-1:00 pm	*Lunch*
1:00-1:20 pm	**Dawn Henke, Ph.D. (SCB)** • SCB's role in coordinating standards development for regenerative medicine therapies • SCB resources (e.g., standards portal) • Overview of relevant existing regenerative medicine standards
1:20-1:30 pm	**Introduction to Breakout Sessions**
1:30-1:45 pm	*Break and Transition to Breakout Groups*
1:45-3:00 pm	**IN-PERSON ONLY**

Time (Duration)	Session

	Breakout Session: 2 parallel groups on:
	A) Assessing Gene Therapy Product Activity
	B) Assessing T-Cell and Other Cell Therapy Product Activity
	• Identify specific standards needs and topics that are ripe for standardization
	
	Focus questions:
	• What assays or related processes, if standardized, would help address current challenges? Standards can include specific protocols about how to conduct a process (e.g., a technical specification or validation protocol) as well as less prescriptive guides that aid in decision making.
	• Which two topics would have the greatest positive impact on the field if standardized in the near term? (voting exercise)
	• For the top 2 prioritized topics:
	  ○ What components of the assay or related process need standardization (e.g., test selection, measurement methods, interpreting results, validation)?
	  ○ What key questions should be answered by a standard on this topic?
	  ○ Do you anticipate any barriers to standardizing these assays (e.g., lack of scientific consensus, difficulty or expense of implementation, potential resistance from the community)?

3:00-3:15 pm	*Break*
3:15-4:30 pm	**Breakout session continued**
4:30-5:00 pm	**Thank you and wrap up**
5:00 pm	**Adjourn**

Friday, November 17, 2023

Time (Duration)	Session
9:00-9:20 am	**Introduction by Dr. Fouad Atouf, Ph.D. (USP) and Justin Barch (SCB)**
9:20-9:45 am	**Patrick Bedford (weCANdev Consulting Group Inc) & Krishna Panchalingam, Ph.D. (Lonza)** • Navigating regulatory milestones throughout cell and gene therapy development
9:45-10:10 am	**David Litwack, Ph.D. (Eli Lilly)** • Gene therapy comparability challenges and best practices – an industry perspective
10:10-10:35 am	**Mehrshid Alai-Safar, Ph.D. and Thilini Fernando, Ph.D. (Kite)** • Kite's experience with CAR-T testing in manufacturing and the role of standards: a case study on a method change
10:35-10:45 am	*Break*
10:45-11:10 am	**HESI CT-TRACS: Yixiang (Sean) Xu, Ph.D. (BMS) and Hui Ling, Ph.D. (Novartis)** Introduce HESI CT-TRACS working group addressing critical gaps and challenges in evaluation of CAR-T cells (evaluating transformation via functional assays; re-evaluating the IL-2 independency assay)
11:10-11:40 am	**Panel Discussion with Day 2 Speakers** • Gaps and challenges in the development process in gene therapy comparability and T-cell assessment
11:40 am-12:40 pm	*Lunch*
12:40-12:50 pm	**Introduction to Breakout Sessions**
12:50-1:00 pm	*Break and Transition to Breakout Groups*

1:00-1:50 pm	**IN-PERSON ONLY**
	Breakout Session: 2 parallel groups on:
	A) Assessing Gene Therapy Product Activity
	B) Assessing T-Cell and Other Cell Therapy Product Activity
	• Define more of the specifics of the standard topics identified on Day 1 and their feasibility
	
	Focus questions:
	• After reviewing the needs identified on day 1, what additional standard areas could help address current challenges?
	• *Continue discussion:* For the top prioritized topics:
	  ○ What components of the assay or related process need standardization (e.g., test selection, measurement methods, interpreting results, validation)?
	  ○ What key questions should be answered by a standard on this topic?
	  ○ Do you anticipate any barriers to standardizing these assays (e.g., lack of scientific consensus, difficulty or expense of implementation, potential resistance from the community)?

1:50-2:05 pm	*Break*

Time (Duration)	Session
2:05-3:00 pm	Breakout session continued
3:00-3:30 pm	Workshop Summary and Next Steps
3:30 pm	Adjourn