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Report from the 2022 NIST Rapid Microbial Testing Methods (RMTM) Workshop

Credit: Natasha Hanacek

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Abstract

Safety and quality of advanced therapies, including cellular, gene, and tissue-engineered medical products, is paramount for success of these products. Sterility assurance testing to confirm the absence of microbial contamination in advanced therapy products is critical to establishing safety before patient dosing. To date, culture-based compendial methods are employed as the gold standard for sterility testing of pharmaceutical products. However, for advanced therapy products, the required cultivation period (e.g., 14 days or more) is incompatible with the short (e.g., 2 days) product shelf life and jeopardizes healthcare outcomes for critically ill patients. Alternative rapid microbial testing methods are increasingly being evaluated to reduce test result turnaround time for advanced therapies but are not yet widely adopted. In September 2020, NIST established the Rapid Microbial Testing Methods (RMTM) Consortium to address the need for measurements and standards, including reference materials, to increase confidence in the use of rapid testing for microbial contaminants in regenerative medicine and advanced therapy products.

Here we report on the activities and conclusions from the Rapid Microbial Testing Methods (RMTMs) Workshop that was hosted (virtually) by the NIST-led RMTM Consortium on April 19, 2022. The workshop's goals were to identify measurement challenges and hurdles to adopting RMTMs for advanced therapy products, and to share and obtain feedback on future efforts of the RMTM Consortium. To this end, subject matter experts from biopharmaceutical, academic, regulatory, and biotechnology sectors were invited to give presentations on two broad themes: 1) Barriers and Potential Solutions to Adoption of RMTMs, and 2) Technologies and Tools for Rapid Microbial Detection. Summaries of the presentations, discussions, and polling indicate that validation, suitability, and comparison studies for RMTMs remain challenging. Priority areas for the RMTM Consortium were identified as 1) interlaboratory studies that provide datasets to the community in support of RMTM implementation, and 2) reference materials with expanded properties relevant to RMTMs, such as total cell count, total genome count, and cell viability. Overall, this workshop served as a venue for shared knowledge and learning on the state of the RMTM field and the hurdles to RMTM broad adoption, consequently benefiting a diverse group of stakeholders.

Keywords

Advanced therapy medicinal products; cell and gene therapy; consortium; FDA regulations; microbial contamination; microbial detection; rapid methods; reference materials; regenerative medicine; standards; sterility testing; validation; workshop report.

Table of Contents

List of Tables

List of Figures

Acknowledgments

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The authors acknowledge Shaswat Koirala (NIST) for administrative support for the workshop and Dawn Henke (SCB) for documenting the workshop.

1. Introduction

1.1. Background

Regenerative medicine therapies are a special class of advanced therapy products that include cellular therapies, gene therapies, and tissue-engineered medical products. These unique therapies offer potential cures for some of today's most debilitating and intractable diseases. As such, these products are well-poised to usher in a new era of healthcare. However, to deliver on their promise, regenerative medicines must be free of microbial contamination to ensure product quality and patient safety.

Currently, biomanufactured therapeutics are evaluated for microbial contamination via culture-based compendial methods as described in USP General Chapters <71> and <62>. Although widely regarded as the "gold standard," such compendial culture-based methods take up to 14 days to acquire conclusive results. Yet the shelf life of many regenerative medicine products is between 24 h and 72 h. Therefore, when compendial methods are used, the product may need to be administered before confirming sterility, posing an obvious risk to the patient's safety. To address this shortcoming, manufacturers have been encouraged to adopt and implement alternative methods for sterility testing that are rapid (RMTMs). Despite the obvious benefits, biopharmaceutical and biomanufacturing industries have been slow to adopt RMTMs, due in part to resource requirements and for myriad reasons including 1) uncertainty around the performance, reliability, and stability of various technologies, 2) lack of appropriately qualified reference standards, 3) cost versus benefit, 4) daunting validation schemes, and 5) regulatory approvals. Therefore, RMTMs have not yet been widely adopted hurdles (whether perceived or real)

In its mission to support innovation and technology development, the National Institute of Standards and Technology (NIST) launched the NIST Rapid Microbial Testing Methods Consortium in 2020 to help facilitate the validation, adoption, and implementation of RMTMs for regenerative medicines and advanced therapy products. The NIST RMTM Consortium operates through an organizational framework consisting of three working groups, each focused on a critical aspect of standards and measurement assurance concepts as follows (**Fig. 1**):

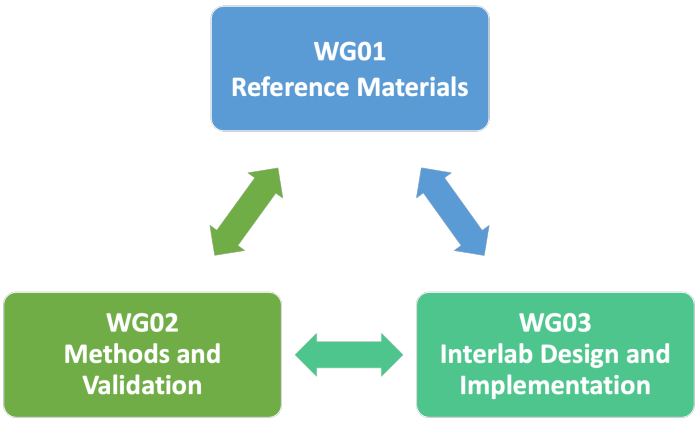

Fig. 1. The RMTM Consortium Consists of Three Interdependent Working Groups.

WG01 MISSION: The Reference Material Working Group (WG01) aims to identify and facilitate the development, characterization, and qualification of reference materials (RMs) to support the broad adoption of new and existing Rapid Microbiology Test Methods (RMTMs) within the Advanced Therapy Industry.

WG02 MISSION: The Methods and Validation Schemes Working Group (WG02) aims to develop a framework for validating methods to support the broad adoption of new and existing Rapid Microbiology Test Methods (RMTMs) by the Advanced Therapy Industry.

WG03 MISSION: The Interlaboratory Study Design and Implementation Working Group (WG03) aims to design and implement interlaboratory studies to assess the analytical performance of various RMTMs while also evaluating the performance and fitness of candidate reference materials.

1.2. Workshop Overview

On April 19, 2022, the NIST RMTM Consortium held its second annual workshop, which focused on the barriers and potential solutions to the adoption of RMTMs. As opposed to other Consortium activities, this annual workshop is open for the public to attend and participate. As outlined in the agenda (Appendix A), the workshop was divided into two main sessions with speakers spanning consulting, legal, regulatory, and scientific/technological sectors, which allowed for the incorporation of diverse perspectives. Speaker bios are provided in Appendix B. Session 1 focused on barriers and potential solutions to the adoption of RMTMs. Session 2 emphasized the technologies and tools for rapid microbial detection. Each session was followed by a panel discussion that sparked conversation among participating experts and thought leaders in the field. Over 100 people registered for the workshop, with the majority representing either industry or the federal government (**Fig. 2A**). In terms of focus area, 41 % of registrants were RMTM producers (**Fig. 2B**).

This workshop report aims to summarize the workshop contents and findings. Speaker presentations are summarized here, and the entire workshop recording is available online,[1] along with presentation slides from those who agreed to share their slides. Responses to the live polling conducted throughout the workshop are provided in full (Appendix D).

[1] https://www.nist.gov/news-events/events/2022/04/nist-rapid-microbial-testing-methods-workshop

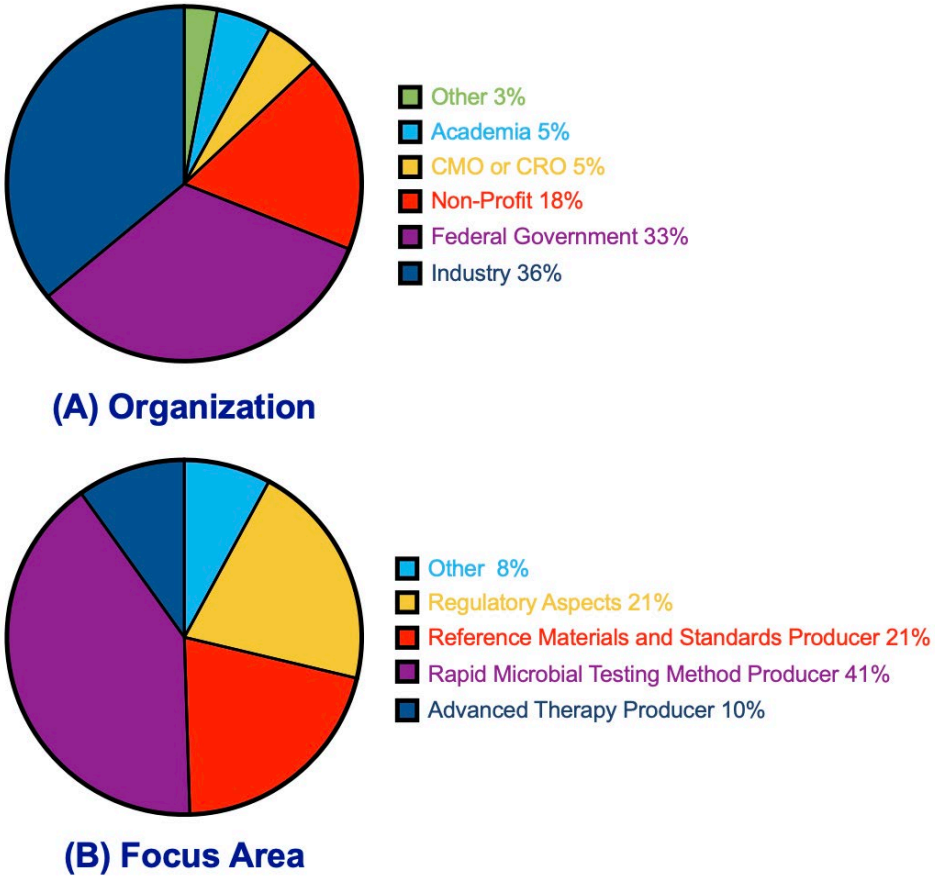

Fig. 2. Breakdown of workshop registrants by **(A)** Organization **(B)** and Focus Area.

2. Session 1: Barriers and Potential Solutions to Adoption of RMTMs

2.1. Overview

Session 1 brought together diverse expertise and perspectives across legal, regulatory, biopharmaceutical, and biotechnology sectors. Speakers discussed the basis for delays in wide-spread RMTM adoption and identified potential next steps to advance a broader implementation of RMTMs.

2.2. Presentations

2.2.1. Regulatory Landscape

Speaker: Margaret Riley, JD, Professor of Law, University of Virginia

Talk Title: The Regulatory Context for Sterility Standards in Cell-Based Therapies
Speaker Margaret Riley provided regulatory context for sterility standards in cell-based therapies. Riley set the stage by describing the evolution of FDA regulation of cell-based therapeutics over time. She described how the current guidance for sterility testing of advanced medicinal products began to take shape at their advent in the 1980s. During the 1980s, deliberations had already begun on how cell therapies would fit into the statutory framework. Although initial attempts were made to fit cell-based therapeutics into device frameworks, she stated that these frameworks proved too rigid. Ultimately, the FDA opted for a scheme designed to balance risk with the necessary flexibility for these emerging technologies.

Next, Riley guided the audience through 21 CFR Par 12171 and 21 CFR 610, emphasizing how the development of these regulations provides an example of the regulators' line of reasoning that goes into developing "rules" for emerging technologies. Riley explicitly called out the FDA's deliberate use of "broad" equivocal wording meant to allow for significant flexibility.

Riley ended her talk with the following bottom line: "The current governing legal framework allows FDA significant flexibility, and FDA most likely wants to maintain this flexibility." This reaffirmed that the regulatory body will probably resist mandatory standard requirements because this would likely create roadblocks to approval for some products. Riley left the audience with the following salient point: "a lack of mandatory standards does not mean that rigorous controls are unnecessary."

2.2.2. End-User Case Study on Implementation of RMTMs

Speaker: Anna Lau, Ph.D., Chief, Sterility Testing Services, National Institutes of Health (NIH) Clinical Center
Talk Title: Creating GMP in an Academic Research Setting and Clinical Hospital Environment – Challenges and Lessons Learned at the NIH

Dr. Anna Lau brought a wealth of experience surrounding the use of existing technology for rapid microbial testing and headlined the end-user viewpoint. Lau's talk began with an introduction to NIH, including its role in therapeutic manufacturing. NIH is home to 13 manufacturing facilities covering a broad range of products, including a variety of cell and gene therapy products.

Lau then elaborated on NIH's long history of sterility testing. Speaking on methodology, Lau noted that initial sterility testing on cell therapy products was performed in the clinical microbiology lab using platforms designed for diagnosing infectious disease. These automated diagnostic platforms showed great promise as alternative methods to the compendial method.[2] The automated systems highlighted during this talk included: BacT/ALERT (BioMérieux), BACTEC (Becton Dickinson), and VersaTREK (ThermoFisher), with the caveat that the BacT systems can pose a particular challenge for fungal detection.

[2] USP Chapter <71> Sterility Test

Lau then shared the results of two seminal research studies, "Comparison of automated culture systems with a CFR/USP- compliant-method for sterility testing of cell-therapy products,"[3] and a subsequent follow-up investigation, "Sterility testing of cell therapy products: parallel comparison of automated methods with a CFR compliant method."[4] Both studies demonstrated that automated culture systems were equivalent to, or better than, the compendial methods used for assessing sterility. Because of strong scientific evidence demonstrating the validity of the automated culture system, the NIH Clinical Center's Investigational New Drug (IND) applications documenting sterility testing with this approach were accepted by the FDA.

Most recently, a more expansive study, "Comprehensive Evaluation of Compendial USP <71>, BacT/Alert Dual-T, and BacTec FX for detection of Product Sterility Testing Contaminants,"[5] was conducted with a more diverse set of challenge organisms (n=118) and seven system comparisons. Intriguingly, as discussed by Lau, this study showed that with an expanded organism set, the compendial method was superior to the respiratory methodologies. Lau concluded her seminar with workshop questions and comments focused on risk assessments, validations, validation level required based on the therapeutic asset's stage in development, and organismal considerations when implementing RMTMs.

2.2.3. Barriers to Adoption of RMTMs

Speaker: Michael Miller, Ph.D., President, Microbiology Consultants LLC
Talk Title: Rapid Microbiological Methods: A Roadmap for Implementation

Dr. Michael Miller began his talk by posing the question, "If rapid microbial methods are so great, why aren't they universally used in all labs worldwide?" Miller then began his address with an overview of perceived barriers to implementing RMTMs.

Five common perceived barriers listed below were reported and disputed by Miller.

1. Perception: Rapid methods are not accepted by the regulatory agencies.
   Reality: Rapid microbial methods are accepted by regulatory agencies worldwide, including the FDA, EMA, TGA, PMDA, and others.

2. Perception: Rapid methods cannot replace compendial methods.
   Reality: Numerous regulatory authorities have approved rapid microbial test methods.

3. Perception: There is not enough guidance on how to validate RMTMs.
   Reality: Current guidance exists and there are three major guidance documents: PDA Technical Report #33, Evaluation, Validation, and Implementation of New Microbiological Testing Methods; USP <1223>, Validation of Alternative Microbiological Methods; and Ph. Eur. 5.1.6, Alternative methods for control of microbiological quality.

[3] Khuu et al. Cytotherapy, 2004;6(3):183-95. doi: 10.1080/14653240410005997
[4] Khuu et al. Transfusion, 2006:46(12):2071-2082. https://doi.org/10.1111/j.1537-2995.2006.01041.x
[5] England et al. Journal of Clinical Microbiology, 2019;57(2). https://doi.org/10.1128/JCM.01548-18

4. Perception: Rapid methods do not provide a return on investment (ROI).
   Reality: Rapid microbial methods do provide returns on investments, some large and some small. End-users should perform a ROI calculation to determine if the cost savings outweigh the initial investment.

5. Perception: Acceptance criteria cannot be changed.
   Reality: Acceptance criteria can be revised with scientific justification.

Miller challenged potential end-users to divest themselves of these perceived barriers and to reconsider implementing these necessary technologies. He concluded his talk with a brief discussion of a process for implementation, calling attention to the following critical considerations for end-users:

1. End-users should understand the available RMTM technologies and their capabilities.
2. RMTM technologies should be matched with a given end-user's requirements.
3. Validation plans should be developed.

2.3. Panel 1: Barriers and Potential Solutions to Adoption of RMTMs

Margaret Riley, Anna Lau, Michael Miller, Sheng Lin-Gibson, and Judith Arcidiacono (FDA)

To focus the panel session, the following four questions were asked of the panel members:

1. What are the barriers to the adoption of RMTMs and how can the Consortium (or NIST) help overcome those barriers?
2. Are the right standards available?
3. How rapid is rapid?
4. Key piece of advice for companies looking to implement RMTMs?

Attendees were queried using the Slido polling option:

1. What is your primary challenge/bottleneck in the use of RMTMs?
2. Are there suitable standards available for you to assess, validate, and adopt RMTMs?
3. What is your required/preferred time-to-results for "rapid" tests?

Twelve responses were received for the first attendee poll question, "What is your primary challenge/bottleneck in the use of RMTMs?" (Appendix D). Most responses fell into one of two categories: (1) capacity to validate and (2) test performance. While some respondents directly identified the capacity to validate as a challenge, others indicated this indirectly by identifying the regulatory requirements or working in a sterile environment. With respect to test performance – limit of detection, specificity, sensitivity, range, organism, and time to results were all identified as bottlenecks/challenges. Similar challenges were also noted by the expert panel. Lau and Miller both emphasized that adopting RMTMs is a resource-intensive activity and perhaps this is the primary barrier. Lau pointed out that validation is easy if you have unlimited resources (e.g., time, personnel, funding); however, academic and research labs that are producing investigational early phase (phase 1, phase 2) products are in a never-ending cycle of validation. In her opinion, a written

document is needed to help researchers identify when method suitability is sufficient without USP <1223> validation.

Another related barrier identified was opacity, or the lack of sharing of experience and data. A role for the RMTM Consortium to help address these barriers could be fostering collaborations in the non-regulatory, pre-competitive space. Such collaborations could inform on how to avoid recreating and redoing studies that have already been done. A suggested immediate area of impact was identifying current matrices being tested and determining where pooling resources to help create matrix "buckets" or "brackets" could help transition from validation to method suitability. The FDA decisions rely on data and a demonstration that the method is robust. Pooling of resources could help generate this data.

The request for a formalized, written document(s) to help researchers identify when method suitability is sufficient without USP <1223> validation seems unlikely to be met, as the response "it depends" was frequently used. Additionally, the FDA is unlikely to put something in writing as that may become restrictive and would likely require a change in policy. While policy change at the FDA is difficult, acceptance of standards, such as those developed by the International Organization for Standardization (ISO) or other standards organizations, is not as arduous to implement. Another path forward that the FDA is pursuing is a guidance document on the use of standards to support regulatory applications.

Miller emphasized that the requirements for validation are clearly defined in USP <1223> and PDA Technical Report (TR) 33. Miller also noted that TR 33 is currently under revision, and contributing to the revision is a good mechanism to support the future direction of best practice guidelines. He noted that these guidelines often end up becoming current good manufacturing practices (cGMP).

The panelists reviewed an audience poll on how rapid is rapid (**Fig. 3)**. Most poll respondents selected < 24-hour turn around. Miller pointed out that anything less than 24 h would eliminate growth-based assays. It was not discussed how viability would be handled in this instance; however, a field to look toward in this respect would be air and water monitoring.

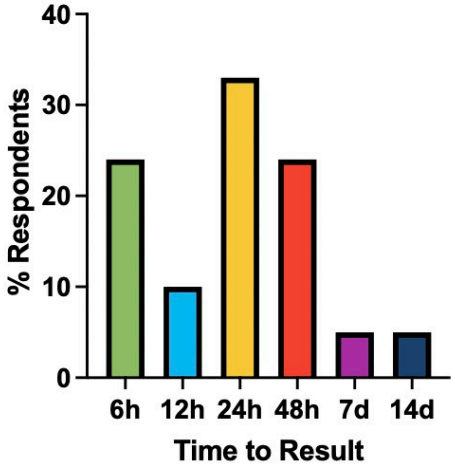

Fig. 3. What is your required/preferred time-to-results for "rapid" tests?

(n=21)

While it was generally agreed upon by panel members and attendees that suitable standards are available (**Fig. 4**), it seemed that a "how to" guide on using the standards would be helpful. Specifically, Lau mentioned that manufacturers and academics are often not as intimately familiar with the requirements and responsibilities for validation as those with pharmaceutical backgrounds. Supporting teaching/educational opportunities is another role that the RMTM Consortium could fill.

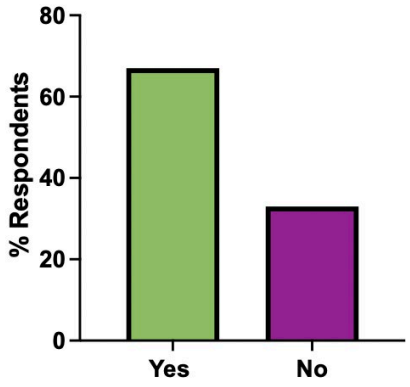

Fig. 4. Are there suitable standards available for you to assess, validate, and adopt RMTMs?
(n = 18)

Key take aways for companies looking to implement RMTMs are:

- Evaluate risk – until there are more rigorous documents and instructions for RMTM, the risk might be too large for small companies/academics.
- Seek guidance – seek advice from consultants and the public domain on how to mitigate the risk.
- Find a champion – implementation of new technology takes commitment, available resources, and a champion.
- Engage senior management – demonstrate how rapid methods fit into the paradigm of continuous improvement, process, and product knowledge.
- Share – be open to exchanging information through meetings, forums, publications, and other venues.

3. Session 2: Technologies and Tools for Rapid Microbial Detection

3.1. Overview

Session 2 of the workshop focused on several emerging key technologies presented by subject matter experts and developers. **Table 1** captures an overview of the RMTM technologies presented.

Table 1. Summary of the Emerging RMTM Technologies Presented at the Workshop

RMTM	Principle	Approximate Time to Result
ATP-based (Source: USP)	Detection of ATP produced by viable cells via luciferase-based bioluminescence	24 h to 48 h (quality control testing)
CO_2-based (Source: USP)	CO_2 produced is detected via a colorimetric reaction indicative of microbial respiration	24 h to 72 h
Nucleic acid-based (PCR) (Source: rapidmicrobialmethods.com)	Amplification of specific or highly conserved regions of nucleic acids in microbes	< 2 h
Raman spectroscopy-based (Source: rapidmicrobialmethods.com)	Chemical identification via molecular vibrational spectroscopic signatures	< 2 h
Solid-phase cytometry-based (Source: rapidmicrobialmethods.com)	Filtration followed by fluorescence-based detection of microbes; optional addition of viability dyes.	< 3 h

For the technology presentations, speakers were asked to address the following:

- Method advantages and challenges for rapid microbial testing of advanced therapy products.
- Reference materials, controls, and standards currently being used and/or needed (e.g., validation and process controls).
- Barriers to method implementation for rapid microbial testing of advanced therapy products.

3.2. Presentations

3.2.1. ATP-Based Technologies

Speaker: Jonathan Kallay, Senior Technology and Marketing Manager, Charles River Laboratory
Talk Title: Celsis ATP Bioluminescence: From Cell Culture to Sterility

Jonathan Kallay of Charles River Laboratory provided an overview of the benchtop Celsis microbial detection platforms. Celsis provides high-throughput ATP bioluminescence-based rapid microbiological detection that is compatible with several sample types and has an initial time to

result between 24 h to 48 h. The method focuses on the detection of ATP, as opposed to turbidity, to detect sterility failure.

The ATP bioluminescence assay is based on a proprietary enzymatic reaction utilizing Celsis bioluminescence reagents. Such reagents allow for production of light when ATP is present. The presence of ATP is an indicator of the presence of cells. A luminometer measures the light produced and compares the result to a validated threshold; results below the threshold represent a negative result, whereas results above the threshold represent a positive result.

Kallay mentioned that a historic limitation of ATP-based methods is the detection of false positives from cells that produce ATP. He described a technology developed to address this concern, the Celsis ADAPT, which is a sample-concentrating platform that removes product cell ATP while retaining intact microbial cells. A mild lysing solution is used to break down product cells, and cell products (such as ATP) are removed as waste. Microbial cells stay intact through this process as they are protected by their outer cell walls. Kallay indicated that the occurrence of false positives is decreased to an acceptable level when the Celsis ADAPT is used prior to running samples on the Celsis instrument.

3.2.2. CO_2-Based Technologies and Solid Phase Cytometry-Based Technologies

Speaker: Felix Montero, PhD, Scientific Director-Health, and Personal Care Business, bioMérieux
Talk Titles: CO2-Based Rapid Microbial Methods and their Use on Cell and Gene Therapy, Application of Solid Phase Cytometry for Rapid Microbial Testing for Advanced Therapy Products

Dr. Felix Montero delivered a combined presentation on automated growth-based technologies and solid phase cytometry-based technologies. Automated growth-based technologies (e.g., via detection of CO_2 production) are applicable to non-filterable cellular and gene therapies, biologics/vaccines, small and large molecule therapeutics, and in-process products - with typical results in 5 days to 7 days. In contrast, solid-phase cytometry involves filterable samples like compounding products, infusion fluids, process/raw materials, and cell and gene therapies requiring specific sample preparation. Selected advantages of these technologies include ease of use, efficiency, automation, and digitization of results for traceability.

CO_2-based methods are colorimetric technologies where the growth of microorganisms produces CO_2, eliciting a change in pH. This change in pH results in an irreversible color change that is detected via a photodiode that collects reflected light. The light signal is then transmitted to a control module analysis and output.

The next technology discussed by Montero was the SCANRDI, a non-growth-based technology. Importantly, as highlighted by Montero, this technology can detect contamination down to a single microorganism, including those that are viable but non-culturable. The basic principle of this methodology is as follows:

1. Membrane-penetrant non-fluorescent substrates enter microbial cells during incubation.
2. Substrates retained in viable cells release fluorochromes that accumulate inside the cells. Viable cells retain the substrate and convert it into a fluorophore.
3. The accumulated fluorochromes are then detected during the laser scanning step of the analysis.

3.2.3. PCR-Based Technologies

Speaker: Alexandra Muller-Scholz, Ph.D., Manager PCR & Microbiology, Sartorius
Talk Title: Rapid sterility of ATMPs Prior treatment - Validation of a qPCR-Based Test

Dr. Alexandra Muller-Scholz presented on the validation study of a PCR-based technology to rapidly assess the sterility of advanced therapy medicinal products (ATMPs). She proposed this method as an alternative to standard compendial growth-based methods that are not feasible for ATMPs with short shelf lives. The quantitative PCR-based method detects bacteria and fungi with high specificity, with results generated in a few hours. A highly specific Taqman probe is used to reduce false positives, and a fluorescently labeled inhibition control is used to reduce false negatives.

The method was validated for specificity, sensitivity, robustness, ruggedness and equivalence. To ensure high specificity, the acceptance criterion was set to < 3 nucleotide mismatches for primers and probes, which allowed for detection of 94.7 % of bacterial species and 37 % of fungal species (including all clinical and bioprocess relevant fungi). For sensitivity testing, the limit of detection (LOD) was checked with multiple compendial strains. LODs fell in a range between 2.5 CFU/mL and 99 CFU/mL. Here, Muller-Scholz asked if the sensitivity of this method is sufficient, when compendial methods claim to be able to detect down to 1 CFU/mL.

To validate robustness and ruggedness, the qPCR test was performed on various instruments with replicates detected positively in all cases. Muller-Scholz also mentioned that live/dead discrimination is a concern for qPCR-based technologies, and an initial centrifugation step can remove other DNA not from intact cells. She also described validation experiments to confirm that cell culture media that might be used in qPCR assays are DNA-free. Further, the method was validated to be able to detect bacterial and fungal DNA with high eukaryotic cell background (up to 25 million cells/mL).

Lastly, Muller-Scholz described comparability tests that were performed to ensure equivalence of the qPCR-based assays to traditional compendial sterility tests. For the 6 bacterial and 2 fungal species tested, nearly all replicates that were detected by the compendial culture method were also successfully detected positive by the qPCR assay.

3.2.4. Raman-Based Technologies

Speaker: Markus Lankers, Ph.D., Founder, mibic GmbH & Co. KG
Talk Title: Fast Automated Raman spectroscopic Detection and Identification of Microbial Contamination

Dr. Markus Lankers presented an automated Raman spectroscopy-based rapid method to detect and identify microbial contaminants. This method utilizes a single, automated instrument capable of conducting both fluorescent microscopy and Raman spectroscopy. The total time to result is typically between 90 minutes and 4 h, making it a promising alternative to time-consuming compendial culture methods.

Lankers gave an overview of the standard workflow, which involves isolation of microbes in samples via washing and dispensing, removal of the extracellular matrix, filtration, and tagging with fluorescent dyes and Raman labels. The microbes are deposited on a filter. The filter surface is subsequently scanned, and 500 to 1000 dark-field images are taken. Microbes in these images are automatically enumerated via image analysis. The images can also be taken in fluorescent mode if fluorescent dyes are added to assess viability. The instrument is equipped with artificial intelligence (AI) to select microbes for Raman spectroscopy. Selected microbes are run through a laser beam that provides a Raman spectrum. The spectra are reflective of vibrational frequencies of the molecules that collectively can serve as a unique fingerprint to help identify microbes. The AI, upon reading the collected spectra, is capable of discerning bacteria, yeast and fungi, and can classify bacteria down to the species and sub-species level. Peaks in Raman spectra can also be used to differentiate living and dead cells.

Due to the ease of use, quick time to results, and ability to identify a wide range of microbes with low false positive and false negative rates, Lankers promoted this technology as a promising rapid microbial detection method. However, he did point out certain challenges, such as the fact that lysing mammalian cells can lead to debris that interferes with measurements. He stressed the importance of efficient cleanup of samples prior to using this instrument.

3.2.5. Consortium Directions

Speaker: Scott Jackson, Ph.D., Leader, Complex Microbial Systems Group, Biosystems and Biomaterials Division, MML, NIST
Talk Title: Current Progress and Activities of the NIST RMTM Consortium

Dr. Scott Jackson provided an overview of the NIST Rapid Microbial Testing Methods Consortium, focusing on current work and future directions. Jackson reiterated the goal of the Consortium - to facilitate validation and adoption of RMTMs in regenerative medicine and advanced cell therapy by convening stakeholders in a pre-competitive space. He described how this goal is being met through three working groups.

A benefit of the Consortium is the ability to gather information from stakeholders. Jackson provided a summary of polling results from previous meetings, including polls where at least 50% of participants were hopeful that molecular-based rapid detection methods (including next-generation sequencing or qPCR) would be adopted in their industry. The development of best practices for method validation and fit-for-purpose reference materials were identified as priorities for the Consortium to work on.

In line with these stakeholder-identified priorities, Jackson outlined NIST's effort to enable expansion of certified values for commercially available whole-cell reference materials. As a starting point, NIST is evaluating lyophilized/dried *Escherichia coli* cells from Microbiologics, MilliporeSigma, and bioMérieux. These products are certified by the manufacturers for CFU only. Jackson stressed that reference materials certified for both CFU and genome copies are required to bridge the gap between compendial-based methods and rapid molecular methods. NIST previously demonstrated that laboratory-grown *E. coli* cultures labeled with a DNA-binding fluorescent probe had distinct subpopulations, where increasing levels of fluorescence correlated with increasing genomes per cell (e.g., 1, 2, 4 genomes per cell). To translate this method to commercial lyophilized materials, NIST conducted a feasibility study to assess commercial *E. coli* reference materials for compatibility with the flow cytometry-based method to quantify genome copy number. Some commercial materials were amenable to flow cytometry measurements, and others were not, primarily dependent on the cell concentration. The NIST team is working to investigate methods to quantify genome copy number for the six compendial organisms used for validation of sterility testing as identified by USP <71>.

Along with genome copy number, Jackson pointed out a variety of other properties that could be measured for commercial materials to support validation of RMTMs, including some properties that were discussed in previous talks in the workshop, such as Raman signature and ATP bioluminescence. He proposed a translational model where NIST's methods are handed off to manufacturers to implement in support of additional certified properties for their own materials.

Jackson also outlined NIST's next directions for the Consortium by discussing an upcoming interlaboratory study using commercial *E. coli* reference materials and commercial detection kits. Future work on compendial organisms will follow a similar process as was conducted for the *E. coli* materials with supporting interlaboratory studies.

3.2.6. Panel 2: Technologies and Tools for Rapid Microbial Detection

Jonathan Kallay, Felix Montero, Markus Lankers, Kevin Wheeler (AlloSource)

The second panel discussion was facilitated by Jackson, who posed questions to the speakers of Session 2 regarding their RMTM technologies. Slido was also used to gain input from attendees on current RMTM usage and reference material needs (Appendix D).

Questions from Jackson and the audience spurred a discussion around the current challenges in using rapid technologies. Lankers clarified that Raman signatures can be influenced by growth conditions. Jackson and Montero pointed out limitations of using flow cytometry measurements for genome copy enumeration - such as the limits of detection, restrictions on sample volume, and background interference. Kevin Wheeler was asked about the challenges he had in validating rapid methods as an end-user, and he emphasized that the largest issue was low or inconsistent extraction efficiencies across microbe types. He also mentioned that a drawback of rapid methods is that they have not yet been able to achieve as low of an LOD as compendial methods.

The process of validating rapid methods was also discussed. On the question of whether manufacturers should provide end-users with validation data, panelists agreed that while manufacturers can perform some pre-validation testing and provide baseline information like LOD, customers must have a good method transfer process and validate the technology for their samples. The use of reference materials in validation was also discussed by the panel, with guidance from Slido poll results. Interestingly, when queried on the importance of various types of microorganisms (compendial, environmental, or stressed) as reference materials, most attendees responded with answers higher than 5 (on a scale from 1 to 10 with 10 being the greatest importance) for all types of microorganisms, suggesting that all are considered important. The average weighted scores were relatively even at 7.2, 7.8, and 8.1 corresponding to stressed, environmental, and compendial organisms, respectively (**Fig. 5**). Panelists generally agreed with Slido poll results. Wheeler mentioned that the set of six compendial organisms were representative, and that the use of other organisms may require additional testing to ensure their detectability by rapid methods. Panelists also suggested that the use of stressed organisms common in environmental samples was important but difficult because of the lack of a representative stressed organism reference material.

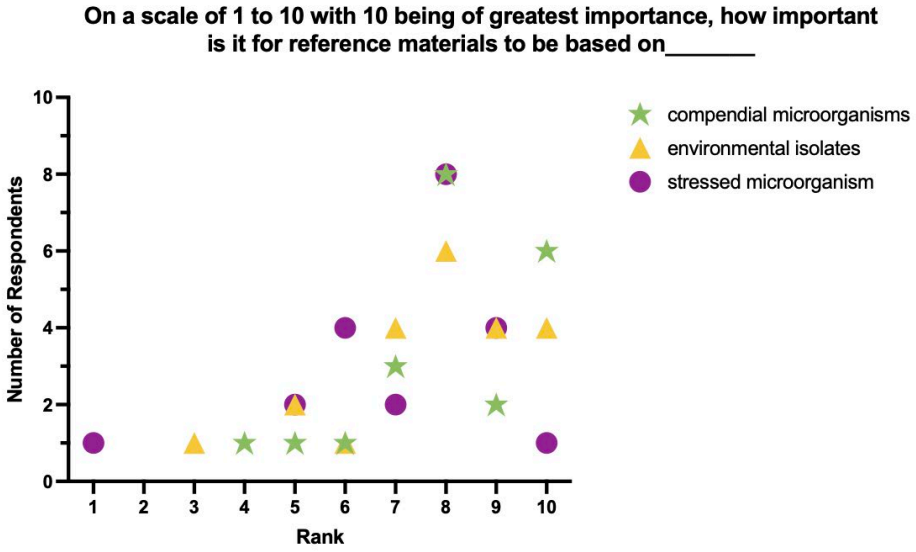

Fig. 5. Poll results on types of whole cell reference materials.
(n=22)

Polling was also used to ascertain current and future priorities of workshop attendees with respect to their level of implementation for various RMTMs (**Fig. 6**). PCR-based technologies had the highest implementation profile. Therefore, it is not surprising that a majority of responders (82%) cited PCR-based methods as the next technology in need of reference materials beyond what is already available (n=22, Appendix D). Jackson mentioned that this response was promising, as this need is being addressed by NIST's and the RMTM Consortium's current efforts. When asked about which properties, beyond total cell number and genome copy number, should be certified next for whole cell reference materials, the top answer was total viable cells (**Fig. 7**). Jackson mentioned that metabolic activity dyes and flow cytometry could potentially be used to measure total viable cells, with some assumptions and limitations. Demonstrated viability methods on

commercial microbial cell reference materials is a potential future direction for the RMTM Consortium.

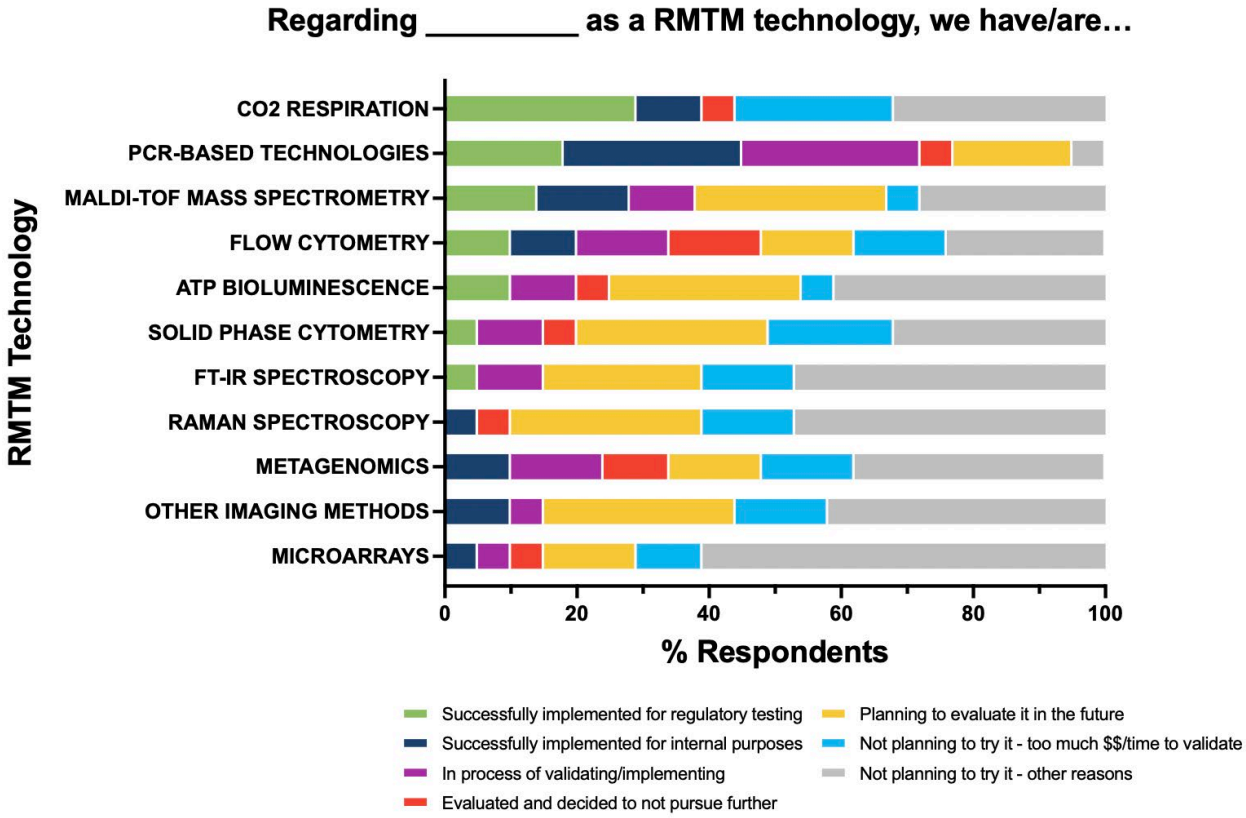

Fig. 6. Poll results on the various technologies and their usage.
(n= 21)

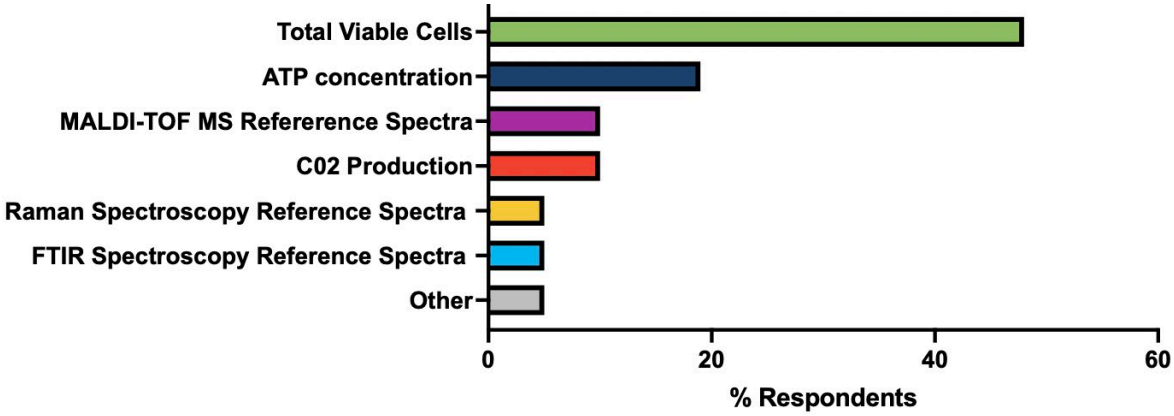

Fig. 7. Poll results on certified properties to add to microbial whole cell reference materials. The RMTM Consortium is currently working on approaches to add certified values for total cell number and total genome copies to existing microbial whole cell reference materials. In your opinion, which property should be prioritized next? (n = 21)

4. Conclusions and Future Directions

During manufacturing, cell therapies, gene therapies, and tissue-engineered products are susceptible to microbial contamination that can jeopardize patient safety. Implementing a microbial quality control strategy that includes sterility testing is critical for the successful development and manufacturing of safe and effective therapies. Current compendial methods for microbial testing are a significant bottleneck for timely product release. Implementation of RMTMs is one promising avenue to overcome this hurdle and deliver lifesaving therapies to patients.

The 2022 NIST RMTM Workshop convened subject matter experts across the regenerative medicine field including industry, academia, and government to synergize resources and provide a solution space for measurement challenges. This forum placed the adoption of RMTMs in context with current regulations, repurposed and emerging technologies, and ongoing challenges and opportunities.

The first session of the workshop focused on identifying barriers and solutions for the adoption of RMTMs. From this session, it was clear that the primary barrier to RMTM adoption was limited necessary resources: human, financial, and time. Each company must complete a rigorous validation process before implementing any new alternative method validation. Even with the available guidance documents from the USP, PDA, and European Pharmacopeia the resources required to conduct a method validation present a substantial cost for many regenerative medicine developers and may not be considered worth the investment. Yet, several prevailing myths and misconceptions that have contributed to the delay in adoption of RMTMs were addressed, including misunderstandings surrounding implementation costs, validation, and regulatory guidance/acceptance hurdles.

Several keys to successful RMTM implementation were identified, including finding a champion, getting support from management, sharing data, and seeking help. The RMTM Consortium could provide support in these key areas through fostering collaboration to avoid recreating and redoing studies that have already been performed, running interlaboratory studies that pool resources in a precompetitive space to generate data which could be used by regulators to support decision making on method robustness, and/or help drafting a consensus document to support method adoption.

RMTMs encompass a wide range of technologies with different strengths and limitations. The second session included several company representatives speaking on various RMTM methods and the technologies behind them. The methods presented are summarized in **Table 1**. Compared to the compendial methods, the turnaround time for initial results from these methods occurs within hours to a couple days (for the growth-based methods) rather than weeks. Interlaboratory studies and reference material development are needed to support RMTM validation and adoption. Since the RMTM technologies continue to evolve, specifying methods or protocols via documentary standards would not be appropriate.

Discussions on interlaboratory studies identified potential objectives for future studies. One such objective was evaluating the effect of different product matrices on RMTM performance. Data generated from across classes of matrices or detection technologies could be a valuable resource informing method selection and implementation. Another idea proposed to address the lack of

information on method comparability was to evaluate and compare RMTM technologies using compendial organisms to develop a dataset that demonstrated method strengths and weaknesses. Datasets from these interlaboratory studies would be published so all interested parties could benefit from their findings.

Participants highlighted the need for reference materials to support RMTM validation and suitability testing. Current microbial whole cell reference materials were developed for compendial methods and are quantified only for CFU. As such, they may not be fit for purpose for some RMTMs including PCR-based methods, which represent the most common class of RMTMs being evaluated (Fig. 6, Appendix D). Expanded characterization of existing reference materials to include properties relevant to RMTMs would support RMTM validation and comparison with compendial methods. Viable cell count (other than CFU) was prioritized as the next property (after total cell count and genome copy number, which are actively being worked on by the NIST-led RMTM Consortium) to certify for microbial whole cell reference materials. The Consortium is well positioned to contribute to advances in reference materials by leveraging existing commercially available reference materials and quantification methods under development at NIST.

In addition, workshop attendees expressed interest in reference materials that covered not only compendial organisms but also common environmental isolates and stressed organisms. While environmental testing will still be required by regulators, data on RMTM performance beyond compendial organisms could help inform decision-making on various technologies. The Consortium may also be able to support end users in understanding how to select and use microbial cell reference materials. This educational component could be achieved through various mechanisms, such as a guidance document or a workshop/webinar.

In summary, the workshop provided both internal and external stakeholders an opportunity to better understand emerging issues, trends, and strategies for adopting and implementing RMTMs. Challenges in RMTM validation and adoption still exist, even with significant resources currently available. The workshop identified multiple gaps where NIST and the RMTM Consortium could contribute, particularly as related to reference material characterization and interlaboratory studies. This information will inform planning and proposed deliverables for the Consortium Working Groups. In addition to the RMTM Consortium, other stakeholder groups are actively working to support adoption of RMTMs. Future Consortium activities could aim to collaborate with other ongoing efforts to combine resources and accelerate the adoption of RMTMs for advanced therapy products.

Appendix A. Workshop Agenda

WELCOME	
11:00 AM-11:15 AM	**Opening Remarks and Brief Overview of NIST RMTM Consortium** *Nancy Lin (NIST) and Sheng Lin-Gibson (NIST)*
Session 1: Barriers and Potential Solutions to Adoption of RMTMs Moderator: Nancy Lin	
11:15 AM-11:30 AM	**Topic: Regulatory Landscape** *Speaker: Margaret Riley, JD, Professor of Law, University of Virginia* *Talk Title: The Regulatory Context for Sterility Standards in Cell-Based Therapies*
11:30 AM-11:50 AM	**Topic: End User Case Study on Implementation of RMTMs** *Speaker: Anna Lau, Ph.D., Chief Sterility Testing Services, NIH Clinical Center* *Talk Title: Creating GMP in an Academic Research Setting and Clinical Hospital Environment – Challenges and Lessons Learned at the NIH*
11:50 AM-12:10 PM	**Topic: Barriers to Adoption of RMTMs** *Speaker: Michael Miller, Ph.D., President, Microbiology Consultants LLC* *Talk Title: Rapid Microbiological Methods: A Roadmap for Implementation*
12:10 PM-1:05 PM	**Panel 1: Barriers and Potential Solutions to Adoption of RMTMs** *Moderator: Nancy Lin* *Panelists: Margaret Riley, Anna Lau, Michael Miller, Sheng Lin-Gibson, and Judith Arcidiacono (FDA)*
BREAK 1:05 PM-1:15 PM	
Session 2: Technologies and Tools for Rapid Microbial Detection Moderator: Jason Kralj (NIST)	
1:15 PM-1:25 PM	**Topic: ATP-Based Technologies** *Speaker: Jonathan Kallay, Senior Technology and Marketing Manager, Charles River Laboratory* *Talk Title: Celsis ATP Bioluminescence: From Cell Culture to Sterility*
1:25 PM-1:35 PM	**Topic: CO2-Based Technologies** *Speaker: Felix Montero, Scientific Director-Health and Personal Care Business,* bioMérieux *Talk Title: CO2-Based Rapid Microbial Methods and their Use on Cell and Gene Therapy*
1:35 PM-1:45 PM	**Topic: Solid Phase Cytometry-Based Technologies** *Speaker: Felix Montero, Scientific Director-Health and Personal Care Business,* bioMérieux *Talk Title: Application of Solid Phase Cytometry for Rapid Microbial Testing for Advanced Therapy Products*
1:45 PM-1:55 PM	**Topic: PCR-Based Technologies** *Speaker: Alexandra Muller-Scholz, Manager PCR & Microbiology, Sartorius* *Talk Title: Rapid sterility of ATMPs Prior treatment - Validation of a qPCR-Based Test*
1:55 PM-2:05 PM	**Topic: Raman-Based Technologies** *Speaker: Markus Lankers, Founder, mibic GmbH & Co. KG* *Talk Title: Fast Automated Raman spectroscopic Detection and Identification of Microbial Contamination*
BREAK 2:05 PM-2:15 PM	
2:15 PM-2:35 PM	**Topic: Consortium Directions** *Speaker: Scott Jackson, NIST* *Talk Title: Current Progress and Activities of the NIST RMTM Consortium*
2:35 PM-3:25 PM	**Panel 2: Technologies and Tools for Rapid Microbial Detection** *Moderator: Scott Jackson* *Panelists: Jonathan Kallay, Felix Montero, Markus Lankers, Kevin Wheeler (AlloSource)*
CLOSING	
3:25 PM-3:30 PM	**Closing Remarks** *Scott Jackson and Nancy Lin*

Appendix B. List of Symbols, Abbreviations, and Acronyms

AI
Artificial intelligence

ATMP
Advanced therapy medicinal product

ATP
Adenosine triphosphate

CMO
Contract manufacturing organization

CRO
Contract research organization

CFU
Colony-forming unit

CFR
Code of Federal Regulations

cGMP
Current good manufacturing processes

EMA
European Medicines Agency

IND
Investigational new drug

FDA
Food and Drug Administration

ISAC
International Society for Advancement of Cytometry

ISO
International Organization for Standardization

PMDA
Pharmaceuticals and Medical Device Agency

NIH
National Institutes of Health

NIST
National Institute of Standards and Technology

PCR
Polymerase chain reaction

PDA
Parenteral Drug Association

qPCR
Quantitative polymerase chain reaction

R&D

Research and development

RM
Reference material

RMTM
Rapid microbial testing methods

SCB
Standards Coordinating Body for Regenerative Medicine

TGA
Therapeutic Goods Administration

USP
US Pharmacopeia

WG
Working group

Appendix C. Biographies for Speakers and Panelists

C.1. Judy Arcidiacono

Judy is the Lead for the Standards Development Program for Regenerative Medicine Therapies (RMT). She leads FDA's participation in ISO TC 276 and serves as a liaison to ASTM F04 Committee on Tissue Engineered Medical Products (TEMPs). She works closely with the National Institute for Standards and Technology (NIST) and the Standards Coordinating Body (SCB) to foster the development of standards that support innovation and product development in the RMT field.

In her position as an International Regulatory Expert, Judy is responsible for representing FDA/CBER/OTAT points of view in developing international regulatory policies and the development standards for regenerative medicine therapies. She serves as the secretariat for the International Pharmaceutical Regulators Forum (IPRP) Cell Therapy Working Group and Gene Therapy Working Group. She is also the co-chair of the Centers for Regulatory Excellence for Advanced Therapies at the APEC Regulatory Harmonization Center Steering Committee.

Judy has been at FDA for almost 32 years. For the first 18 years, she worked in the Division of Cell and Gene Therapy as a research/reviewer. In this role, she researched the human immunological response to xenotransplantation products and reviewed clinical trial applications for NK cell and T cell therapies and xenotransplantation products. Currently, Judy is the lead for policy development for xenotransplantation products.

C.2. Scott Jackson

Dr. Scott Jackson joined The National Institute of Standards and Technology (NIST) in May of 2014. At NIST, Dr. Jackson is currently the leader of the Complex Microbial Systems Group in the Biosystems and Biomaterials Division. In this current role, Dr. Jackson is leading international efforts to improve microbiome and metagenomic measurements by organizing inter-lab studies, developing reference materials and reference methods.

Prior to joining NIST in 2014, Dr. Jackson spent 11 years as a principal investigator at FDA where he developed advanced genomic tools for characterizing the global genomic diversity of enteric pathogens, with applications in food safety, bio-forensics, and public health.

Dr. Jackson completed his PhD research in biochemistry and biophysics at The University of Maryland and Johns Hopkins University where he focused on the evolution of mobile genetic elements. Dr. Jackson performed his undergraduate studies in Chemistry and Geology at the University of South Carolina.

C.3. Jonathan Kallay

Jonathan (Jon) Kallay is a Senior Technical & Market Development Manager working remotely for the Microbial Solutions product lines. He is a subject matter expert on microbiological

investigations for manufacturing facilities that make regulated products. Jon provides practical laboratory experience to help clients identify the optimal path forward for their labs.

Jon received his Bachelor's degree in biochemistry from Denison University before earning a post-graduate diploma in pharmaceutical microbiology from the University of Manchester.

C.4. Markus Lankers

Markus is one of the co-founders of MIBIC GmbH a company that develops rapid bacteria identification systems. Within MIBIC Markus is responsible for research and development of new spectroscopic methods for bacteria analysis. He has 25 years of experience in the field of particle identification. In 2002 he founded rap.ID Particle systems GmbH and served as Managing Director until the sale of the company in 2018. Prior to this position he worked as scientist in different development departments at Schering AG, Berlin, Germany.

Markus holds a diploma in Chemistry and a Ph.D. in Physical Chemistry from University of Würzburg. He is an active member of the Parenteral Drug Association (PDA). Since 2003 he helped to establish the Visual Inspection of Parenterals Interest Group in Europe as European interest group leader. He served as program cochair for PDA Visual Inspection Forum of Parenterals 2001-2018 in Europe and USA.

C.5. Anna Lau

Dr. Lau earned her PhD from the University of Sydney, Australia, where her research focused on the development of novel diagnostic platforms for invasive fungal diseases. In 2011, she joined the NIH to complete a fellowship in Clinical Microbiology in the Department of Laboratory Medicine. Following her fellowship, she joined the Clinical Microbiology Service as a Staff Scientist where she co-directed the Bacteriology, Specimen Processing, Parasitology, and Molecular Epidemiology sections. In 2018, Dr. Lau was promoted to Chief of the newly created Sterility Testing Service to support the NIH-wide cGMP aseptic processing and manufacturing of cellular therapy and drug pharmaceuticals for NIH clinical protocols.

Dr. Lau's translational research has focused on the development of rapid diagnostic platforms using molecular-based techniques and mass spectrometry. Her current research involves advancing testing platforms used in the biopharmaceutical setting whilst also meeting the Food and Drug Administration requirements for quality and patient safety. Her work is reflected in nearly 50 publications and book chapters, and she has been recognized with numerous awards to include eight NIH Clinical Center CEO and Director's awards, and the Forbes 30 Under 30 Award for Healthcare Science.

Dr. Lau serves on the Editorial board for the Journal of Clinical Microbiology; is a member of the American Society for Microbiology, the Parenteral Drug Association and the United States Pharmacopeia; and she chairs the NIH Environmental Monitoring Advisory Committee for cGMP. Dr. Lau is board certified through the American Board of Medical Microbiology.

C.6. Sheng Lin-Gibson

Dr. Sheng Lin-Gibson is the Chief of the NIST Biosystems and Biomaterials Division. She oversees a multidisciplinary research portfolio that includes regenerative medicine and advanced therapies, precision medicine, synthetic biology, and complex microbial systems. She leads and coordinates the development of global standards for emerging biotechnology, many of which support regenerative medicine and advanced therapy. She has coauthored over 80 peer-reviewed publications, serves on many Interagency Working Groups as well as numerous expert review panels and advisory boards. She has received two Department of Commerce Gold Medals.

C.7. Michael Miller

Dr. Michael J. Miller is an internationally recognized microbiologist and subject matter expert in pharmaceutical microbiology, contamination control and the validation and implementation of rapid microbiological methods (RMM). He is currently the President of Microbiology Consultants, LLC (http://microbiologyconsultants.com), and owner of http://rapidmicromethods.com, an educational website dedicated to the advancement of rapid microbiological methods within a variety of healthcare, pharmaceutical, consumer and related industry sectors.

For more than 30 years, he has held numerous R&D, manufacturing, quality, business development and executive leadership roles at Johnson & Johnson, Eli Lilly and Company and Bausch & Lomb. In his current role, Dr. Miller consults with multinational companies in providing technical, quality, regulatory and training solutions in support of rapid methods, sterile and non-sterile pharmaceutical manufacturing, contamination control and remediation, environmental monitoring, sterilization and laboratory operations.

Dr. Miller has authored more than 100 technical publications and presentations and is the editor of PDA's Encyclopedia of Rapid Microbiological Methods. He currently serves on the editorial and scientific review boards for American Pharmaceutical Review, European Pharmaceutical Review and the PDA Journal of Science and Technology. Dr, Miller serves as the chairperson for the revision.

C.8. Felix Montero

Felix is a Scientific Director of the Healthcare Business of bioMérieux. Felix has over 25 years of experience in industrial and clinical diagnostics and previously served as the Chemunex R&D Director in bioMérieux. Félix graduated from the Autonomous Metropolitan University in Mexico as Industrial Biochemistry Engineer and obtained a PhD in Immunology from the Aix Marseille II University in France. Felix is a member of different scientific organizations (PDA, ISAC) and served as an expert in a panel for the Development of Compendial Rapid Sterility Tests for the USP. Félix has been and continues to be extensively involved in the implementation and acceptance of rapid and alternative microbiological methods. He has authored more than 40 scientific publications in basic and applied immunology/microbiology and is an inventor on more than 6 patents on immune therapeutic approaches. He is a prominent speaker at congresses and conferences and a regular contributor to bioMérieux scientific whitepapers. Félix have extensive

technical experience includes development of in vitro diagnostic and research use reagents and applications, cell and tissue culture systems, microbiology, alternative and rapid microbiological methods, sterility testing, mycoplasma detection, compendia methods, methods for blood bank testing, cell and gene therapy process.

C.9. Alexander Muller Scholz

Alexandra holds a Master's degree in Biotechnology from the Technical University of Braunschweig (Germany, 2010) and a PhD in Live Science from the University of Hannover (Germany, 2014). Before her start in the current role as Manager PCR & Microbiology Applications, she began her career at Sartorius as PhD Student and later as scientist in the Microbiology Product Development Department within LPS being responsible for PCR related projects.

C.10. Margaret Riley

Margaret Foster Riley, Dorothy Danforth Compton Professor at the Miller Center, is professor of law at UVA Law School, professor of public health sciences at the UVA School of Medicine, and professor of public policy at the University's Frank Batten School of Leadership and Public Policy. A scholar working in the intersection of law, regulation, policy, and ethics in the Life Sciences, Riley has written and presented extensively about health care law, biomedical research, genetics, food and drug regulation, reproductive technologies, human and animal biotechnology, and public health. She is currently a member of the NIH NExTRAC, a FACA committee that advises the NIH Director on issues concerning emerging biotechnologies. Riley has advised numerous state and federal agencies, including the Food and Drug Administration; the Environment Protection Agency; the Department of Defense; committees of the National Institutes of Health, the National Science Foundation, and the National Academies of Science, Engineering and Medicine; the Virginia Department of Health; and the Virginia Bar.

C.11. Kevin Wheeler

Kevin currently is a Scientist in Quality and Research Microbiology at AlloSource. Kevin holds a Master of Science in Biology with special emphasis on microbial ecology and a Bachelor of Arts in Biology. He also is a National Registry Certified Microbiologist and Certified tissue bank specialist.

Appendix D. Audience Poll Responses

Opening Survey					
Poll Type	**Poll Question**	**Poll Option**	**Count**	**Total Votes**	**Results**
Multiple choice (Single answer)	What type of organization do you work for?	Academia	2	39	5%
Multiple choice (Single answer)	What type of organization do you work for?	Contract/testing laboratory	2	39	5%
Multiple choice (Single answer)	What type of organization do you work for?	Federal government	13	39	33%
Multiple choice (Single answer)	What type of organization do you work for?	Non-federal government (e.g., state, local, tribal, territorial)	0	39	0%
Multiple choice (Single answer)	What type of organization do you work for?	Industry	14	39	36%
Multiple choice (Single answer)	What type of organization do you work for?	Non-profit	7	39	18%
Multiple choice (Single answer)	What type of organization do you work for?	Other	1	39	3%
Multiple choice (Single answer)	What is your primary focus area related to today's workshop?	Advanced therapy producer	4	39	10%
Multiple choice (Single answer)	What is your primary focus area related to today's workshop?	Rapid microbial testing method producer	16	39	41%
Multiple choice (Single answer)	What is your primary focus area related to today's workshop?	Reference materials and standards producer	8	39	21%
Multiple choice (Single answer)	What is your primary focus area related to today's workshop?	Regulatory aspects	8	39	21%
Multiple choice (Single answer)	What is your primary focus area related to today's workshop?	Other	3	39	8%
Open Text	If you answered "other" to question 3, please elaborate here.	Testing laboratory	1	4	
Open Text	If you answered "other" to question 3, please elaborate here.	rapid method consumer.	1	4	
Open Text	If you answered "other" to question 3, please elaborate here.	Bioinformatics	1	4	
Open Text	If you answered "other" to question 3, please elaborate here.	NIIMBL - focus on advanced manufacturing technologies, including rapid microbial testing for biopharma	1	4	
Multiple choice (Single answer)	Are you familiar with the NIST RMTM Consortium and its activities?	Yes, I am a member.	12	39	31%
Multiple choice (Single answer)	Are you familiar with the NIST RMTM Consortium and its activities?	Yes, I am familiar with it (but not a member).	9	39	23%
Multiple choice (Single answer)	Are you familiar with the NIST RMTM Consortium and its activities?	I have heard a little bit about it.	7	39	18%
Multiple choice (Single answer)	Are you familiar with the NIST RMTM Consortium and its activities?	No, I only learned of it through this workshop.	11	39	28%
Open Text	What is your primary purpose in attending today's workshop?	To get a glimpse of all efforts in this area.	1	14	
Open Text	What is your primary purpose in attending today's workshop?	Educational and potential to aid the work I do	1	14	
Open Text	What is your primary purpose in attending today's workshop?	presenting	1	14	
Open Text	What is your primary purpose in attending today's workshop?	Recently started as Executive Director of SCB. Excited to learn more about RMTM.	1	14	

Open Text	What is your primary purpose in attending today's workshop?	to investigate the issues that occur when getting FDA approval using RMTM	1	14	
Open Text	What is your primary purpose in attending today's workshop?	to learn more about techniques used for the industry and how other companies are dealing with regulatory concerns	1	14	
Open Text	What is your primary purpose in attending today's workshop?	To gain more knowledge of RMTM needs and analytical techniques.	1	14	
Open Text	What is your primary purpose in attending today's workshop?	Learn more	1	14	
Open Text	What is your primary purpose in attending today's workshop?	To get knowledge about RMTM	1	14	
Open Text	What is your primary purpose in attending today's workshop?	Provide feedback on the validation and regulatory aspects of rapid microbial methods.	1	14	
Open Text	What is your primary purpose in attending today's workshop?	To know more about RMs and RMTMs from SMEs.	1	14	
Open Text	What is your primary purpose in attending today's workshop?	Learning	2	14	
Open Text	What is your primary purpose in attending today's workshop?	Understand current rapid micro methods for cell and gene therapy	1	14	
Panel 1					
Multiple choice (Single answer)	What is your required/preferred time-to-results for "rapid" tests?	6 h	5	21	24%
Multiple choice (Single answer)	What is your required/preferred time-to-results for "rapid" tests?	12 h	2	21	10%
Multiple choice (Single answer)	What is your required/preferred time-to-results for "rapid" tests?	24 h	7	21	33%
Multiple choice (Single answer)	What is your required/preferred time-to-results for "rapid" tests?	48 h	5	21	24%
Multiple choice (Single answer)	What is your required/preferred time-to-results for "rapid" tests?	7 d	1	21	5%
Multiple choice (Single answer)	What is your required/preferred time-to-results for "rapid" tests?	14 d	1	21	5%
Open Text	What is your primary challenge/bottleneck in the use of RMTMs?	heath authority acceptance	1	12	
Open Text	What is your primary challenge/bottleneck in the use of RMTMs?	We are a startup biotech company, so understanding which tests to start with is our first hurdle	1	12	
Open Text	What is your primary challenge/bottleneck in the use of RMTMs?	na	1	12	
Open Text	What is your primary challenge/bottleneck in the use of RMTMs?	Limit of detection. Spore specificity.	1	12	
Open Text	What is your primary challenge/bottleneck in the use of RMTMs?	sterile environment	1	12	
Open Text	What is your primary challenge/bottleneck in the use of RMTMs?	Time to result and safety of materials	1	12	

Open Text	What is your primary challenge/bottleneck in the use of RMTMs?	validation of the RMTM for numerous different test articles.	1	12	
Open Text	What is your primary challenge/bottleneck in the use of RMTMs?	will it detect any possible contaminant	1	12	
Open Text	What is your primary challenge/bottleneck in the use of RMTMs?	sensitivity	1	12	
Open Text	What is your primary challenge/bottleneck in the use of RMTMs?	Regulatory request to use compendial method	1	12	
Open Text	What is your primary challenge/bottleneck in the use of RMTMs?	Capacity for validation	2	12	
Multiple choice (Single answer)	Are suitable standards (e.g., reference materials, best practices, etc.) available for you to assess, validate, and adopt RMTMs?	yes	12	18	67%
Multiple choice (Single answer)	Are suitable standards (e.g., reference materials, best practices, etc.) available for you to assess, validate, and adopt RMTMs?	no	6	18	33%
Open Text	If you answered no to "Are suitable standards (e.g., reference materials, best practices, etc.) available", what is missing?	N/A	3	5	
Open Text	If you answered no to "Are suitable standards (e.g., reference materials, best practices, etc.) available", what is missing?	best practices	2	5	
Panel 2					
Rating (1-10)	On a scale of 1 to 10 with 10 being of greatest importance, how important is it for reference materials to be based on compendial microorganisms?	4	1	22	8.1
Rating (1-10)	On a scale of 1 to 10 with 10 being of greatest importance, how important is it for reference materials to be based on compendial microorganisms?	5	1	22	8.1
Rating (1-10)	On a scale of 1 to 10 with 10 being of greatest importance, how important is it for reference materials to be based on compendial microorganisms?	6	1	22	8.1
Rating (1-10)	On a scale of 1 to 10 with 10 being of greatest importance, how important is it for reference materials to be based on compendial microorganisms?	7	3	22	8.1
Rating (1-10)	On a scale of 1 to 10 with 10 being of greatest importance, how important is it for reference materials to be based on compendial microorganisms?	8	8	22	8.1
Rating (1-10)	On a scale of 1 to 10 with 10 being of greatest importance, how important is it for reference materials to be based on compendial microorganisms?	9	2	22	8.1
Rating (1-10)	On a scale of 1 to 10 with 10 being of greatest importance, how important is it for reference materials to be based on compendial microorganisms?	10	6	22	8.1
Rating (1-10)	On a scale of 1 to 10 with 10 being of greatest importance, how important is it to have reference materials consisting of representative environmental isolates?	3	1	22	7.8

Rating (1-10)	On a scale of 1 to 10 with 10 being of greatest importance, how important is it to have reference materials consisting of representative environmental isolates?	5	2	22	7.8
Rating (1-10)	On a scale of 1 to 10 with 10 being of greatest importance, how important is it to have reference materials consisting of representative environmental isolates?	6	1	22	7.8
Rating (1-10)	On a scale of 1 to 10 with 10 being of greatest importance, how important is it to have reference materials consisting of representative environmental isolates?	7	4	22	7.8
Rating (1-10)	On a scale of 1 to 10 with 10 being of greatest importance, how important is it to have reference materials consisting of representative environmental isolates?	8	6	22	7.8
Rating (1-10)	On a scale of 1 to 10 with 10 being of greatest importance, how important is it to have reference materials consisting of representative environmental isolates?	9	4	22	7.8
Rating (1-10)	On a scale of 1 to 10 with 10 being of greatest importance, how important is it to have reference materials consisting of representative environmental isolates?	10	4	22	7.8
Rating (1-10)	On a scale of 1 to 10 with 10 being of greatest importance, how important is it to have reference materials consisting of stressed microorganism	1	1	22	7.2
Rating (1-10)	On a scale of 1 to 10 with 10 being of greatest importance, how important is it to have reference materials consisting of stressed microorganism	5	2	22	7.2
Rating (1-10)	On a scale of 1 to 10 with 10 being of greatest importance, how important is it to have reference materials consisting of stressed microorganism	6	4	22	7.2
Rating (1-10)	On a scale of 1 to 10 with 10 being of greatest importance, how important is it to have reference materials consisting of stressed microorganism	7	2	22	7.2
Rating (1-10)	On a scale of 1 to 10 with 10 being of greatest importance, how important is it to have reference materials consisting of stressed microorganism	8	8	22	7.2
Rating (1-10)	On a scale of 1 to 10 with 10 being of greatest importance, how important is it to have reference materials consisting of stressed microorganism	9	4	22	7.2
Rating (1-10)	On a scale of 1 to 10 with 10 being of greatest importance, how important is it to have reference materials consisting of stressed microorganism	10	1	22	7.2
Multiple choice (Multiple answer)	Which methods are in greatest need of reference materials beyond what is currently available? (Pick 3)	CO2 detection/respiration	6	22	27%
Multiple choice (Multiple answer)	Which methods are in greatest need of reference materials beyond what is currently available? (Pick 3)	ATP detection	7	22	32%
Multiple choice (Multiple answer)	Which methods are in greatest need of reference materials beyond what is currently available? (Pick 3)	Solid phase cytometry	8	22	36%
Multiple choice (Multiple answer)	Which methods are in greatest need of reference materials beyond what is currently available? (Pick 3)	MALDI TOF/mass spectrometry	4	22	18%

Multiple choice (Multiple answer)	Which methods are in greatest need of reference materials beyond what is currently available? (Pick 3)	Fourier Transform–Infrared (FT-IR) Spectrometry	0	22	0%
Multiple choice (Multiple answer)	Which methods are in greatest need of reference materials beyond what is currently available? (Pick 3)	Raman spectrometry	1	22	5%
Multiple choice (Multiple answer)	Which methods are in greatest need of reference materials beyond what is currently available? (Pick 3)	PCR-based technologies	18	22	82%
Multiple choice (Multiple answer)	Which methods are in greatest need of reference materials beyond what is currently available? (Pick 3)	Metagenomics	5	22	23%
Multiple choice (Multiple answer)	Which methods are in greatest need of reference materials beyond what is currently available? (Pick 3)	Microarrays	0	22	0%
Multiple choice (Multiple answer)	Which methods are in greatest need of reference materials beyond what is currently available? (Pick 3)	Flow cytometry	7	22	32%
Multiple choice (Single answer)	Would microbial whole cell reference materials characterized for relevant properties help enable the validation and adoption of RMTM technologies?	Yes	15	22	68%
Multiple choice (Single answer)	Would microbial whole cell reference materials characterized for relevant properties help enable the validation and adoption of RMTM technologies?	No	1	22	5%
Multiple choice (Single answer)	Would microbial whole cell reference materials characterized for relevant properties help enable the validation and adoption of RMTM technologies?	Not sure	6	22	27%
Open Text	If whole cell reference materials are not beneficial, what other types of reference materials would be useful?	Equivalent material that is suitable for the method (e.g. genomic copies)	1	2	
Open Text	If whole cell reference materials are not beneficial, what other types of reference materials would be useful?	N/A	1	2	
Multiple choice (Single answer)	The RMTM Consortium is currently working on approaches to add certified values for total cell number and total genome copies to existing microbial whole cell reference materials. In your opinion, which property should be prioritized next?	CO2 production	2	21	10%
Multiple choice (Single answer)	The RMTM Consortium is currently working on approaches to add certified values for total cell number and total genome copies to existing microbial whole cell reference materials. In your opinion, which property should be prioritized next?	ATP concentration	4	21	19%
Multiple choice (Single answer)	The RMTM Consortium is currently working on approaches to add certified values for total cell number and total genome copies to existing microbial whole cell reference materials. In your opinion, which property should be prioritized next?	Total viable cells	10	21	48%
Multiple choice (Single answer)	The RMTM Consortium is currently working on approaches to add certified values for total cell number and total genome copies to existing microbial whole cell reference materials. In your	MALDI-TOF mass spectrometry reference spectra	2	21	10%

	opinion, which property should be prioritized next?				
Multiple choice (Single answer)	The RMTM Consortium is currently working on approaches to add certified values for total cell number and total genome copies to existing microbial whole cell reference materials. In your opinion, which property should be prioritized next?	Raman spectroscopy reference spectra	1	21	5%
Multiple choice (Single answer)	The RMTM Consortium is currently working on approaches to add certified values for total cell number and total genome copies to existing microbial whole cell reference materials. In your opinion, which property should be prioritized next?	FT-IR spectroscopy reference spectra	1	21	5%
Multiple choice (Single answer)	The RMTM Consortium is currently working on approaches to add certified values for total cell number and total genome copies to existing microbial whole cell reference materials. In your opinion, which property should be prioritized next?	Other	1	21	5%
Open Text	If you answered "other" to the above question, please elaborate here.	and CFU	1	2	
Open Text	If you answered "other" to the above question, please elaborate here.	metagenomics	1	2	
Multiple choice (Multiple answer)	Which factors are most critical when selecting a RMTM technology? (Pick 2)	Cost	5	22	23%
Multiple choice (Multiple answer)	Which factors are most critical when selecting a RMTM technology? (Pick 2)	Time to results	14	22	64%
Multiple choice (Multiple answer)	Which factors are most critical when selecting a RMTM technology? (Pick 2)	Availability of relevant standards and reference materials	3	22	14%
Multiple choice (Multiple answer)	Which factors are most critical when selecting a RMTM technology? (Pick 2)	Whether or not it is a compendial method	3	22	14%
Multiple choice (Multiple answer)	Which factors are most critical when selecting a RMTM technology? (Pick 2)	Ease of validation	13	22	59%
Multiple choice (Multiple answer)	Which factors are most critical when selecting a RMTM technology? (Pick 2)	Return on investment	4	22	18%
Open Text	Are there other factors (not listed above) that would affect the selection of a RMTM technology?	sensitivity	1	3	
Open Text	Are there other factors (not listed above) that would affect the selection of a RMTM technology?	Consistent performance and sensitivity.	1	3	
Open Text	Are there other factors (not listed above) that would affect the selection of a RMTM technology?	simplicity of test in a GMP environment	1	3	
Multiple choice (Single answer)	Regarding CO2 RESPIRATION as a RMTM technology, we have/are…	Successfully implemented for regulatory testing	6	21	29%

Multiple choice (Single answer)	Regarding CO2 RESPIRATION as a RMTM technology, we have/are…	Successfully implemented for internal purposes	2	21	10%
Multiple choice (Single answer)	Regarding CO2 RESPIRATION as a RMTM technology, we have/are…	In process of validating/implementing	0	21	0%
Multiple choice (Single answer)	Regarding CO2 RESPIRATION as a RMTM technology, we have/are…	Evaluated and decided to not pursue further	1	21	5%
Multiple choice (Single answer)	Regarding CO2 RESPIRATION as a RMTM technology, we have/are…	Planning to evaluate it in the future	0	21	0%
Multiple choice (Single answer)	Regarding CO2 RESPIRATION as a RMTM technology, we have/are…	Not planning to try it - too much $$/time to validate	5	21	24%
Multiple choice (Single answer)	Regarding CO2 RESPIRATION as a RMTM technology, we have/are…	Not planning to try it - other reasons	7	21	33%
Multiple choice (Single answer)	Regarding ATP BIOLUMINESCENCE as a RMTM technology, we have/are…	Successfully implemented for regulatory testing	2	21	10%
Multiple choice (Single answer)	Regarding ATP BIOLUMINESCENCE as a RMTM technology, we have/are…	Successfully implemented for internal purposes	0	21	0%
Multiple choice (Single answer)	Regarding ATP BIOLUMINESCENCE as a RMTM technology, we have/are…	In process of validating/implementing	2	21	10%
Multiple choice (Single answer)	Regarding ATP BIOLUMINESCENCE as a RMTM technology, we have/are…	Evaluated and decided to not pursue further	1	21	5%
Multiple choice (Single answer)	Regarding ATP BIOLUMINESCENCE as a RMTM technology, we have/are…	Planning to evaluate it in the future	6	21	29%
Multiple choice (Single answer)	Regarding ATP BIOLUMINESCENCE as a RMTM technology, we have/are…	Not planning to try it - too much $$/time to validate	1	21	5%
Multiple choice (Single answer)	Regarding ATP BIOLUMINESCENCE as a RMTM technology, we have/are…	Not planning to try it - other reasons	9	21	43%
Multiple choice (Single answer)	Regarding SOLID PHASE CYTOMETRY as a RMTM technology, we have/are…	Successfully implemented for regulatory testing	1	21	5%
Multiple choice (Single answer)	Regarding SOLID PHASE CYTOMETRY as a RMTM technology, we have/are…	Successfully implemented for internal purposes	0	21	0%
Multiple choice (Single answer)	Regarding SOLID PHASE CYTOMETRY as a RMTM technology, we have/are…	In process of validating/implementing	2	21	10%
Multiple choice (Single answer)	Regarding SOLID PHASE CYTOMETRY as a RMTM technology, we have/are…	Evaluated and decided to not pursue further	1	21	5%
Multiple choice (Single answer)	Regarding SOLID PHASE CYTOMETRY as a RMTM technology, we have/are…	Planning to evaluate it in the future	6	21	29%
Multiple choice (Single answer)	Regarding SOLID PHASE CYTOMETRY as a RMTM technology, we have/are…	Not planning to try it - too much $$/time to validate	4	21	19%
Multiple choice (Single answer)	Regarding SOLID PHASE CYTOMETRY as a RMTM technology, we have/are…	Not planning to try it - other reasons	7	21	33%
Multiple choice (Single answer)	Regarding MALDI-TOF MASS SPECTROMETRY as a RMTM technology, we have/are…	Successfully implemented for regulatory testing	3	21	14%
Multiple choice (Single answer)	Regarding MALDI-TOF MASS SPECTROMETRY as a RMTM technology, we have/are…	Successfully implemented for internal purposes	3	21	14%
Multiple choice (Single answer)	Regarding MALDI-TOF MASS SPECTROMETRY as a RMTM technology, we have/are…	In process of validating/implementing	2	21	10%
Multiple choice (Single answer)	Regarding MALDI-TOF MASS SPECTROMETRY as a RMTM technology, we have/are…	Evaluated and decided to not pursue further	0	21	0%

Multiple choice (Single answer)	Regarding MALDI-TOF MASS SPECTROMETRY as a RMTM technology, we have/are…	Planning to evaluate it in the future	6	21	29%
Multiple choice (Single answer)	Regarding MALDI-TOF MASS SPECTROMETRY as a RMTM technology, we have/are…	Not planning to try it - too much $$/time to validate	1	21	5%
Multiple choice (Single answer)	Regarding MALDI-TOF MASS SPECTROMETRY as a RMTM technology, we have/are…	Not planning to try it - other reasons	6	21	29%
Multiple choice (Single answer)	Regarding FT-IR SPECTROMETRY as a RMTM technology, we have/are…	Successfully implemented for regulatory testing	1	21	5%
Multiple choice (Single answer)	Regarding FT-IR SPECTROMETRY as a RMTM technology, we have/are…	Successfully implemented for internal purposes	0	21	0%
Multiple choice (Single answer)	Regarding FT-IR SPECTROMETRY as a RMTM technology, we have/are…	In process of validating/implementing	2	21	10%
Multiple choice (Single answer)	Regarding FT-IR SPECTROMETRY as a RMTM technology, we have/are…	Evaluated and decided to not pursue further	0	21	0%
Multiple choice (Single answer)	Regarding FT-IR SPECTROMETRY as a RMTM technology, we have/are…	Planning to evaluate it in the future	5	21	24%
Multiple choice (Single answer)	Regarding FT-IR SPECTROMETRY as a RMTM technology, we have/are…	Not planning to try it - too much $$/time to validate	3	21	14%
Multiple choice (Single answer)	Regarding FT-IR SPECTROMETRY as a RMTM technology, we have/are…	Not planning to try it - other reasons	10	21	48%
Multiple choice (Single answer)	Regarding RAMAN SPECTROMETRY as a RMTM technology, we have/are…	Successfully implemented for regulatory testing	0	21	0%
Multiple choice (Single answer)	Regarding RAMAN SPECTROMETRY as a RMTM technology, we have/are…	Successfully implemented for internal purposes	1	21	5%
Multiple choice (Single answer)	Regarding RAMAN SPECTROMETRY as a RMTM technology, we have/are…	In process of validating/implementing	0	21	0%
Multiple choice (Single answer)	Regarding RAMAN SPECTROMETRY as a RMTM technology, we have/are…	Evaluated and decided to not pursue further	1	21	5%
Multiple choice (Single answer)	Regarding RAMAN SPECTROMETRY as a RMTM technology, we have/are…	Planning to evaluate it in the future	6	21	29%
Multiple choice (Single answer)	Regarding RAMAN SPECTROMETRY as a RMTM technology, we have/are…	Not planning to try it - too much $$/time to validate	3	21	14%
Multiple choice (Single answer)	Regarding RAMAN SPECTROMETRY as a RMTM technology, we have/are…	Not planning to try it - other reasons	10	21	48%
Multiple choice (Single answer)	Regarding PCR-BASED TECHNOLOGIES as a RMTM technology, we have/are…	Successfully implemented for regulatory testing	4	22	18%
Multiple choice (Single answer)	Regarding PCR-BASED TECHNOLOGIES as a RMTM technology, we have/are…	Successfully implemented for internal purposes	6	22	27%
Multiple choice (Single answer)	Regarding PCR-BASED TECHNOLOGIES as a RMTM technology, we have/are…	In process of validating/implementing	6	22	27%
Multiple choice (Single answer)	Regarding PCR-BASED TECHNOLOGIES as a RMTM technology, we have/are…	Evaluated and decided to not pursue further	1	22	5%
Multiple choice (Single answer)	Regarding PCR-BASED TECHNOLOGIES as a RMTM technology, we have/are…	Planning to evaluate it in the future	4	22	18%
Multiple choice (Single answer)	Regarding PCR-BASED TECHNOLOGIES as a RMTM technology, we have/are…	Not planning to try it - too much $$/time to validate	0	22	0%
Multiple choice (Single answer)	Regarding PCR-BASED TECHNOLOGIES as a RMTM technology, we have/are…	Not planning to try it - other reasons	1	22	5%

Multiple choice (Single answer)	Regarding METAGENOMICS as a RMTM technology, we have/are…	Successfully implemented for regulatory testing	0	21	0%
Multiple choice (Single answer)	Regarding METAGENOMICS as a RMTM technology, we have/are…	Successfully implemented for internal purposes	2	21	10%
Multiple choice (Single answer)	Regarding METAGENOMICS as a RMTM technology, we have/are…	In process of validating/implementing	3	21	14%
Multiple choice (Single answer)	Regarding METAGENOMICS as a RMTM technology, we have/are…	Evaluated and decided to not pursue further	2	21	10%
Multiple choice (Single answer)	Regarding METAGENOMICS as a RMTM technology, we have/are…	Planning to evaluate it in the future	3	21	14%
Multiple choice (Single answer)	Regarding METAGENOMICS as a RMTM technology, we have/are…	Not planning to try it - too much $$/time to validate	3	21	14%
Multiple choice (Single answer)	Regarding METAGENOMICS as a RMTM technology, we have/are…	Not planning to try it - other reasons	8	21	38%
Multiple choice (Single answer)	Regarding MICROARRAYS as a RMTM technology, we have/are…	Successfully implemented for regulatory testing	0	21	0%
Multiple choice (Single answer)	Regarding MICROARRAYS as a RMTM technology, we have/are…	Successfully implemented for internal purposes	1	21	5%
Multiple choice (Single answer)	Regarding MICROARRAYS as a RMTM technology, we have/are…	In process of validating/implementing	1	21	5%
Multiple choice (Single answer)	Regarding MICROARRAYS as a RMTM technology, we have/are…	Evaluated and decided to not pursue further	1	21	5%
Multiple choice (Single answer)	Regarding MICROARRAYS as a RMTM technology, we have/are…	Planning to evaluate it in the future	3	21	14%
Multiple choice (Single answer)	Regarding MICROARRAYS as a RMTM technology, we have/are…	Not planning to try it - too much $$/time to validate	2	21	10%
Multiple choice (Single answer)	Regarding MICROARRAYS as a RMTM technology, we have/are…	Not planning to try it - other reasons	13	21	62%
Multiple choice (Single answer)	Regarding FLOW CYTOMETRY as a RMTM technology, we have/are…	Successfully implemented for regulatory testing	2	21	10%
Multiple choice (Single answer)	Regarding FLOW CYTOMETRY as a RMTM technology, we have/are…	Successfully implemented for internal purposes	2	21	10%
Multiple choice (Single answer)	Regarding FLOW CYTOMETRY as a RMTM technology, we have/are…	In process of validating/implementing	3	21	14%
Multiple choice (Single answer)	Regarding FLOW CYTOMETRY as a RMTM technology, we have/are…	Evaluated and decided to not pursue further	3	21	14%
Multiple choice (Single answer)	Regarding FLOW CYTOMETRY as a RMTM technology, we have/are…	Planning to evaluate it in the future	3	21	14%
Multiple choice (Single answer)	Regarding FLOW CYTOMETRY as a RMTM technology, we have/are…	Not planning to try it - too much $$/time to validate	3	21	14%
Multiple choice (Single answer)	Regarding FLOW CYTOMETRY as a RMTM technology, we have/are…	Not planning to try it - other reasons	5	21	24%
Multiple choice (Single answer)	Regarding OTHER IMAGING METHODS as a RMTM technology, we have/are…	Successfully implemented for regulatory testing	0	21	0%
Multiple choice (Single answer)	Regarding OTHER IMAGING METHODS as a RMTM technology, we have/are…	Successfully implemented for internal purposes	2	21	10%
Multiple choice (Single answer)	Regarding OTHER IMAGING METHODS as a RMTM technology, we have/are…	In process of validating/implementing	1	21	5%
Multiple choice (Single answer)	Regarding OTHER IMAGING METHODS as a RMTM technology, we have/are…	Evaluated and decided to not pursue further	0	21	0%

Multiple choice (Single answer)	Regarding OTHER IMAGING METHODS as a RMTM technology, we have/are…	Planning to evaluate it in the future	6	21	29%
Multiple choice (Single answer)	Regarding OTHER IMAGING METHODS as a RMTM technology, we have/are…	Not planning to try it - too much $$/time to validate	3	21	14%
Multiple choice (Single answer)	Regarding OTHER IMAGING METHODS as a RMTM technology, we have/are…	Not planning to try it - other reasons	9	21	43%