An Overview on

PDA Technical Report No. 33

EVALUATION, VALIDATION AND IMPLEMENTATION OF ALTERNATIVE AND RAPID MICROBIAL METHODS

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PIONEERING DIAGNOSTICS

BIOMÉRIEUX

- What are Alternative and Rapid Microbiological Methods?
- History of TR33
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What are Alternative and Rapid Microbiological Methods?

Alternative or Rapid Microbiological Method (RMM):

A novel, modern and/or fast microbiological testing method that is different from a classical or traditional growth-based method, such as agar-plate counting or recovery in liquid broth media.

The alternative or rapid method may utilize instrumentation and software to manage the testing and resulting data, and may provide quantitative, qualitative and/or microbial identification test results.

Automated technologies that utilize classical growth-based methods may also be designated as being novel, modern or rapid, based on their scientific principle and approach to microbial detection.

- TR33 Glossary

History of PDA TR33

Why TR33? What was the purpose?

TR33 is intended to provide guidance for the successful evaluation, validation, and implementation of alternative and rapid microbiological methods.

Applications for these methods include but are not limited to Microbial Limit Testing, Sterility Testing, Antimicrobial Effectiveness Testing, Microbiological Monitoring of Clean Rooms and Other Controlled Environments, Water for Pharmaceutical Purposes Monitoring, Microbial Characterization and Identification, and microbiological in-process control testing.

- TR33 Introduction

History of PDA TR33

Why PDA TR33? What was the purpose?

The majority of microbial testing performed today relies on century-old, conventional methods based on the recovery and growth of microorganisms using solid or liquid microbiological growth media.

In spite of the limitations of classical culture methods, acceptance of alternative and potentially superior methods has only started to gain momentum within the pharmaceutical, biotechnology and medical device industries.

We believe this continues to be due in part to a lack of clear guidance regarding the demonstration of their equivalence to existing methods acceptable to regulatory agencies and validation of the equipment associated with the alternative methods.

The original PDA Technical Report No. 33 was published in 2002.

- TR33 Introduction

History of PDA TR33

Why PDA TR33? What was the purpose?

USP General Information Chapter <1223> Validation of Alternative Microbiological Methods, and Ph. Eur. Informational Chapter 5.1.6 Alternative Methods for Control of Microbiological Quality, provide guidance on the steps needed to validate an alternative microbiological method.

However, additional [*and updated*] guidance is needed, as an understandable and holistic approach to the qualification and implementation of novel alternate microbiological methods, including rapid microbiological methods, still does not exist that would satisfy all regulatory agencies.

This Technical Report is intended to provide a comprehensive approach to the introduction of alternative microbiology methods in a government-regulated environment.

It is anticipated that by providing agreed upon performance standards, the development, qualification and implementation of alternative microbiological methods will be greatly accelerated.

- TR33 Introduction

TR33 Team

Task Force Leader

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Authors

- John Albright, bioMérieux, Inc.
- Claude Anger, CBA MicroEnterprises
- Dilip Ashtekar, Ph.D, Consultant
- Peter Ball, Ph.D., Pall Life Sciences
- Joseph Chen, Ph.D., Genentech Inc.
- Steve Douglas, Hospira, Inc.
- William Fleming, III., Ph.D., DosDocs Company, LP
- Ren-Yo Forng, Ph.D., MedImmune, LLC
- Gary Gressett, Excellent Pharma Consulting
- Jianping Jiang, Instant BioScan, Inc.
- Robert Johnson, Ph.D., Dialogue
- David Jones, Ph.D. Rapid Micro Biosystems
- Richard Levy, Ph.D., PDA
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- Patrick McCarthy, Millipore Corporation
- Patrick McCormick, Ph.D., Bausch & Lomb, Inc.
- Jeanne Moldenhauer, Excellent Pharma Consulting
- Paul Newby, Ph.D., GlaxoSmithKline
- Bryan Riley, Ph.D. US Food and Drug Administration
- Miriam S. Rozo, Johnson & Johnson
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- Elizabeth Young, formerly Baxter Healthcare, Inc.
- Pascal Yvon, formally AES–Chemunex, Inc.

Contributor

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Contents of PDA TR33

- **Scope and Purpose**
- **Classical Microbiology Methods** [*Deficiencies*]
- **Regulatory Perspectives, including US, EU, Japan, Australia**
- **Points to Consider on Evaluating RMMs, including:**
  - Business, Economic, Quality and Technical Considerations
  - Recommendations on how to Evaluate Vendors
- **A Technological Review, including information on the various RMMs available:**
  - Growth-based, Viability-based, Cellular Component-based, Optical Spectroscopy, Nucleic Acid Amplification, Micro-Electro-Mechanical Systems (MEMS), and Other Technologies
- **The Validation Process**
  - Pre-Validation Activities
  - Validation of Equipment, Software, and Method
  - Establishment of Method Validation Criteria
  - Suitability Testing
  - Variability of Microbiological Methods
- **Implementation**
  - Transfer of the RMM, IQ/OQ/PQ

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Summary of Recommended Validation Testing

Validation Criteria	Quantitative Method	Qualitative Method
Accuracy	Yes	No
Precision	Yes	No
Specificity	Yes	Yes
Limit of Detection	Yes	Yes
Limit of Quantification	Yes	No
Linearity	Yes	No
Range	Yes	No
Ruggedness	Yes	Yes
Robustness	Yes	Yes
Equivalence/Comparative Testing	Yes	Yes

- TR33 Table 5.3-1 Method Validation Criteria

Using TR33

- **Can I use an RMM for my product?**
  - Yes
- **How do I know that?**
  - Other products and companies use RMMs.
- **Will FDA and other Regulatory Agencies accept RMMs?**
  - Yes. They've repeatedly said so. And see point 2.
- **What does FDA and the other Regulatory Agencies want?**
  - Proof that it works.
- **What kind of proof?**
  - TR33 outlines the recommended testing.

Panel Discussion

Daniel Achina	**Lonza**
Erin Patton	**Charles River Laboratories**
Julie Sperry	**Rapid Microbio**