Rapid Microbiological Methods: Overcoming the "Barriers"

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Barriers to Rapid Microbiological Methods (RMM)

- In reality, there are NO barriers!
- However, there are perceptions that rapid methods cannot be validated or implemented, due to . . .
  - Lack of knowledge (e.g., QA/QC, manufacturing, regulatory)
  - Not being visible or important to senior management
  - No commitment to change, unless forced to do so
- Let's discuss the most prevalent "perceived barriers"

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"RMMs are not accepted by regulatory authorities."

- **Yes, they are.**
- FDA, EMA, TGA, PMDA, others around the world
- Many validation and implementation approvals
- Regulatory policy changes encourage RMM use, especially for ATMPs in the US and EU

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"RMMs cannot replace compendial assays."

- **Yes, they have.**
- Currently, RMMs are alternatives to compendial testing and usually require regulatory approvals
- Numerous authorities have approved RMMs to replace compendial sterility and bioburden tests
- Firms have provided robust validation protocols and data to support equivalence/non-inferiority

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"There is no guidance on validating RMMs."

- **Of course, there is!**
- PDA Technical Report #33, *Evaluation, Validation and Implementation of New Microbiological Testing Methods* (new revision in the works)
- USP <1223>, *Validation of alternative microbiological methods*
- Ph. Eur. 5.1.6, *Alternative methods for control of microbiological quality*

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"RMMs do not provide a return on investment."

- **Yes, they can; some large and some small.**
- Return on investment (ROI) should not be the most important factor in implementing a RMM
  - e.g., faster results, medical need, short shelf-life of product
- Perform a ROI calculation to determine if the cost savings outweigh the initial investment (e.g., capital expense, validation)

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"You cannot change acceptance levels or the signal (cfu)."

- **Yes, you can, when supported with data**
- e.g., correlate existing CFU data with an alternative signal (e.g., fluorescent count)
- Revision to Annex 1 specifically allows this
  - *"Manufacture of Sterile Medicinal Products"* of the EU Guideline for good manufacturing practice for drug products and drug substances

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Revision to EU Annex 1

- Quality Control section:
- For products with short shelf life, the environmental data for the time of manufacture may not be available; in these cases, the certification should include a review of the most recent available data. Manufacturers of these products should consider the use of rapid monitoring systems.
- Where rapid and automated microbial methods are used for general manufacturing purposes, these methods should be validated for the product(s) or processes concerned.

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Revision to Annex 1: Limits During Manufacturing

Note 1: It should be noted that the types of monitoring methods listed in the table above are examples and other methods can be used provided they meet the intent of providing information across the whole of the critical process where product may be contaminated (e.g. aseptic line set-up, filling and lyophilizer loading).

Note 2: Limits are applied using cfu throughout the document. If different or new technologies are used that present results in a manner different from cfu, the manufacturer should scientifically justify the limits applied and where possible correlate them to cfu.

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The Need for Rapid Methods

- Advanced therapy medicinal products
  - ATMPs, cell and gene therapies
- COVID-19 vaccines
- Sterile compounded products
- PET drugs

- Current regulatory policy encourage RMMs . . .

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2020 FDA Final Guidance on Gene Therapy for INDs

- The compendial sterility test may not be suitable for products with a limited shelf life or immediate need
- Examples of alternative methods include:
  - Rapid sterility, mycoplasma (including PCR-based tests) and endotoxin tests
- For these non-compendial tests we recommend that you qualify/validate them to ensure they are fit for their intended use

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2018 EU Guidelines for ATMP

- The sterility test may not be appropriate due to the scarcity of materials available, short shelf-life or medical need
- Validated RMMs may be considered when method suitability for the product has been demonstrated

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Ph. Eur. 2.6.27, *Microbiological Examination of Cell-Based Preparations*

- Discusses limitations of the compendial sterility test (shelf-life and availability of product)
- Can use automated growth-based methods or alternative methods
- Allows sterility testing of 1% of the total batch
- If testing the final product is not possible, surrogate samples, such as liquids last in contact with cells being processed, may be analyzed

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USP <1071>, *Rapid Microbial Tests for Release of Sterile Short-Life Products: A Risk-Based Approach*

- Provides guidance when the compendial sterility test is unsuitable for product release due to short shelf-life or immediate need
- Allows for a 1% total batch size sampling plan
- Also refers to CFR 610.12, where one could test an in-process sample when it is not possible to test the finished product

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A Strategy for Implementation

- Understand available RMM technologies
- Match a RMM technology with your user requirements
  - e.g., time to result, level of sensitivity, types of organisms to be detected
- Develop and execute the validation plan
  - Includes statistical analyses of the data

Example: Validation of Rapid Sterility Tests

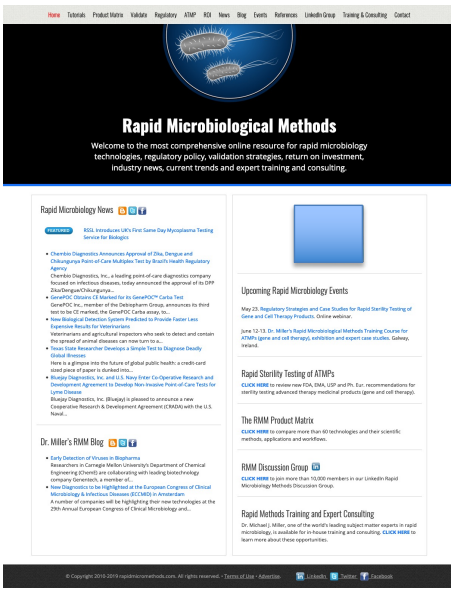
- Specificity
  - Relevant panel of microorganisms; e.g., slow growers and stressed organisms for growth-based systems
- Limit of detection
  - e.g., single cell level
- Method suitability
  - No false positives or false negatives with the test sample
- Equivalence/non-inferiority to compendial sterility test

Summary

- Regulatory policies and compendial chapters have been revised to meet the needs of rapid testing requirements
  - New medicines with an immediate medical need
  - Short shelf-life
  - Challenges with conventional, compendial assays
- Many companies have utilized these changes to validate RMMs and gain regulatory approval for routine use
- There are NO barriers!

For More Info on Rapid Methods

- rapidmicromethods.com
- Validation strategies
- Regulatory overviews
- Technology tutorials
- Extensive reference list
- Product comparison matrix
- Current news articles



Thank you!

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