Alternative / Rapid Microbiological Methods

RMM

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Scope

• Introduction
• The Myths
• Considerations
• Validation
• Current Situation
Introduction

- RMM is a unifying term that covers a wide range of detection technologies.

- The different technologies can be grouped in three types:
  - Growth based
  - Direct measurement
  - Cell components analysis

Each of these technologies have their own advantages and limitations and all need of specialist microbiological knowledge for their implementation
• Growth Based Methods

Early Detection of Growth:
• Electrochemical Methods
• Measurement of gas
• Bioluminescence
• Microcalorimetry
• Turbidimetry
Introduction

• Direct Measurement
  • Solid Phase Cytometry
  • Flow Cytometry
  • Direct Epifluorescence Filtration Technique (DEFT)
Introduction

• Cell Component Analysis

Phenotypic & Genotypic Identification

• Phenotypic & genotypic systems are widely used within laboratories
  ▪ Biochemical reaction (API kits)
  ▪ DNA replication techniques

  *PCR (Polymerase Chain Reaction)*; Single cell detection through presence of DNA, results in around one hour (+).
Introduction – Why

• Conventional methods typically slow, between 5 – 14 days incubation
• Corrective actions – Reactive to historical data
• RMM Enable a proactive approach
• RMM Enable quicker response to out of specification / out of trend results
• Real time / near real time results
• Earlier corrective actions
The Myths

• Regulators do not support introduction of Alternative / Rapid micro methods
  ✔ IMB and other agencies actively encourage introduction of such methods
  ✔ Openly discuss various methods with vendors / manufacturers
  ✔ IMB encourages meetings with manufacturers looking to introduce an alternative / rapid micro method
The Myths

- Rapid Micro methods will never fully replace finished product testing

✓ Already happening
The Myths

- Rapid Micro methods will result in changes to specifications/acceptance levels

✓ Some RMMs, especially those that do not rely on growth, may provide a higher recovery count as compared with traditional methods. Can correlate the new measurements, such as a fluorescing unit, with the old measurement (i.e., colony forming units) and establish new acceptance levels.
• Rapid Micro methods will solve all contamination issues

✓ Not necessarily true.
BUT: Rapid methods can support a comprehensive contamination control program, and when contamination arises, RMMs can be used as investigative tools. Better than waiting days or weeks for micro results.
3 major types of microbiological methods

1. Qualitative
2. Quantitative
3. Identification

Consider what it is you want to achieve and what you need to utilise the method for
Considerations

• Applicability

Information should be scientifically justified and limitations not as severe as conventional Method

• The RMM technology to be used in each case will be limited by the type of test. Not all technologies can be used for all determinations.

• The validation requirements will also be different depending on the type of test.
Considerations

• Use of RMM

Different types of microbiological tests are performed during manufacture of a pharmaceutical product:
- Raw material bioburden
- Pre-filtration bioburden
- Microbial purity
- Sterility
- Utility monitoring (ie: process water, compressed gas)
- Environmental monitoring (ie: air, surfaces, personnel)
- Others

• Any of these tests could be replaced by a RMM.
Considerations

• Risk – Benefit analysis
  - Defined purpose for the test method
  - Define the type and depth of information required
  - Limitations of the conventional method

Comparative risk-benefit analysis
Conventional Vs Alternative method
Considerations

• Validation

  • Ph.Eur. 5.1.6 – Alternative methods for control of microbial quality
  • Satisfactory completion of DQ, IQ and OQ including compliance with Annex 11 should be confirmed
  • Comparative study against Pharmacopoeial method

  Any alternative method must be proven to be, at least, equivalent to the method described in the Pharmacopoeia
Considerations

• Validation

• The validation of the RMM should include:

  • The evaluation of metabolically and physically injured cells, starved cells and spores, where applicable

  • Cells grown under ideal and adverse conditions to determine any differences

  • Environmental isolates

The results should be compared against the compendial method
Considerations

• Non Destructive – id of isolates

• Site flora diversity Vs those qualified

• Detection of ‘new’ or stressed flora

• Potential Interference
  • Product
  • Background
Considerations

• False Negative or Positive results

• Assess ‘new’ test process for potential issues. E.g.
  • Impact of machine hotspots on media fertility?
  • Machine/instrument breakdown and impact to test samples?

• Microbiologist variation
Considerations

- Result Handling
  - Beware of data overload
    - Understand what you want from the data.
    - Understand what the method data is telling you.
  - Higher Counts Observed
    - A problem with the process?
    - Increased sensitivity of methods?
    - Assess the data
Current Situation

- Qualitative
  - Growth Based Methods

- Quantitative
  - Direct Methods

- Identification
  - Cell Component Methods

Not so Widespread

Widespread
Current Situation

- Large number of companies utilising rapid ID techniques

- Quantitative techniques routinely used in Biological processes IPC
  - E.g. cell viability tests

- Slow uptake on other test types

- Mainly growth based methods
  - water testing
Current Situation

• Very limited number of RMM applications

• Several vendors have presented their technologies to the IMB.

• Encourage manufacturers considering use of RMM to approach IMB for meeting with Inspectors and Assessors
In Summary

• European Pharmacopeia Chapter 5.1.6 provides detailed guidance.

• IMB welcomes their adoption and encourages company’s to engage with IMB on them

• The IMB do not endorse or certify any vendor or their technology whether or not the vendor has approached the IMB.

• The responsibility for the applicability and adequacy of the method remains with the testing laboratory/manufacturing site.
Thank You for Listening

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