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Alternative / Rapid Microbiological Methods

RMM

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Scope

- Introduction
- The Myths
- Considerations
- Validation
- Current Situation

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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

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Introduction

- Growth Based Methods

Early Detection of Growth:

- Electrochemical Methods
- Measurement of gas
- Bioluminescence
- Microcalorimetery
- Turbidimetry

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Introduction

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

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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(+).

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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

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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

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The Myths

- Rapid Micro methods will never fully replace finished product testing

✓ Already happening

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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.

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The Myths

- 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.

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Considerations

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

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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.

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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.

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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

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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

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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

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Considerations

- Non Destructive – id of isolates
- Site flora diversity Vs those qualified
- Detection of ‘new’ or stressed flora
- Potential Interference
  - Product
  - Background

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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

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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

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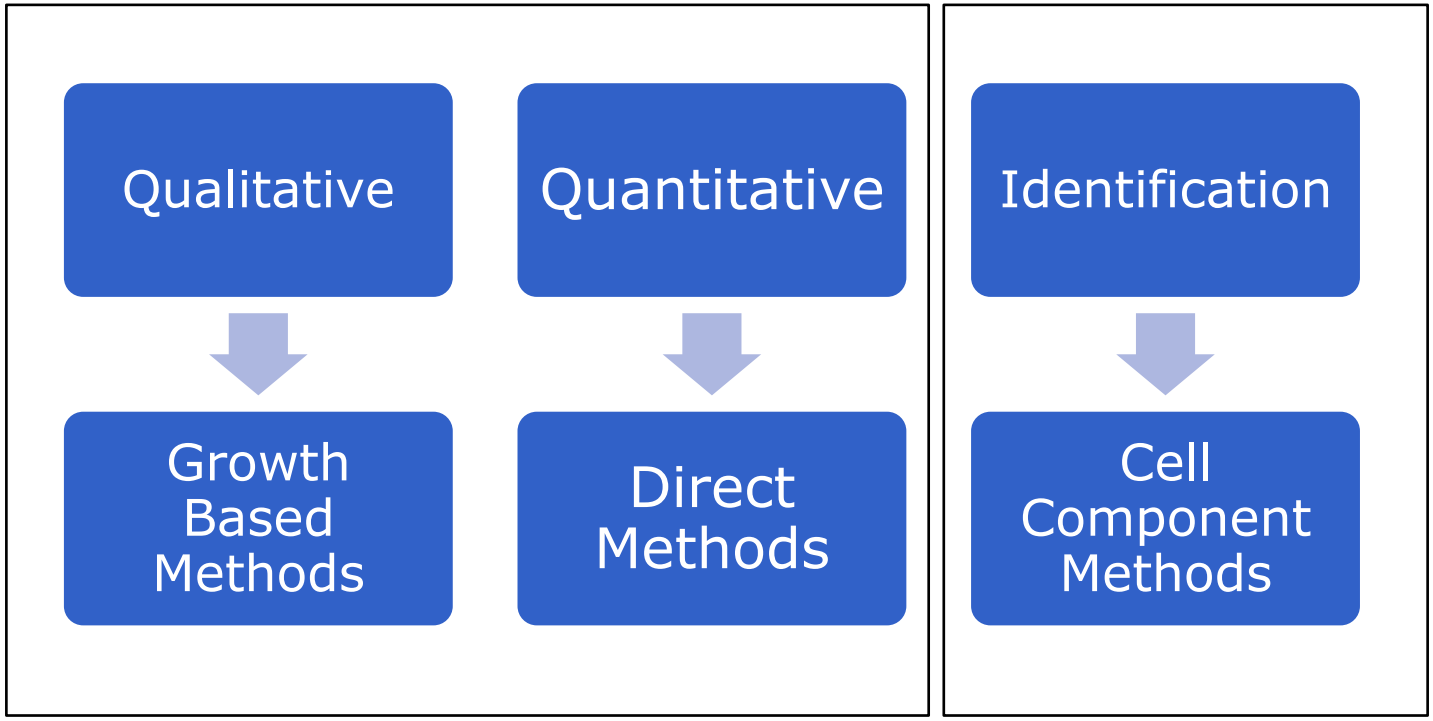
Current Situation



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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

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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

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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.

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Thank You for Listening

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