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## **A Laboratory Perspective on Issues and Barriers to the Implementation of Rapid Microbiological Methods**

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- Importance of having Rapid Microbiological Methods (RMM)
- Obstacles in using new RMM in production environment
- Regulatory approval/recognition

- Time consuming
- Does not allow in-process checks
- Only culturable cells are counted
- Detection and counting are often separate

?????

Can we devise a better way to identify the presence of viable cells?

- Increased speed
- Increased sensitivity
- Potential for in-line testing
- Reduced in-process test time
- Reduced potential for batch rejection and re-work

- Conservative nature of the industry - Reluctance to move from compendial methods
- Uncertainty about the acceptance by the regulators
- QA standards are developed for older technologies.
- Little international harmonization

- Application of GMP during manufacturing –  
Experience in use of electronic records (21 CFR Part II)  
Manufacturing failures and non-compliance require rigorous action
- Increased public demand for “zero” risk
- Older technologies are seen as being “safer”, which encourages “status quo”

- Growth-based techniques
- Viability based techniques
- Nucleic acid based techniques, etc.

## Some Examples:

- ATP Bioluminescence
- Fluorescence labeling
- Dye reduction
- Metabolic finger printing
- Immunoaffinity
- Laser scanning
- PCR

All methods detect organisms but some provide identification

## ■ Questions from a testing laboratory

- ▶ Is the method regulatory approved?
- ▶ Cost of analysis
- ▶ Recognition by the industry and other countries
- ▶ What are the detection limits?
- ▶ What are the false negative and positive rates?

# Method Validation

- RMMs are not equivalent to conventional methods.  
Changing methods → Change results
- Little guidance available for validation
- Validation definitions are more suitable for chemistry methods
- Some new methods have computer related 21 CFR Part 11 issues
- New technologies requires new learning curves

Provide assurance that a specific process will consistently produce a product meeting pre determined specifications.

- What is being measured?
- What are the variables? Are they different from traditional methods?
- How are they controlled?
- Does the method differentiate between viable, non-culturable, and dead cells?
- Is the method equivalent to existing methods?

Sometime pathogens might not be culturable but could be detected by new technologies or differentiated between viable and non-viable.

- Independent third-party review of proprietary test method performance
- Methods that demonstrate to meet acceptable performance criteria are granted PTM status
- PTM granted methods can use PTM certification mark

PTM Program has six distinct phases:

- Consulting
- PTM application
- Method developer validation study
- Independent validation study
- Validation study report
- PTM review

- Request application
- Submit performance data
- Review of submitted data
- Development of independent testing lab protocols
- Independent testing
- Review of independent testing lab data
- Recommendation

- Matrix
- Linearity – Results are proportional to the concentration of microbes present
- Range – Upper and lower level of microbes
- Accuracy – A measure of exactness
- Precision – reproducibility and repeatability
- Specificity – Method is fit for use
- Comparison to existing methods
- Cross reactivity
- Stability
- Detection Limit
- Limit of Quantification
- False Positives / False Negative Rates
- Ruggedness – Degree of reproducibility
- Equivalence – How similar the test results are to the method it is intended to replace

- Publication
- Annual review
- Complaints

## ■ Application Fees

- ▶ ~\$21,000 base application fee
- ▶ Discounts for contributing members
- ▶ Discounts for 5 or more simultaneous applications

## ■ Consulting Fees

- ▶ PTM review
- ▶ Annual review fee
- ▶ Copies of study reports

- Increased communication with regulators
- Allowing funding for method application research
- Minimize regulatory risks by focusing on validation plans addressing specific questions of interest

**Thank You!**