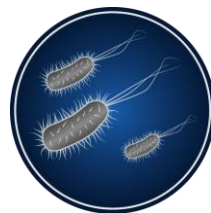


Evaluation, Validation and Implementation of Alternative and Rapid Microbiological Methods

Introduction

Michael J. Miller, Ph.D.

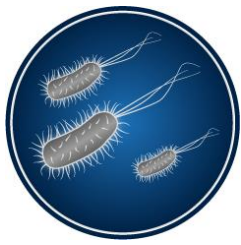


MICROBIOLOGY
CONSULTANTS, LLC



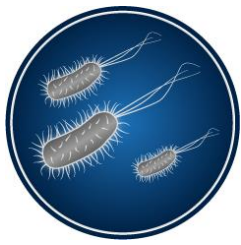
Housekeeping

- Turn off mobile phones; leave room to take/make calls
- Rest rooms
- Breaks and lunch
- CE credits
- Course survey
- Sign attendance sheet; certificate of attendance
- Questions may be asked at any time



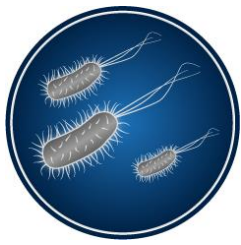
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Your Instructor

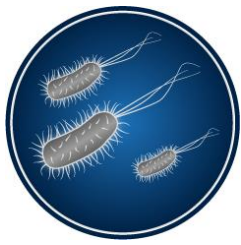
- Ph.D. in Microbiology and Biochemistry
 - Georgia State University, Atlanta, Georgia
- B.A. in Anthropology and Sociology
 - Hobart College, New York
 - Minor in Chemistry
- ~30 years industry and consulting experience
 - Research and Development, Manufacturing, Quality Assurance and Business Development



Your Instructor

- Editor of the PDA Encyclopedia of Rapid Microbiological Methods
- Chair, PDA Technical Report #33 revision task force
- Advisor to the USP Expert Committee

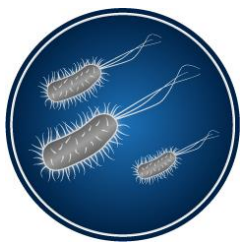




Your Instructor

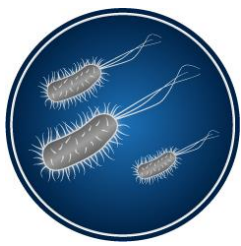
- President, Microbiology Consultants, LLC
 - <http://microbiologyconsultants.com>
 - CEO is pictured below
- Owner, rapidmicromethods.com
- Located in Tampa, Florida





Course Agenda

- Microbiology: past, present and future
- Classical microbiology
- Opportunities for change
- Introduce rapid microbiological methods (RMM)
- Perceptions, myths and misconceptions
- Regulatory acceptance, policies and expectations
- ATMPs and rapid sterility testing
- Review current microbiological methods and identify opportunities for improvement



Course Agenda

- Review RMM technologies; scientific principles and applications
- How to validate RMMs
 - PDA Technical Report No. 33, USP 1223 and Ph. Eur. 5.1.6
 - Performing statistical analyses
 - My recommendations
- Generate a business case and economic justification
- Closing, review additional RMM resources



Microbiology: A History Lesson

- 430-436 B.C. - The Athenian Plague
 - 30,000 dead
- 165-180 A.D. – The Roman Antonine Plague
 - 25 million dead
- 540-590 - The Plague of Justinian
 - 100 million dead





Microbiology: A History Lesson

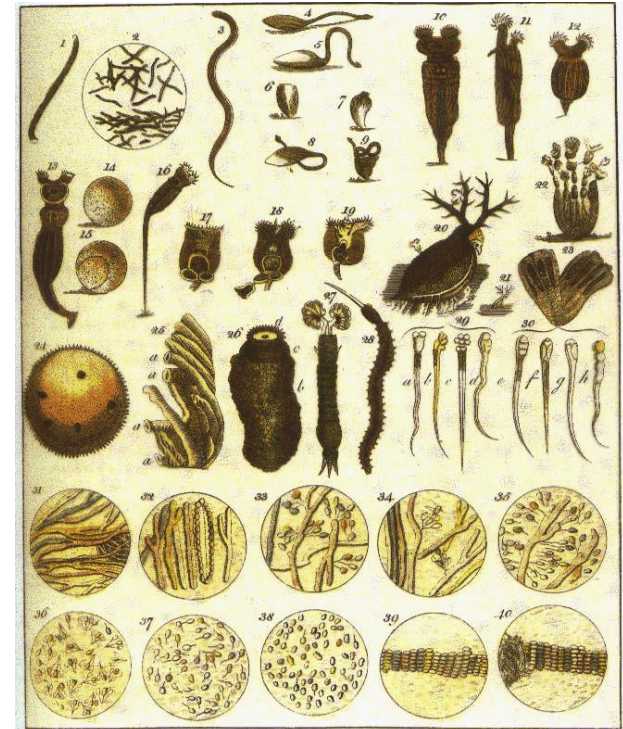
- 1346-1361 - The Black Death
 - 25 million dead in Europe; 75 million worldwide
- 1665-1666 - The Great Plague of London
 - 100,000 dead

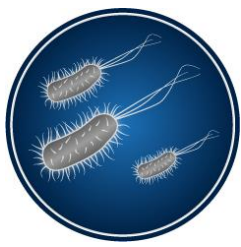




Microbiology: A History Lesson

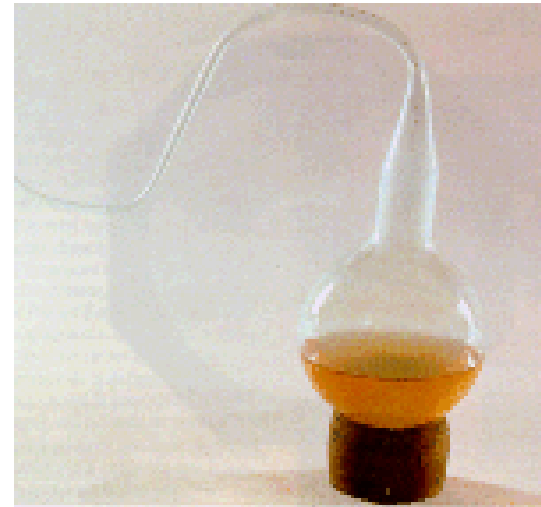
- 1683: Anton van Leeuwenhoek observes bacteria

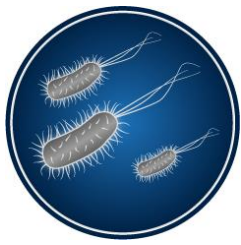




Microbiology: A History Lesson

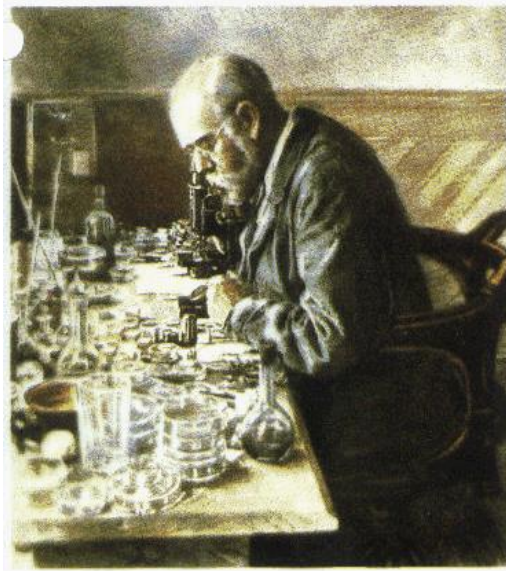
- 1857: Louis Pasteur saves France's wine industry and hypothesizes that microbes cause infectious disease
- 1861: Pasteur disproves spontaneous generation

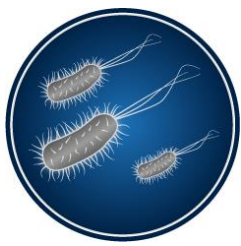




Microbiology: A History Lesson

- 1876: Robert Koch validates germ theory of disease (Koch's Postulates); defines *pure culture* and *colony*
- 1881: Fanny Angelina Hesse (wife of Walther Hesse, a student of Koch) introduces agar-agar, which replaces gelatin

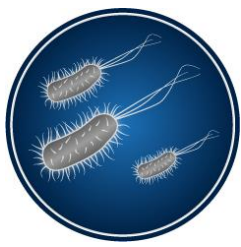




Microbiology: A History Lesson

- 1884: Hans Christian Joachim Gram (Koch's colleague) develops the Gram stain
- 1887: Julius Richard Petri (Koch's assistant) invents shallow glass plates for growing bacteria

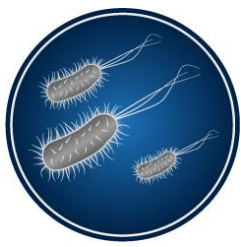




Microbiology: The Present

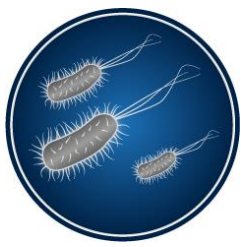
- Still using 19th-Century methods...counting colonies on agar plates and Gram staining





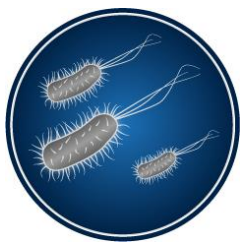
Microbiology: The Present

- Classical microbiology methods are limited by slow microbial growth rates
- Variability of microorganisms in their response to culture methods
- Most microorganisms in the pharmaceutical manufacturing environment and in raw materials used to make drugs are stressed or injured; current media and incubation conditions are not optimal for the resuscitation and growth of these microorganisms
- Many times we will observe zero colony forming units (CFU) on agar plates when in fact, viable microorganisms are present



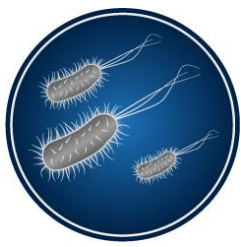
Microbiology: The Future

- Alternative and Rapid Microbiological Methods
- Novel technologies that provide microbial detection, quantification and identification results much faster than classical methods
- Increased accuracy, reproducibility and sensitivity
- Automated, miniaturized and high-throughput processing
- Enhanced sampling, data handling and trend analysis
- For some technologies, results in real-time



Rapid Microbiological Methods

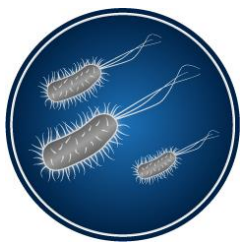
- Many RMMs do not require microbial growth
- Enhanced detection of single cells, stressed or injured microorganisms
 - Healthy or stressed viable but non-culturable (VBNC) cells
 - Cells induced into dormancy at the beginning of the stationary phase following environmental stress
- Improved microbial identification and strain differentiation



Rapid Microbiological Methods

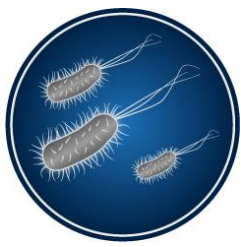
- Companies have been successful in validating and implementing RMMs
- However, they represent only a handful of firms within the industry
- *What are the myths or perceptions that prevent companies from moving forward?*





RMM Perceptions

- No clear guidance on validation expectations
- No return on investment
- Little regulatory direction, acceptance or understanding of RMMs
- We will see things we have never seen before and be forced to reject product
- We will have to change our acceptance levels or specifications which will put our products and business at risk



RMM Perceptions - Sources

- Ignorance on the part of our microbiology, QA, QC and/or regulatory departments, some vendors
- Not visible to senior management
- Generally not committed to technical change unless forced to do so
- There is no one person to champion the efforts of evaluating RMMs, educating colleagues and developing the right validation and implementation plans
- However, many companies have overcome these perceptions and successfully validated and implemented RMMs at various facilities and for many applications