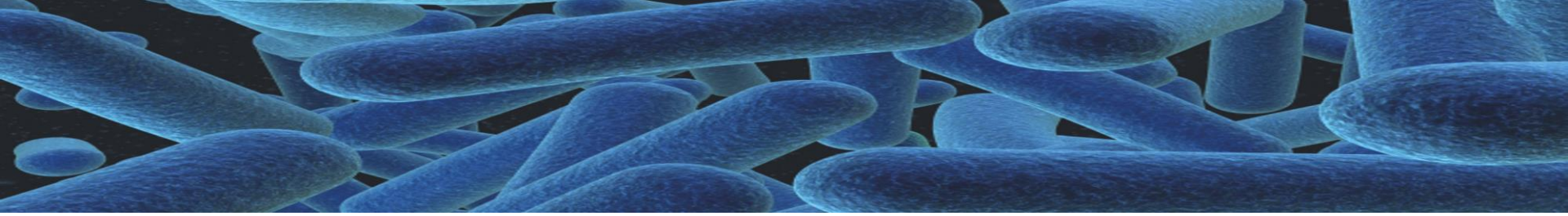
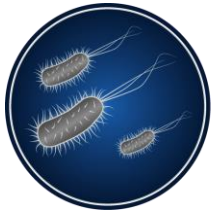
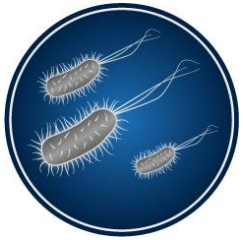


# Regulatory Acceptance, Policies and Expectations

Michael J. Miller, Ph.D.

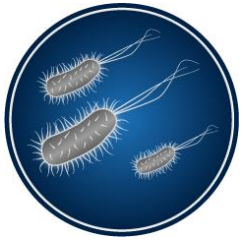


MICROBIOLOGY CONSULTANTS, LLC



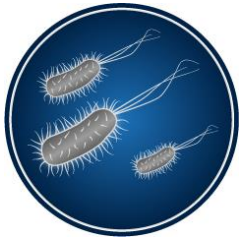
# Regulatory Perceptions

- Regulatory agencies do not accept or understand of RMMs
- We will see things we have never seen before and our products will be at risk
  - We will have to change our acceptance levels or specifications
  - We will have to reject more batches
- No clear guidance on validation expectations



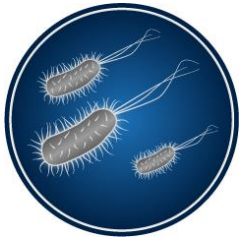
# Enablers

- Process Analytical Technology (PAT)
- U.S. Food and Drug Administration (FDA)
- European Medicines Agency (EMA)
- Australian Therapeutic Goods Administration (TGA)
- Japanese Pharmaceuticals and Medical Devices Agency (PMDA)
- World Health Organisation (WHO)



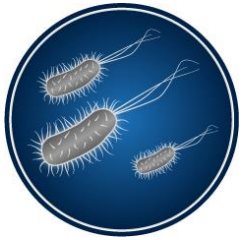
# Quality, GMPs and Rapid Methods

- One of the basic fundamentals of the GMPs is that quality should be built-in or should be by design, and product cannot be tested into compliance
- Release testing should seldom result in an out of specification result
- If we properly design and validate our processes and include analytical testing points throughout manufacturing, *release testing can be reduced or eliminated*
- This is the basis for Process Analytical Technology (PAT)



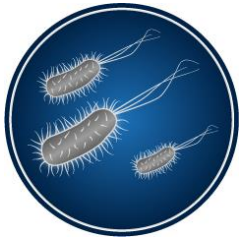
# FDA PAT Initiative

- A system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring predefined product quality at the end of the manufacturing process
- "Analytical" means chemical, physical, *microbiological*, mathematical, and risk analysis
- Encourages real-time product release and increases in automation



# FDA Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach

- Based on science and engineering principles for assessing and mitigating risks related to poor product and process quality
- Product quality and performance are ensured through the design of effective and efficient manufacturing processes
- Manufacturers are encouraged to use the latest scientific advances in manufacturing and technology
- Move toward a model of continuous improvement and *real time quality assurance*

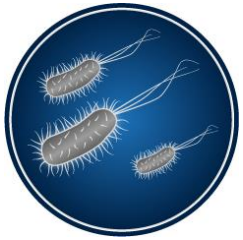


# Rapid Methods Fit Nicely in a Quality Risk Management Strategy

- Design robust processes that prevent contamination
- Ensure a state of microbial control is maintained
- Develop more effective strategies to correct a contamination problem
- Continually improve processes and products
- Assess the potential impact of failing results on the patient and do so in real-time

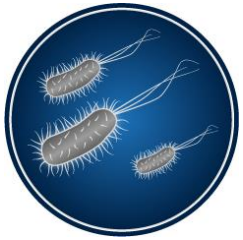
# FDA Perspectives

- Documents that address the use of RMMs
- Publications and presentations
- Validation strategies
- Submissions and approvals
- Research exemption



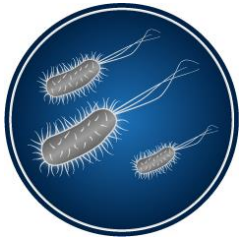
# FDA Aseptic Processing Guidance - cGMPs

- This 2004 guidance recommends the use of rapid genotypic methods for microbial identification, as these methods have been shown to be more accurate and precise than biochemical and phenotypic techniques
  - Especially valuable for investigations into failures (e.g., sterility test; media fill contamination)
- Other suitable microbiological tests (e.g., rapid methods) can be considered for environmental monitoring, in-process control testing, and finished product release testing
  - Must demonstrate that these new methods are equivalent or better than conventional methods (e.g., USP)



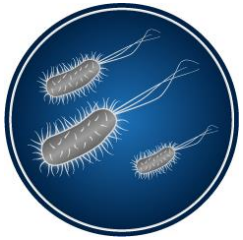
# CBER Guidance on Sterility Testing

- 2008 Center for Biologics Evaluation and Research (CBER) Draft Guidance
- *"Validation of Growth-Based Rapid Microbiological Methods for Sterility Testing of Cellular and Gene Therapy Products"*
- Demonstrates that an alternative, growth-based RMM is equivalent to the conventional sterility test method



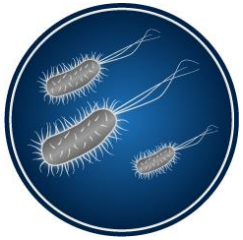
# U.S. Federal Register

- June 21, 2011 (Volume 76, Issue 119) proposal to amend the sterility test requirements for biological products
- “Advances in technology in recent years have allowed the development of new sterility test methods that yield accurate and reliable test results in less time and with less operator intervention than the currently prescribed culture-based methods”



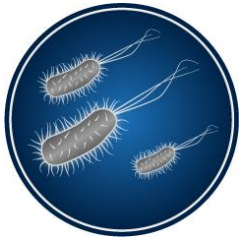
# U.S. Federal Register

- Applicable RMMs identified include ATP bioluminescence, chemiluminescence, and carbon dioxide head space measurement
- The proposed revision would provide manufacturers the flexibility to take advantage of modern methods as they become available, provided that they meet certain criteria
  - e.g., validated according to USP <1223>
- The proposal was also supported by RMM studies conducted by the FDA in its own lab



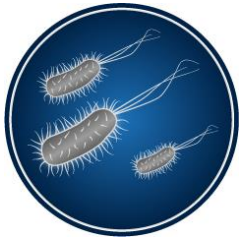
# FDA Final Rule in 2012

- FDA amended the sterility test requirements for biological products in its Final Rule, "*Amendments to Sterility Test Requirements for Biological Products*."
- Effective June 4, 2012; **§ 610.12**
- Many changes associated with the traditional sterility test, but also provides guidance on validating RMMs
  - We will discuss the Final Rule in greater detail



# FDA Strategic Plan for Regulatory Science

- In August 2011, the FDA published a strategic plan for regulatory science
- “Develop sensitive, rapid, high-throughput methods to detect, identify, and enumerate microbial contaminants and validate their utility in assessing product sterility”
- “Develop reference materials for use by industry and academia to evaluate and validate novel methods for detecting microbial contamination”



# FDA Presentations

- Dr. Brenda Uratani, CDER, Compliance Officer (2007)
  - Ability to initiate investigations earlier as compared with conventional methods
  - Reduction of risk associated with microbial contamination
  - Use of the data as a continuum for process improvement
- Dr. David Hussong, CDER, Director, Microbiology (2010)
  - RMMs are very important for meeting QbD principles, smart processing and PAT
  - CDER actively encourages the use of new technologies

# FDA Publications


**Alternative Microbiology Methods and Pharmaceutical Quality Control**

*David Hussong, Ph.D., and Robert Mello, Ph.D.*
*New Drug Microbiology Staff, Office of Pharmaceutical Science,*
*Center for Drug Evaluation of Research*
*U.S. Food and Drug Administrations*

**American Pharmaceutical Review, Jan/Feb 2006**

- New microbiology methods can offer advantages of speed and precision
- Quality by design principles and risk analysis methods must be extended to the development of new microbiological technologies

# FDA Publications


**Rapid Microbiological methods in the Pharmaceutical Industry**

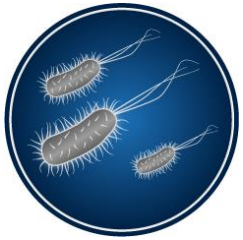
*Bryan S. Riley, Ph.D.*
*New Drug Microbiology Staff, Office of Pharmaceutical Science,*
*Center for Drug Evaluation of Research*
*U.S. Food and Drug Administrations*

**American Pharmaceutical Review, Mar/Apr 2004**

- The use of rapid microbiology methods by the pharmaceutical industry should offer many advantages
- Receiving microbiology test results sooner will provide for better control and understanding of the manufacturing process via faster feedback
- Industry should not feel that FDA will be a hindrance to the appropriate use of these methods

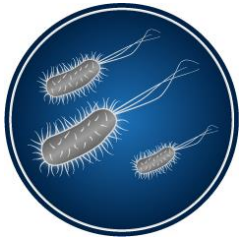
# FDA Validation Expectations

- The FDA accepts USP Chapter <1223>, Ph. Eur. 5.1.6 and/or PDA Technical Report #33 as a starting point for RMM validation activities
  - PDA Technical Report #33, *Evaluation, Validation and Implementation of New Microbiological Testing Methods*
  - USP <1223>, *Validation of alternative microbiological methods*
  - *Ph. Eur. 5.1.6, Alternate Methods for Control of Microbiological Quality*
- You can develop your own validation strategy as long as it is scientifically sound and defendable



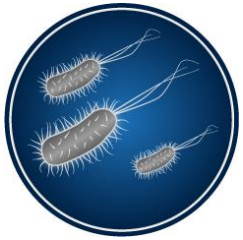
# FDA Validation Strategies

- Where to conduct the testing?
- Laboratory
- Pilot facility
- Manufacturing
- Utilize a Research Exemption process for generating feasibility or validation data in an active manufacturing area or with existing finished product



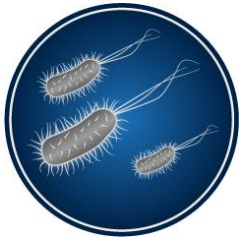
# FDA Research Exemption

- FDA has acknowledged industry's concerns that an increased amount of *process data* may indicate a problem in a product that meets its current registered release methods
- In response to this concern, the FDA introduced the "safe harbor" or "research exemption" concept
- Designed to encourage the industry to investigate tools that will provide increased process information without the fear of having a negative impact on the ability to release products
- Described in FDA’s PAT initiative



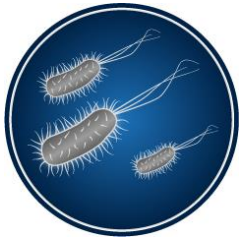
# FDA Research Exemption

- All data generated by the RMM under investigation is for research purposes only
- All GMP decisions, including batch release, are based on the current approved validated methods
- Use an internal written document and/or comparability protocol to communicate this strategy



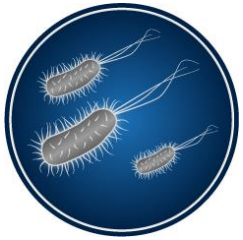
# FDA Submissions and Approvals

- Can include RMMs in an NDA , ANDA, IND, BLA for new products
- Existing products may require a post-approval change (annual report for minimal impact) or a prior-approval supplement (for a major change)
- A moderate or minor change may benefit from using a reduced reporting category (CBE-0 or 30)



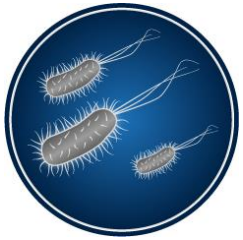
# FDA Submissions and Approvals

- Changes Being Effected (CBE) 0 or 30
  - CBE 0: implement the RMM immediately when the Special report is issued (minor change)
  - CBE-30: wait 30 days after the Special Report is issued (moderate change)
- The desired reduced reporting category can be discussed with FDA and/or specified in a comparability protocol



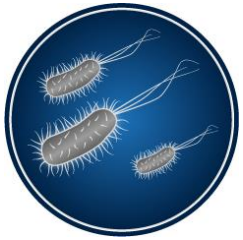
# FDA Comparability Protocol

- A comparability protocol is a well-defined written test plan (and a prior-approval supplement)
- Includes analytical procedures that will be used and acceptance criteria that will be achieved to demonstrate that the changes do not adversely affect the product
- Can include multiple applications and product types under a single RMM
- Once approved, the protocol is performed. FDA is notified of the results in a Special Report.



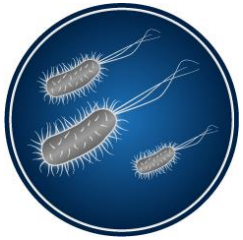
# Special Report

- Includes a brief description of the RMM and its use, confirmation that the acceptance criteria have been met and the date of implementation (e.g., under a CBE-0 or CBE-30)
- Can be a brief document as there is usually no need to provide data in the report
- However, data may be required for certain products (biologics, BLA); therefore, discuss plans with the Agency



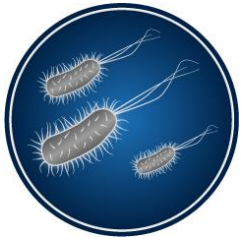
# FDA Submissions and Approvals

- Future changes using the RMM (e.g., testing additional products) can be made without the need for additional approvals, as long as the same approved comparability protocol is used
- Subsequent product filings may include the RMM in an Annual Product Report



# FDA Submissions and Approvals

- For in-process tests and methods that are not in a regulatory filing, implementing a RMM may not require a formal submission may not be necessary
  - Environmental monitoring, purified water testing, in-process or pre-filtration bioburden testing
- Will need to review current submissions to determine if there will be method and/or specification changes associated with the RMM being implemented



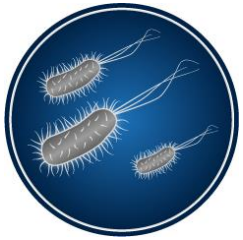
# FDA Discussions

- Discuss your plans with the FDA early in the process
- Informal meetings via telephone or face-to-face meetings are encouraged
- FDA may not require formal submissions depending on the technology and application

# EMA Perspectives

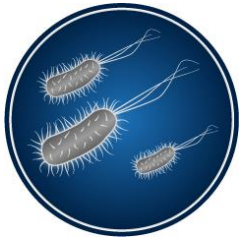
- Guidance documents and policies that address the use of RMMs
- Presentations
- Submissions and approvals
  - Revisions to type variations regulations
  - Scientific Advice
  - Change Management Protocol
- Validation strategies

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH



# EMA Perspectives

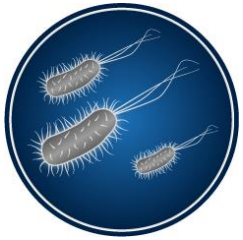
- Riccardo Luigetti, EMA (2009)
- RMMs can support QbD principles
- They are generally supported by the competent authorities in the European Union
- The implementation of the revision of the variations regulations will further simplify the introduction of changes to Marketing Authorisations, including the introduction of RMMs



# MHRA Perspectives

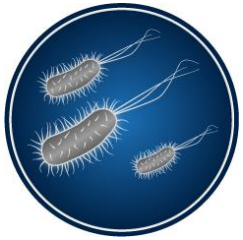
- Paul Hargreaves, MHRA (2009)
- MHRA has actively encouraged the pharmaceutical industry to investigate and implement RMMs in order to improve patent safety
- Is willing to discuss RMMs, review validation protocols and discuss possible uses ranging from screening tests, bioburden and sterility testing
- RMM suitability will be subject to scientific assessment

MHRA
Regulating Medicines and Medical Devices



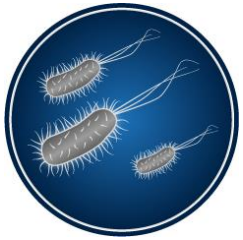
# Revision to EU Annex 1

- Annex 1 "*Manufacture of Sterile Medicinal Products*" of the EU Guideline for good manufacturing practice for drug products and drug substances
- On Dec 20, 2017, the European Commission published a revision draft
- Comments were accepted until March 20, 2018
- The final document has yet to be published



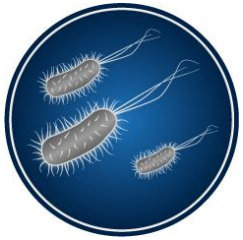
# Revision to EU Annex 1

- Environmental monitoring (Sec. 9.28)
  - “Rapid microbial monitoring methods may be adopted after validation as long as they are demonstrated to be at least equivalent to the established methodology”
- Quality control (Sec. 10.11); pre-sterilization bioburden and finished product sterility testing
  - “The use of rapid microbial methods can also be considered. These methods should be validated for the product(s) or processes concerned and be approved in the registered product testing specification”



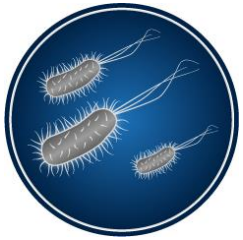
# EMA Quality Working Party and Water

- In 2005, EMA explored the use of alternative methods for the rapid control of WFI and purified water
- Since it was expected that the water will continue to meet Ph. Eur. specification, no change to product Marketing Authorisations would be required
- However, this would depend on the level of detail in the original submissions



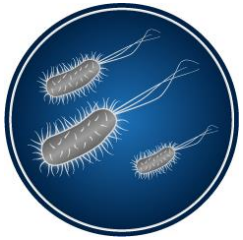
# EMA Quality Working Party and Water

- On August 5, 2016, the Water Working Party published a set of discussion points while Annex 1 was under revision
- Q. “What testing should be employed during initial qualification and routine operation sampling?”
- A1. Use of RMMs should be employed as a prerequisite to the control strategy to aid with rapid responses to deterioration of the system



# EMA Quality Working Party and Water

- A2. Methods to be considered should include, “rapid endotoxin testing – use of more sensitive and point of use test methods,” and “quantitative microbiological test methods – in line with Ph. Eur. 5.1.6 monograph, *Alternative Methods for Control of Microbiological Quality*
- A3. Due consideration should be given to employing alternate methods for the rapid quantitative determination of the contamination levels existing within the water system. The validation of such system should be in line with the above referenced monograph.

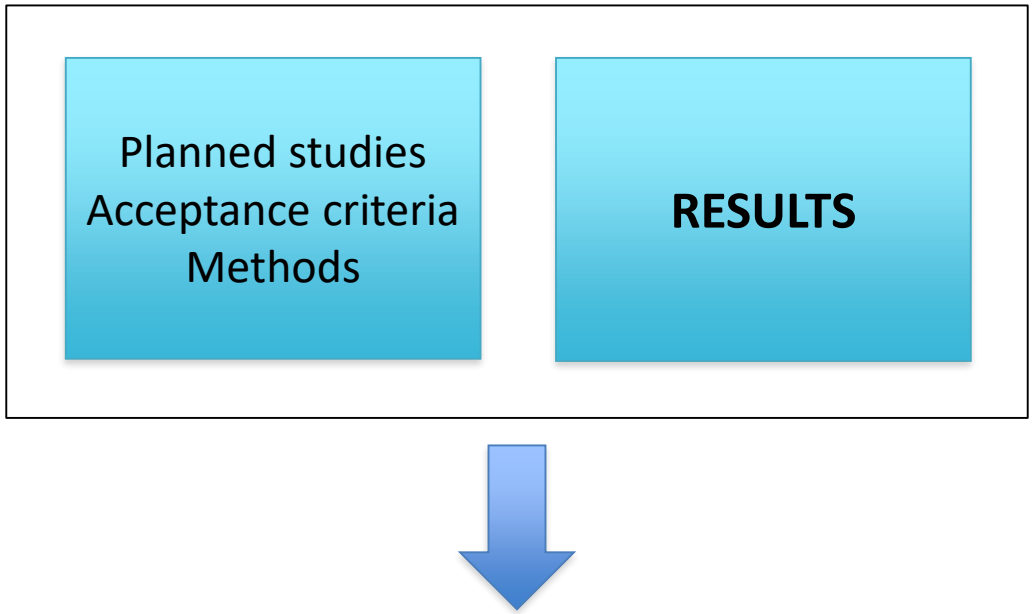


# EMA Submissions and Approvals

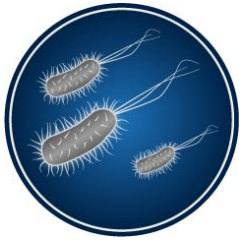
- Individual member states have approved RMMs for routine use
- Historically, changes to a method in a Marketing Authorisation required a separate Type Variation (for each product/process) to be submitted, which could be very costly and time consuming
- Each competent authority could ask questions or require additional testing, thereby delaying the time to approval
  - GSK's first RMM validation approval took 18 months with the EMA as compared to 18 days using an FDA comparability protocol

# EMA Submissions and Approvals

- EMA historical process for RMM validation:

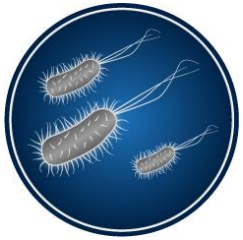



**Everything was reviewed at the same time**



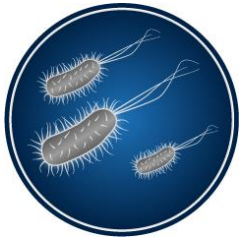
# EMA Submissions and Approvals

- On January 1, 2010, the EU published its revised variations regulations
- Clearer, simpler and flexible options
- Reduced regulatory administrative burden
- Adaptation to ICH concepts
- Harmonization across the national authorities



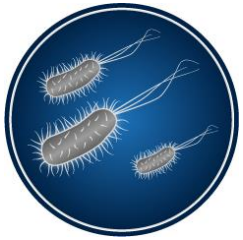
# EMA Submissions and Approvals

- Group variations under the same Marketing Authorisation such that they can all be assessed at the same time
- Combine the same variations or group of variations from *different* Marketing Authorisations and have all of these assessed at the same time under a “work sharing process” or “common assessment”
  - This can include a single RMM technology being used for multiple products



# EMA Change Management Protocol

- 2011: Post Approval Change Management Protocol
- Similar to FDA's comparability protocol (CP)
- Formal review and approval prior to the start of testing
- Data is submitted
- Take advantage of a reduced reporting structure when implementing the new method, similar to FDA's CBE-0 or CBE-30

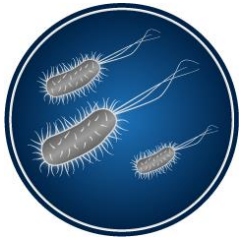


# EMA Submissions and Approvals

- Post Approval Change Management Protocol:

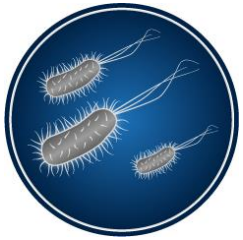
**STEP 1:** Planned studies, Acceptance criteria, Methods → **Submit for Approval as a Type II Variation**

**STEP 2:** **RESULTS** → **Submit Data as a Type IA or IB Variation**



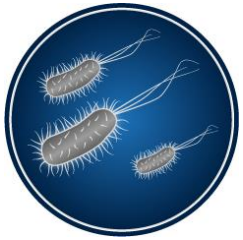
# EMA Submissions and Approvals

- Commission Regulation (EC) No 1234/2008 defines a Type II variation as a '**major variation**' which may have a significant impact on the quality, safety or efficacy of the medicinal product



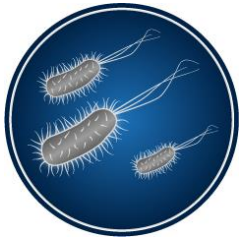
# EMA Submissions and Approvals

- Commission Regulation (EC) No 1234/2008 defines a Type IA variation as having a **minimal impact, or no impact at all**, on the quality, safety or efficacy of the medicinal product, and do not require prior approval before implementation
- “Tell and Do” procedure
  - Similar to FDA’s CBE-0; rapid methods can be implemented immediately



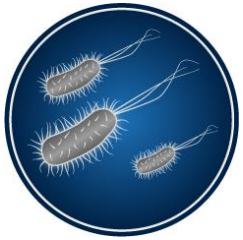
# EMA Submissions and Approvals

- Commission Regulation (EC) No 1234/2008 defines a Type IB minor variation as a **variation which is neither a Type IA variation nor a Type II variation**
- These variations must be notified to the National Competent Authority before implementation, but do not require a formal approval
- The submitter must wait for 30 days to ensure that the notification is deemed acceptable before implementation
- “Tell, Wait and Do” procedure
  - Similar to FDA’s CBE-30



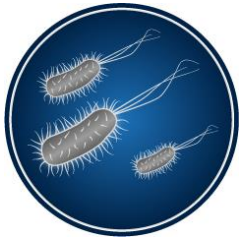
# EMA Change Management Protocol

- When is data submitted as a Type IA or IB?
- Determined when you discuss your plans with EMA
- Based on the method, applications, other factors



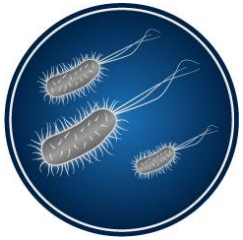
# EMA Submissions and Approvals

- **Scientific Advice** (SA) procedure provides opportunities for scientific dialog with regulators
- SA working party includes representation from all member states
- Applies to the entire EU; however, individual national authorities may require additional discussions in addition to the advice received under this procedure
- May be invited to the EMA for a discussion meeting and there may be an opportunity to ask for further clarification following receipt of the SA letter



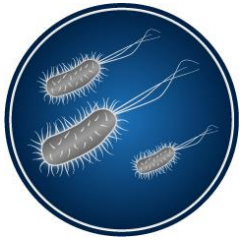
# EMA Submissions and Approvals

- The SA letter is an official document from the SA working party
- However, it is not legally binding and can be contradicted once the application is under official review
- The SA procedure is also subject to a fee



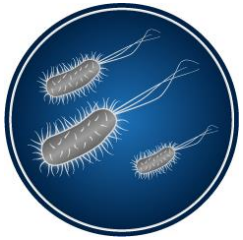
# EMA Validation Expectations

- Use Ph. Eur. chapter 5.1.6 as a starting point for RMM validation
- PDA TR33 has also been utilized by end-users
- Ph. Eur. 5.1.6 does not need to be followed exactly, yet all deviations from the guidelines should be clearly stated and reasons provided
- The use of compendial test strains, in-house (environmental) isolates and stressed or slow-growing organisms is recommended



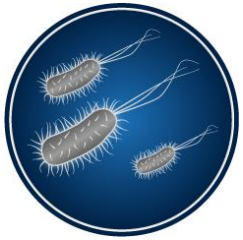
# EMA Validation Expectations

- The Quality Expert Report is the document used to convey the information from RMM validation studies
  - Should be written by a quality expert, such as a microbiologist, an expert in the field of RMMs or a relevant technical person
  - Should include a description of the technique, application principle, risk-benefit analysis, validation of the equipment, validation of the test method and a study against the Pharmacopeial method
  - Reference to the application principle should be described in a peer-reviewed journal



# EMA Discussions

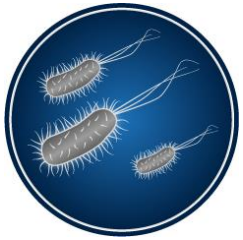
- EMA does not recognize FDA's Research Exemption; you should understand what the EMA and/or local inspectorates expectations are with regard to generating data in a manufacturing environment or using commercial product
- It is highly recommended to discuss your plans with the EMA and/or the local inspectorate, especially if you plan on implementing a RMM for an in-process test that does not require a Type Variation
- Therefore, a meeting with the appropriate EMA regulators is warranted and this should occur very early in the implementation-planning phase



# Australian TGA

- Dr. Vivienne Christ, Chief Microbiologist, OLSS (2010)
- TGA relies on USP 1223, Ph. Eur. 5.1.6, PDA TR #33, and ISO 17025 (validation of non-standard methods)
- TGA also references Australian GMPs, which allows for other methods as long as they are equivalent to those in the GMP guide, as well as Annex 11 (computer validation) and Annex 15 (IQ, OQ, PQ)
- Views RMMs to be used in a wide range of applications, including finished product testing and in-process testing

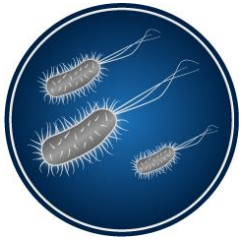
TGA Approved Medical Device



# Japanese PMDA

- Dr. Tsuguo Sasaki (2010)
- The PMDA will work with companies in the development of RMM strategies for use in Japan
- Requires evaluation and approval for alternative or rapid methods that will be used for product release, such as a rapid sterility test (approvals have already been granted)
- For in-process control tests, manage a method change internally

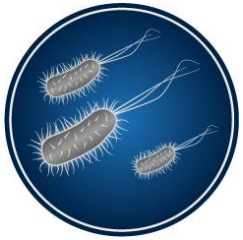
pmda 独立行政法人 医薬品医療機器総合機構
Pharmaceuticals and Medical Devices Agency



# Japanese PMDA

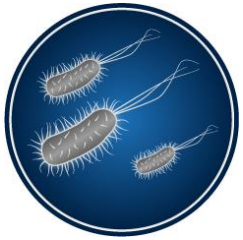
- Japanese Pharmacopoeia (JP) has developed chapters on RMMs (JP 17 effective April 2016):

1. Rapid Counting of Microbes using Fluorescent Staining
2. Rapid Identification of Microorganisms Based on Molecular Biological Method
3. Rapid Microbial Methods
   - Discussion of scientific principles
   - Potential applications
   - The need to validate



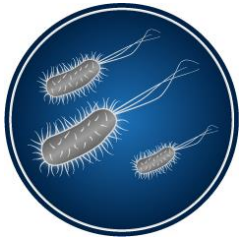
# Rest of the World

- Other regulatory authorities may not have formal guidance on RMMs
  - Europe but not part of EMA
  - Mexico, Central and South America
  - Asia-Pacific
  - Africa and Middle East
- May need to follow each country's Pharmacopeia
- Discuss your plans with these agencies
- Note that your RMM may be approved in some countries but not others



# World Health Organisation (WHO)

- GMPs for Sterile Pharmaceutical Products (Annex 6; 2011)
- The use of rapid microbiological methods to replace the traditional microbiological methods, and to obtain earlier results on the microbiological quality of, for example, water, the environment or bioburden, could be considered if appropriately validated and if a comparative assessment of the proposed rapid method is performed against the pharmacopoeial method

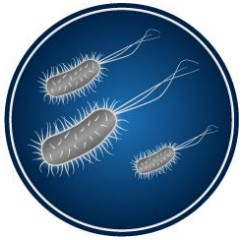


# Changing Acceptance Levels

- Regulatory agencies will generally accept a change in a manufacturing or testing process if the change has been proven to be equivalent to or not worse than the system currently in place
- However, some RMMs, especially those that do not rely on the growth of microorganisms, may provide a higher count or microbial recovery as compared with conventional methods
- Some perceptions…

# Changing Acceptance Levels

- We may be "seeing" things we haven't in the past
- Rapid measurements may be different than what we have been used to historically (e.g., fluorescent units as opposed to colony forming units)
- We won't be able to meet the existing specifications or acceptance levels or will need to change these levels to reflect the data generated by the new method



# Changing Acceptance Levels

- Brenda Uratani, FDA, CDER (2007)
- FDA expects higher counts will be recovered when using some RMMs, especially if the techniques are more sensitive than conventional methods
- For example, if you use a RMM for air monitoring, the 1 CFU/$m^3$ specification may need to be changed, because this was based on the less sensitive agar-based method
- The change needs to be supported by scientific studies

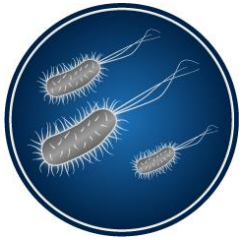
# Changing Acceptance Levels


**Alternative Microbiology Methods and Pharmaceutical Quality Control**

*David Hussong, Ph.D., and Robert Mello, Ph.D.*
*New Drug Microbiology Staff, Office of Pharmaceutical Science,*
*Center for Drug Evaluation of Research*
*U.S. Food and Drug Administrations*

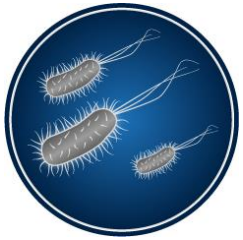
**American Pharmaceutical Review, Jan/Feb 2006**

- "Often, new methods rely on a completely different body of information, some may be direct measurements, some indirect . . . previous acceptance criteria may not be applicable."
- "Therefore, implementation of newly developed, or more rapid, microbiology methods may also require the establishment of new acceptance criteria."



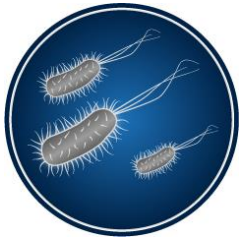
# Changing Acceptance Levels

- Paul Hargreaves, MHRA (2009)
- “Since most organisms won’t grow on agar plates, it is expected that newer, more sensitive methods will obtain higher counts than traditional methods”
- Limits can be changed as long as your rationale is explained to the inspector
- However, some EMA regulators or other competent authorities may not agree, so discuss this upfront!



# Changing Acceptance Levels

- Understand when acceptance levels or specifications may need to be changed
- May be based on the method, reporting units and actual data
  - **NOTE:** In reality, significant increases in counts are usually not observed, especially in areas or test samples that are expected to have very low bioburden
- Review regulatory submissions to determine if formal post-approval changes will be required



# Take-Home Regulatory Advice

- Discuss your validation and implementation plan early
- Include an overview of the method, the study design, acceptance criteria, organisms to be used and the test samples
- Ask very specific questions to ensure you and the regulators are on the same page