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# Rapid Microbiological Methods (RMM)

## Regulatory Acceptance:
## Policies and Expectations

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TGA Health Safety Regulation

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# Presentation Scope

- Rapid microbiological methods:
  - Overview of relevant TGA legislation
  - Relevant guidance documents
  - TGA's expectations
  - TGA's experience

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## Who is Australia's Regulator?

- The Therapeutic Goods Administration was established in 1990 to "**safeguard** and **enhance** the health of the Australian community through **effective** and **timely regulation** of therapeutic goods"
- It provides a national system of controls relating to the **quality, safety, efficacy** and timely availability of therapeutic goods used in, or exported from, Australia




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## TGA – How We Operate

- Part of the Australian Government Department of Health
- Decisions based on the *Therapeutic Goods Act 1989*
- Main offices in Canberra – satellite offices in Sydney, Melbourne, Adelaide and Brisbane
- Operations are primarily cost recovered (98%):
  - Industry pays fees for making applications & annual charges for products they are responsible for

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# Laboratories Branch: Fast Facts

- Origins in the National Biological Standards Laboratory 1958
- Laboratories hold ISO 17025 accreditation
- Average staffing level: ~ 90 FTE
- Five Sections (plus small management & coordination unit):
  - ■Biochemistry ■Biomaterials and Engineering
  - ■Chemistry ■ Immunobiology ■Microbiology
- All sections perform essentially the same work:
  - Testing
  - Evaluation of quality aspects for products seeking entry on ARTG
  - Advice
  - Standards development



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# Laboratory Testing Assesses *QUALITY*

- Quality:
  - Composition, strength, potency, stability, purity, bioburden, design, construction and performance
- Testing:
  - Assess compliance with required standards or guidelines, e.g.:
    - Default Pharmacopoeias
    - Therapeutic Goods Orders
    - International standards
    - Compositional guidelines

# TGA's Default Standards

- USP, Ph. Eur. and BP recognized as 'default standards' since 1 July 2009 under *Therapeutic Goods Act 1989*

- Permit alternative methods of analysis for control purposes
- Referee Method:
  - Official pharmacopoeial method





# TGO 77 Microbiological Standards for Medicines

- Requirements for ***finished products*** (effective January 1, 2010):
  - Sterile medicines
  - Multidose medicines
  - Non-sterile medicines

- Refers to Ph. Eur., BP and USP test for sterility, preservative efficacy and microbial limits test methods:
  - Allows alternative methods of analysis

## RMM Guidance Documents

- No TGA guideline document
- Default Standards:
  - USP <1223> *Validation of Alternative Microbiological Methods*
  - BP SC IVL/Ph. Eur. 5.1.6 *Alternative Methods for Control of Microbiological Quality*
- PDA Technical Report No. 33 (2013) *Evaluation, Validation and Implementation of Alternative and Rapid Microbiological Methods*
- ISO17025 *General requirements for the competence of testing and calibration laboratories:*
  - Validation of non-standard methods (cl. 5.4.4 & 5.4.5.)



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## RMM: Administrative Aspects

- TGA Legislation:
  - Approval based on individual finished product registration
  - No mechanism to provide separate approval for equipment/RMM
- TGA cost recovery:
  - Evaluation fees charged in relation to specific product not process
  - GMP inspection and manufacturer licensing fees
  - Investigate possible options to recover costs for evaluation of an RMM:
    - Evaluate RMM, then charge fee for each product variation application?
    - Charge fee for RMM master evaluation and allow self-assessable changes for subsequent product using that RMM?
    - Consider changes to existing legislation to facilitate evaluation of new technologies?

# RMM: Administrative Aspects

- TGA acknowledges and is supportive of new technologies:
  - No specific policy statement published on requirements
- RMM evaluation by the TGA:
  - As GMP inspection follow-up (e.g. in-process testing)
  - During marketing application (e.g. batch release testing, stability)
  - Via post-market variation (e.g. batch release testing, media fills)
- Commercial-in-confidence considerations:
  - Primary validation studies conducted by equipment supplier
  - Ability to access technology master file:
    - Might require separate liaison with RMM supplier to access information not available to RMM user



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# Examples of RMMs Used for Product Supplied to Australia

- RMMs not common:
  - Primarily compendial methods:
    - Raw material, process water, in-process and batch release testing
    - Locally and overseas manufactured product
- Test for Sterility:
  - Milliflex® Rapid System (ATP Bioluminescence)
  - ScanRDI® (fluorescent cell labelling and laser scanning (solid phase cytometry)
- Microbiological contamination testing of blood and tissue-based products:
  - BacT/ALERT® Microbial Detection System

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## Examples of RMMs Used for Product Supplied to Australia

- Bioburden:
  - Celsis® Systems (ATP bioluminescence):
    - Non-sterile manufacturing:
      - Screening out negatives in low bioburden product
  - Soleris® Optical System:
    - Non-sterile manufacturing:
      - Finished product testing complementary medicines
      - Validation in progress
  - BioLumix System (optical system):
    - Aware of general interest in system



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## Examples of RMMs Used for Product Supplied to Australia

- Media Fills:
  - ScanRDI®
- Organism Identification:
    - MALDI-TOF (matrix assisted laser desorption ionisation time-of-flight)
    - MicroSEQ® Rapid Microbial Identification System
    - Whole genome sequencing (isolate ➡ reference laboratory)
      - Phylogenetic analysis outbreak clusters

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# TGA's Validation Expectations

- DQ:
  - RMM manufacturer
- IQ and OQ:
  - RMM manufacturer
- PQ (MPQ):
  - Often jointly by RMM manufacturer and user on sample types
  - Then verification in-house by user
- Validation criteria (as applicable):
  - Accuracy
  - Precision
  - Specificity
  - Limit of detection
  - Limit of quantification
  - Linearity
  - Range
  - Ruggedness
  - Robustness
  - Equivalence/comparative testing



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# TGA's Expectations Versus Experience

- Some companies think and talk about using RMM
- Discuss intentions with TGA:
  - We encourage adoption of RMM
  - We discuss regulatory expectations on case-by-case basis
- Validation work often already performed by Company
- Company might continue with compendial method:
  - Why?
    - Expect regulatory hurdles?
    - Delays to product marketing?
    - Prefer to rely on referee method for product batch release?
    - Cost?

## Reluctance to change from compendial method

- Access to relevant microbiological expertise:
  - Limited or no microbiological expertise on site
  - Samples ➡ contract testing laboratory
  - Contract testing laboratory uses compendial method

- High initial costs for RMM:
  - Complex technological platforms and sophisticated equipment:
    - More complex than traditional compendial techniques
    - Validation:
      - Whole system, software, database customisation, data integrity, microbiological performance
      - Validation effort and possible challenge by Regulator might be a barrier
  - Low sales volume for inexpensive product
  - Starting to see change:
    - Consider business risk and management of product quality
    - Cost/savings over the long term





## Reluctance to change from compendial method

- Not willing to be the first to ‘dip toes into the water’

- RMM cell count might be higher than compendial method:
  - Historical trends might be affected
  - Does it mean my product is unsafe?
    - Does product have a history of safe use?
    - Is it manufactured using a well-controlled process?

    Higher cell count doesn’t necessarily mean a new patient safety risk exists

  - User to assess risk of using RMM for potential for more ‘positive’ results
  - New method might allow for improved quality decisions on product

## Reluctance to change from compendial method

- Referee method:
  - Compendial method is referee method
- Dispute a test result with Regulator:
  - Generally use referee method and abide by result
  - Option for all parties to agree on actual method to be used:
    - Compendial method might not be suitable:
      - E.g. *Burkholderia cepacia complex* contamination and microbial limits test method
  - Results of 'agreed' method prevail





## Summary

- Recognition that timely microbiological data is vital for:
  - Process monitoring and control
  - Product release
- RMM offer risk reduction, faster time to result and cost savings:
  - Manufacturers, laboratories and Regulators are adapting to change
  - Starting to move cautiously from traditional methods to implement RMM
- New method:
  - Provide scientifically sound measure of microbial quality
  - Its limitations should not exceed those of compendial method
  - Should be able to detect same adverse trends as compendial method
- Important to identify user requirements and determine how these can be met:
  - Work closely with RMM suppliers, technical advisors, and regulators
  - Equipment selection, validation, documentation, training, maintenance, ongoing support etc.

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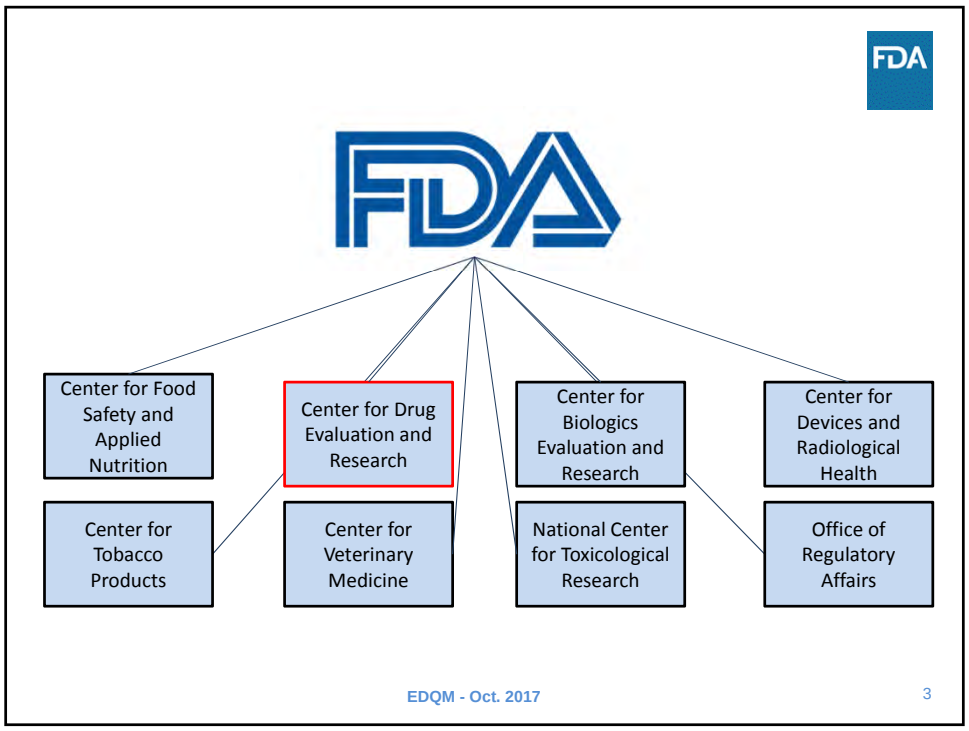
# Opportunities for Rapid Microbiology Methods in Pharmaceutical Manufacturing

**Dr. Lynne A. Ensor**
Director
Division of Microbiology Assessment
Office of Process & Facilities
Office of Pharmaceutical Quality
Center for Drug Evaluation & Research/FDA

## Disclaimer

This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies.


FDA
Center for Food Safety and Applied Nutrition
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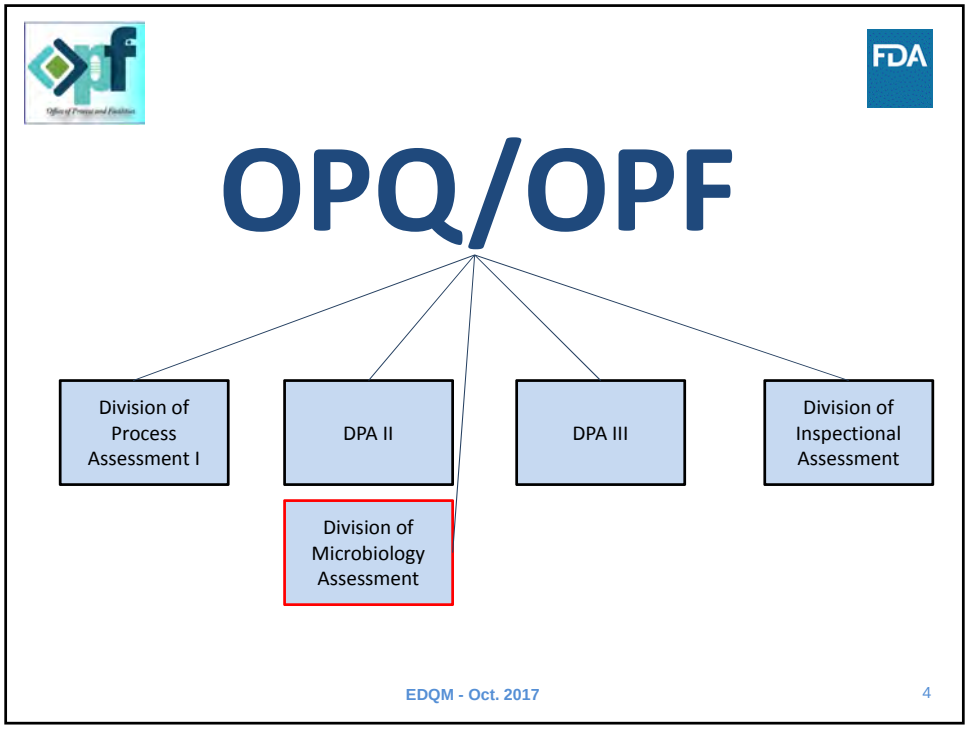
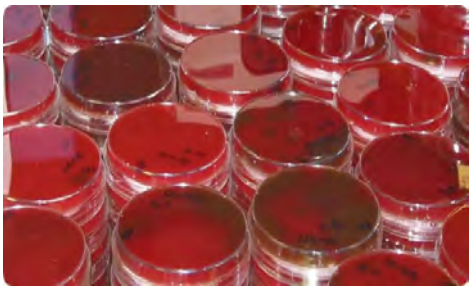
Center for Devices and Radiological Health
Center for Tobacco Products
Center for Veterinary Medicine
National Center for Toxicological Research
Office of Regulatory Affairs




FDA
OPQ/OPF
Division of Process Assessment I
DPA II
DPA III
Division of Inspectional Assessment
Division of Microbiology Assessment

## Explore the Possibilities – focus on your specific needs

- **Validation**
  - Biological Indicators
- **In-Process**
  - Environmental monitoring
  - Water
  - Bioburden
  - Sterility
- **Finished Product**
  - Sterility
  - Microbial Limits
- **Other????**





## Validation Guidance & Recommendations

- **USP <1223>**
  *Validation of Alternative Microbiological Methods*
- **PDA Technical Report 33**
  *Evaluation, Validation and Implementation of Alternative & Rapid Microbiological Methods*
- **ICH Q2A**
  *Validation of Analytical Procedures*
  "The objective of validation of an analytical procedure is to demonstrate that it is suitable for its intended purposes"
- **EP 5.1.6**
- **USP Stimuli Article**
  *The Development of Compendial Rapid Sterility*

# RMM Validation Criteria

**Table 1. Validation Parameters by Type of Microbiological Test** (USP<1223>)

| Validation Parameter | Qualitative Tests | Quantitative Tests |
|---|---|---|
| Accuracy | No | Yes |
| Precision | No | Yes |
| Specificity | Yes | Yes |
| Limit of detection | Yes | Yes |
| Limit of quantification | No | Yes |
| Linearity | No | Yes |
| Operational (dynamic) range | No | Yes |
| Robustness | Yes | Yes |
| Repeatability | Yes | Yes |
| Ruggedness | Yes | Yes |
| Equivalency | Yes | Yes |



# RMM Validation Recommendations

- **Provide "Equivalent" Product Quality**
- **Method yield equivalent or better results**
- **Choose your statistical analysis methods carefully**
- **Use microorganisms that are relevant to your product and manufacturing environment**
- **Understand limitations of your RMM and perform studies using worst-case scenarios**
  - **Product interference with test method?**

# Potential Submission Strategies – NDA, ANDA or BLA

- **Original Submission**
- **Supplement**

  Guidance for Industry (GFI): Changes to an approved NDA or ANDA (2004)
  GFI: Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products (1997)
  - Prior Approval (for Release Test)
  - Changes Being Effected (CBE-0 or CBE-30)
- **Annual Report**

  GFI: CMC Postapproval Manufacturing Changes to be Documented in Annual Reports (2014)
  GFI: CMC Postapproval Manufacturing Changes for Specified Biological Products to be Documented in Annual Reports (2017)
- **Comparability Protocol**

  GFI: Comparability Protocols for Human Drugs & Biologics: Chemistry, Manufacturing, and Controls Information (Draft 2016)
- **Drug Master File**



# Potential Submission Strategies (2)

- **Emerging Technology Team**
  - CDER/OPQ & ORA representatives
  - Mechanism for pre-submission interactions
  - CDER-ETT@FDA.HHS.GOV
- **Encourage Pre-submission Interactions**
  - Increases likelihood for first review cycle approval

# Current Pharma Usage of RMM

- **Environmental Monitoring**
  - Surface
  - Viable Air
- **Water Monitoring**
- **In-Process Bioburden**
- **Release testing**
  - Microbial enumeration in drug product release (non-sterile)
  - Sterility



# Potential Barriers to change

- **Reservations for Industry**
  - Resources
  - Validation
  - Increased sensitivity of test
  - Concern for regulatory scrutiny or approval (review & inspection)

# Case study #1

- **Non-sterile, aqueous drug product**
- **Proposed Microbial Limit RMM Test 2 Tier decision tree process**:
  - **Tier 1**: RMM using ATP bioluminescence test

Negative for ATP
No further testing

Positive for ATP
**Tier 2**: Classic USP<61> & <62> testing performed, along with in-house test method for BCC



# Case study #1 (2)

- **Provided:**
  **RMM validation data & BCC method and validation data**
- **Requested:**
  **RMM method/SOP**
  **Method verification for Tier 2 test (USP <61> & <62>) requested**
- **Resolution: Requested RMM method and USP <61> & <62> method verification data provided**

# Case study #2

- **Non-sterile, multi-dose topical drug product**
- **In Process & Release Specifications for DP:**

| Microbial Limits | Limit |
|---|---|
| Total aerobic microbial count (TAMC) | NMT 200 cfu/ml (Max) |
| Total yeast and mold count (TYMC) | NMT 20 cfu/ml (Max) |
| *Pseudomonas aeruginosa* | Negative |
| *Staphylococcus aureus* | Negative |
| *Salmonella* | Negative |
| *E.coli* | Negative |
| *Burkholderia cepacia* | Negative |



# Case study #2(2)

- **Proposed Microbial Limit RMM Test 2 Tier decision tree process**:
  - **Tier 1**: RMM using ATP bioluminescence test

Negative for ATP

No further testing

Positive for ATP

**Tier 2**: Classic USP<61 & <62> testing performed (pour plates), along with in-house test method for BCC

# Case study #2(3)

- Adequate validation data provided in application
- Facility concerns



# Case study #2(4)

*The FDA acknowledges the* Burkholderia cepacia *complex (BCC) testing is included in the release specification and data are also provided for the exhibit batches. However, more information is needed. Please address the following points:*

1. ***Identify potential sources*** *for introduction of BCC during the manufacturing process and describe the* ***steps to minimize the risk*** *of BCC organisms in the final drug product.*
2. *We recommend that* ***potential sources are examined and sampled*** *as process controls. These may include raw materials and the manufacturing environment.*
3. ***A risk assessment*** *for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria.*

# Case study #2(5)

- Provided expanded EM program to collect in-process bioburden data & cleaning surveillance data
- Data used to developed criteria for these in-process tests (for various samples and stages of manufacturing)
- Cleaning Validation Master Plan developed



# Case study #2(5)

Cleaning Validation Master Plan:

- Risk Assessment
- Uses both USP and In-house isolates for cleaning & sanitization efficacy studies
- Established bioburden baseline criteria (prior to cleaning)
- Confirmation of cleaning process effectiveness for objectionable organisms
- Established frequency for re-validation of cleaning processes

# Case study #2(5)




# Case study #3

- Sterile lyophilized powders & Sterile solutions
- Proposed change
  - Switch from USP <71> sterility testing on product release to a RMM
  - RMM based on membrane filtration and fluorescent cell labeling

# Case study #3(2)

- **Provided:**
  - **Validation:**
    - Generally followed lists of validation parameters from USP <1223> & PDA TR 33
    - Studies included a variety of microorganisms (including slow growers and environmental isolates)
    - Used relevant inoculation levels
    - Included examination of all products for interference with fluorescent detection system
  - **Criteria for invalidating the test and retesting described**
    - Can revert to USP <71>
  - **Sterility test results on 10 batches of product using both test methods – not necessary!**



# Case study #4

- **Sterile aqueous solution**
- **Proposed change**
  - **Switch from USP <71> sterility testing on release to a RMM**
  - **RMM based on $CO_2$ production and detection of colorimetric change**

# Case study #4(2)

- **Provided:**
  - RMM validation data
- **Requested:**
  - Sample incubation temperatures, which appeared to be undefined
  - A variety of microorganisms be used in validation studies
    (including slow growers or stressed cells)
  - A tighter limit of detection study acceptance criterion
    (as ≤ 10 CFU was too high)


- **Resolution:**
  - Method validation deficiencies addressed in amendment



# Contact Information

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FDA U.S. FOOD & DRUG ADMINISTRATION

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# Rapid Microbiological Methods:

Current Status and
Regulatory Perspective

Dr. Oleg Krut
Section Head
EDQM-Conference
10-11. 10. 2017

## PEI as NCA for biologicals products ensures Microbial and Pyrogenic Safety of

- **Vaccines and Monoclonal Antibodies**
- **Blood Products e.g.**
  - **albumin, IVIG**
  - **platelet- or erythrocyte concentrates**
- **Tissue preparations e.g.**
  - **cornea**
  - **musculoskeletal tissue**
  - **heart valves, vessels**
  - **bone marrow-derived stem cells**
- **Advanced Therapy Medicinal Products (ATMPs) e.g.**
  - **genetically engineered cells**
  - **somatic cell therapy**
  - **tissue engineered products**

**Cell and tissue products**

## Cell and tissue products are challenging for microbial safety testing

- **Final product cannot be sterilized (loss of function):**
  - Viable human material (cells/tissues)
- **Source material sterility cannot be "guaranteed"**
  - contamination rates up to 50-90% -> "aseptic" procurement
  - establishment of cell banks usually not possible
  - limitations of donor exclusion criteria -> subclinical infections
- **Cultivation or storage at conditions permissive for growth of pathogens**
- **Interference with testing procedures**
  - highly heterogeneous material (solid organs, skin biopsies, bone marrow, adipose tissue)
  - contain antibiotics to reduce initial bioburden
    **=>** masking possible contamination
- **Compendial methods for microbiological control are not rapid**



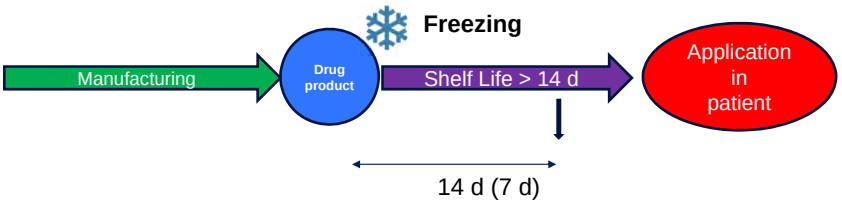
## Current status of microbiological control for cell and tissue medicinal products

| Parameter | Test | Compendial Method | Duration |
|---|---|---|---|
| bacterial / fungal contamination | Sterility / Microbiological Control | 2.6.1<br>2.6.27<br>2.6.12 | 14 days<br>7 days |
| mycoplasma | Mycoplasma | 2.6.7 | (NAT 1 day) |
| pyrogen | BET / MAT / Pyrogen | 2.6.14<br>2.6.30<br>2.6.8 | (1-2 days) |

No applications for rapid microbiological methods were submitted to PEI recently

**Is the situation satisfactory?**

# Compendial methods are adequate only for some cellular and tissue medicinal products



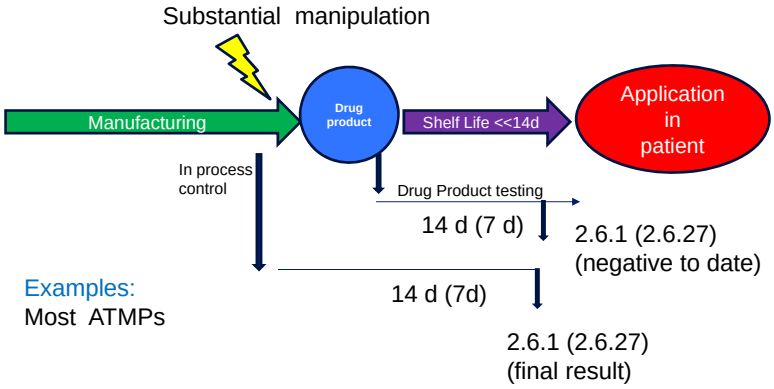

Examples:
Acellular tissue
Hematopoetic Stem Cells

Ph. Eur 2.6.1 (2.6.27)
Final Result

⇒ **Implementation of Rapid Microbial Methods are optional and up to Manufacturer**



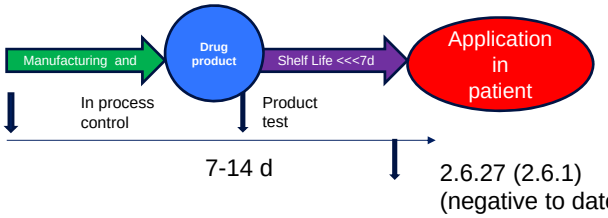
# Frequently compendial methods are suboptimal




Examples:
Most ATMPs

**=> RMM development for the Drug Product characterization is desirable**

## Sometimes compendial methods are inadequate




Examples:
Platelet Concentrates
Some ATMPs

"Quality by Design"
+ donor selection
+ preventive treatment
+ strict limit of shelf life

**=> Urgent need for RMM**



## Are there rapid microbiological methods on the market?

| Detection | Name* | | Properties | To replace? | Duration |
|---|---|---|---|---|---|
| metabolic byproducts | Bactec/ Bact/Alert Bactometer | Culture Automates | **Growth qualitative** | 2.6.1 | 2-7 days |
| Fluorescence | Growth Direct | Microcolony Detection | **Growth quantitative** | 2.6.1 2.6.12 | 10 hours - 2 days |
| Bioluminescence | Miliflex | ATP Biolumine-scence | **Growth quantitative** | 2.6.1 2.6.12 | 1-5 days |

*® by respective manufacturers

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| Bioluminescence | Miliflex | ATP Biolumine-scence | Growth quantitative | 2.6.1 2.6.12 | 1-5 days |
| Flow cytometry | Bactiflow FACS MicroCount | Live / Dead Fluorescent staining | **Direct detection** | 2.6.12 | **Hours** |
| Cell component detection | MicroSeq ID PyroSense | DNA / RNA Detection Endotoxin | **No clear Live / Dead discrimination** | 2.6.12? 2.6.1?? | **Hours** |

*® by respective manufacturers



## Problem: direct / component detection methods are not suitable for sterility testing

| Detection | Name* | | Properties | To replace? | Duration |
|---|---|---|---|---|---|
| metabolic byproducts | Bactec/ Bact/Alert Bactometer | Culture Automates | Growth qualitative | 2.6.1 | 2-10 days |
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| Flow cytometry | Bactiflow FACS MicroCount | Live / Dead Fluorescent staining | Direct detection | 2.6.12 | Hours |
| Cell component detection | MicroSeq ID PyroSense | DNA / RNA Detection Endotoxin | No clear Live / Dead discrimination | 2.6.12? 2.6.1?? | Hours |

Sterility

Bioburden

**=> Choose a right method or change product characteristics!**

*® by respective manufacturers

# Question for Discussion:

Do we require sterility for inherently
"non-sterile" cell and tissue medicinal products?

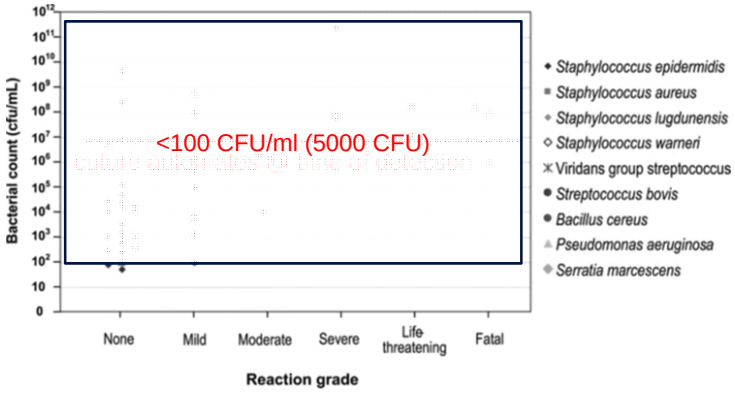
Is it not better to accept a certain limit for bioburden?
(and exclude objectionable organisms)

⇒ This would allow broader application of growth-independent methods for microbiological control



## Rationale for this question

Relationship of bacterial species and bacterial load to occurrence and severity of transfusion reactions.




**It may be more safe release product with result "< 100 CFU/ml" by direct method vs "negative to date" by sterility test**

=> Vigilance is important

Jacobs MR Clin Infect Dis. 2008

## Why RMM are not preferred to compendial methods?

| Detection | Name* | | Properties | To replace? | Duration |
|---|---|---|---|---|---|
| metabolic byproducts | Bactec/ Bact/Alert Bactometer | Culture Automates | Growth qualitative | 2.6.1 | 2-10 days |
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**= > Validation Necessary (Ph Eur 5.1.6)**

*® by respective manufacturers



## Validation accordingly to Ph. Eur 5.1.6

| Activity | Normally carried out by | |
|---|---|---|
| | Supplier | User |
| Primary validation | + | - |
| User Requirement Specification (instrument, application) | - | + |
| Description of the technique | + | - |
| Risk benefit analysis | - | + |
| Design qualification (DQ) | - | + |
| Installation qualification (IQ) | - | + |
| Operational qualification (OQ) | - | + |
| Performance qualification (PQ): | | |
| - verification of primary validation data given by the supplier; | - | + |
| - verification for the intended use (e.g. sterility testing, TAMC/TYMC, …); | - | + |
| - method suitability test | - | + |

## Validation criteria in PQ

| Criterion | Qualitative test | Quantitative test | Identification test |
|---|---|---|---|
| Accuracy | + | + | + |
| Precision | - | + | - |
| Specificity | + | + | + |
| Detection limit | + | - | - |
| Quantitation limit | - | + | - |
| Linearity | - | + | - |
| Range | - | + | - |
| Robustness | + | + | + |
| Suitability testing | + | + | - |
| Equivalence testing | + | + | |

**=> Must be performed by every user even for the same product?!**



## Burden of repeated performance qualification

Example 1:

- Large contract laboratory
- Validation of ATP-based test as a sterility test (7 vs 14 days)
- Selection of microorganisms (aerobic, anaerobic, yeast, fungi, spores, slow-growing, fast-growing, mixture, stressed, environmental isolates)
- **>700 Samples** tested alone for equivalence test
- **3-4 Person-year spent**

Example 2:

- Big Pharma Co.

"Validation of single RMM (incl. authorization by regulators) will take 3-5 years and have estimated costs of **1-2 Mil. €**"

## Most applicants are unable to perform proper validation of rapid microbiological methods

- > 90% small & medium enterprises, start-ups, research facilities & universities, tissue banks
- > 80% with less than 50 employees

-> limited human & financial resources
-> limited regulatory experience



## Question for Discussion: should PQ be performed once for particular method?

**Prerequisites:**

- Same product (matrix)
- Appropriate method has been validated (elsewere)
- Validation data are available for user
- Method is established at user site

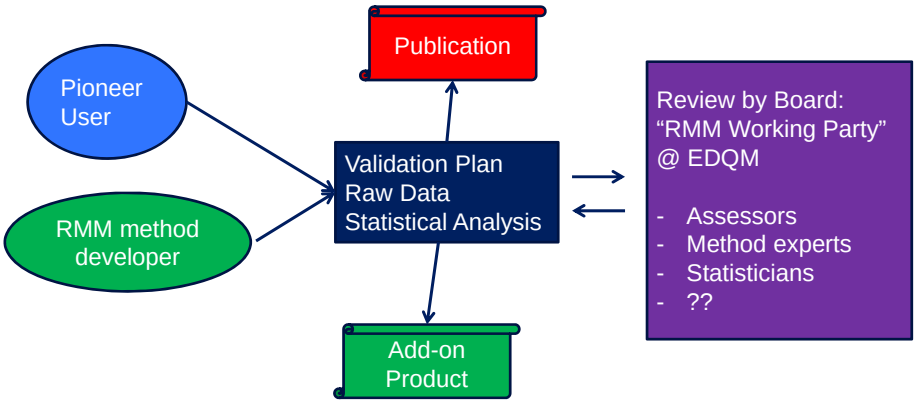
**Example:**

Microbial control of cornea transplants
- same tissue type
- same culture media
- same detection methods (culture automates as sterility test)

⇒ Full ("Master") validation performed by single tissue bank
validation plan, protocol and results are provided to other banks
⇒ reduced validation plan performed by others (method transfer)

=> changes in 5.1.6 might be necessary

## How to Regulate such two-stage Validation?



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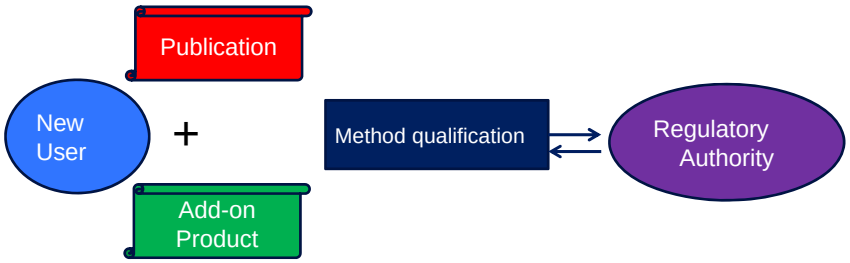


≈ compendial method

# Thank you for the Attention

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