

USP Evolving Position on Use of Rapid Microbial Methods

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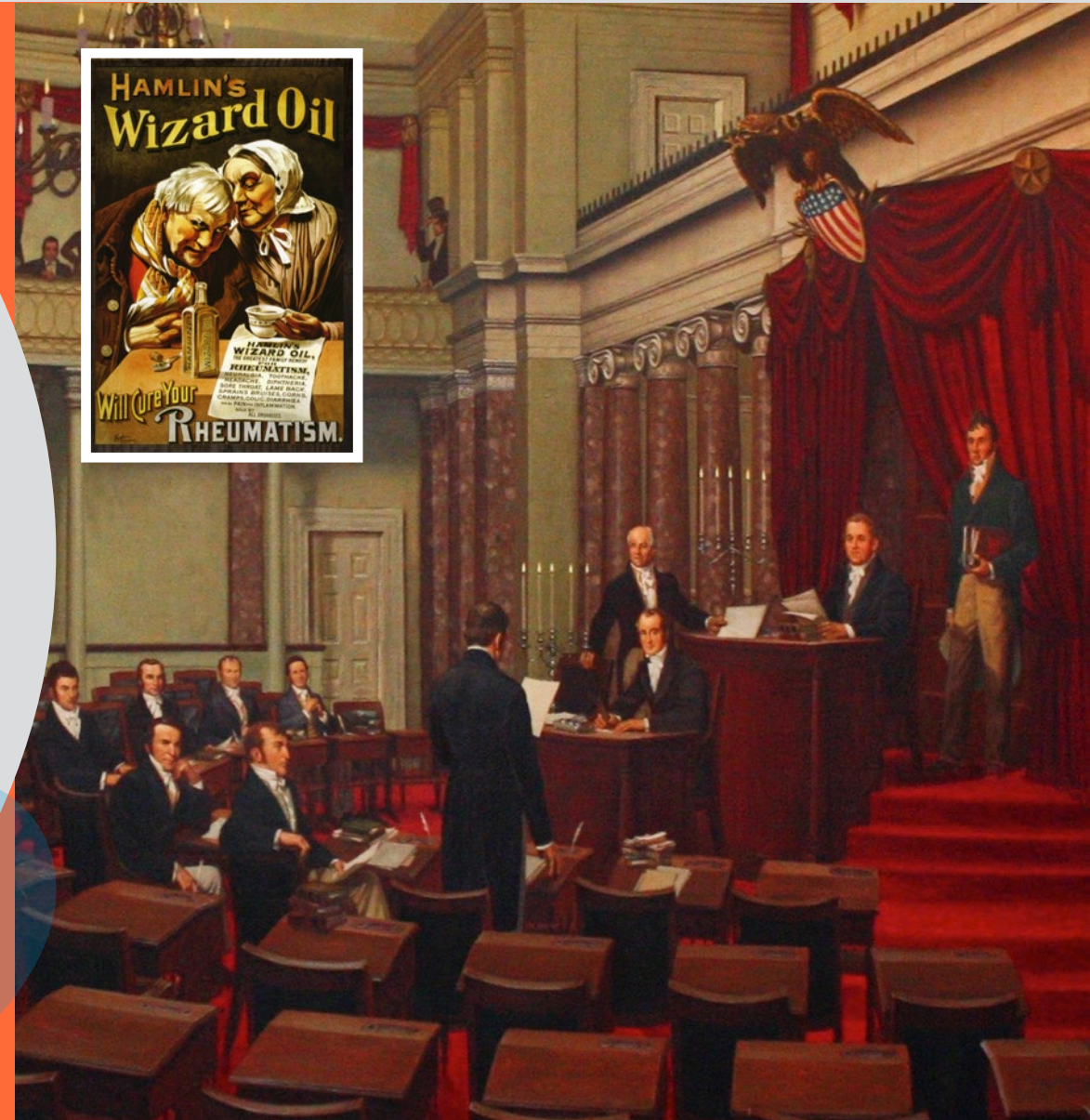
CASSS Cell & Gene Therapy Products
June 27, 2023



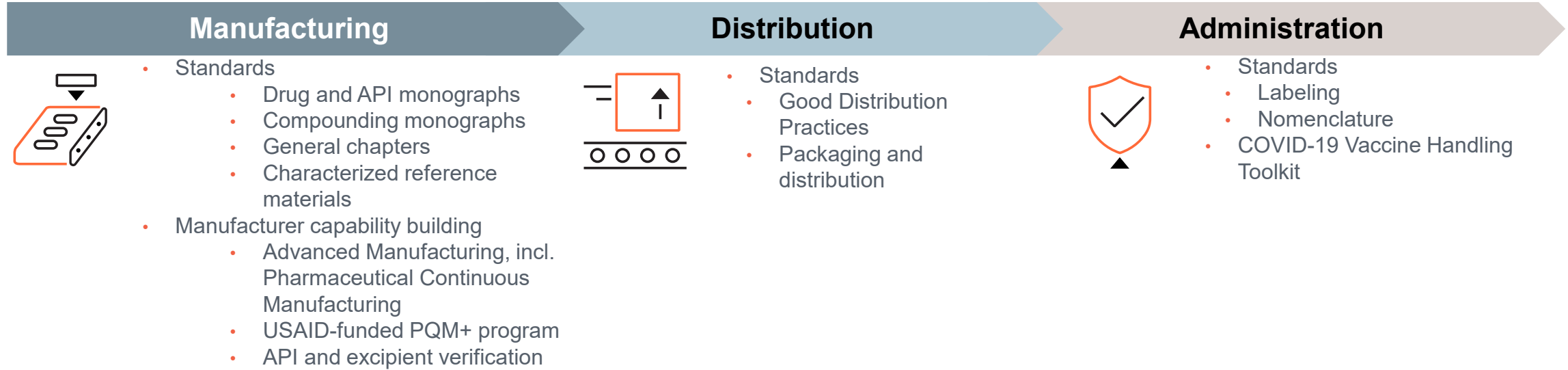
USP's Enduring Mission



To improve global health through public standards and related programs that help ensure the quality, safety, and benefit of medicines and foods.



More than 7,000 USP standards support quality across the supply chain



- ▶ USP does not enforce its standards
- ▶ USP has longstanding role in determination of whether drugs (including biologics) are deemed “adulterated” or “misbranded”
- ▶ Enforcement of USP standards is the responsibility of FDA and states that have adopted or adapted USP standards

USP standards: Types



▶ General Notices

- Key information supporting use of standards
- Required unless noted otherwise in monograph

▶ General Chapters

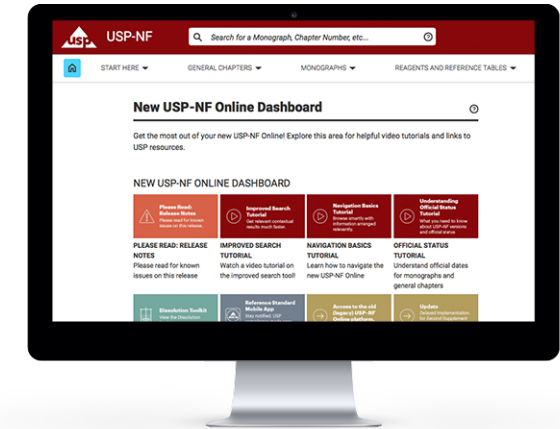
- Required when monograph, another applicable chapter or General Notice cites them (numbered <1000)
- Some are informational ONLY (numbered 1000-1999)
- Support monographs by centralizing methods and procedures

▶ Monographs

- Specifications for pharmaceutical articles in commerce (from release through product shelf life), linked through name
- Specifications – Tests, assays and acceptance criteria needed to demonstrate the article meets required quality standards

▶ Physical Reference Materials

- Provide traceable standards to demonstrate broad-based acceptability of procedures



USP standard setting committees

1000 expert volunteers and 200 FDA liaisons



Biologics



**Biologics Monographs 1 -
Peptides & Oligonucleotides**
Michael De Felippis

**Biologics Monographs 2 -
Proteins**
Wendy Saffell-Clemmer

**Biologics Monographs 3 -
Complex Biologics & Vaccines**
Earl Zablackis

**Biologics Monographs 4 -
Antibiotics**
Matthew Borer

**Biologics Monographs 5 -
Advanced Therapies**
Mehrshid Alei

Small Molecules



Small Molecules 1
Mary Seibel

Small Molecules 2
Justin Pennington

Small Molecules 3
Eric Kessler

Small Molecules 4
Kim Huynh-Ba

Small Molecules 5
Amy Karren

**Over-the-Counter (OTC)
Methods & Approaches**
Raphael Orna

Excipients



Simple Excipients
Eric Munson

Complex Excipients
Otilia Koo

Excipients Test Methods
Chris Moreton

General Chapters



General Chapters-Dosage Forms
Martin Coffey

**General Chapters -
Chemical Analysis**
Nancy Lewen

General Chapters-Microbiology
Mark Schweitzer

**General Chapters-
Packaging & Distribution**
Renaud Janssen

**General Chapters - Measurement
& Data Quality**
Jane Weitzel

General Chapters-Statistics
Charles Tan

**General Chapters -
Physical Analysis**
Richard Meury (pro tempore)

Healthcare Quality & Safety



Nomenclature & Labeling
Stephanie Crawford

Healthcare Safety & Quality
Melody Ryan

Compounding
Brenda Jensen

**Healthcare Information
& Technology**
Jeanne Tuttle

Dietary Supplements & Herbal Medicines, Food Ingredients



**Botanical Dietary Supplements
& Herbal Medicines**
Robin Marles

**Non-botanical Dietary
Supplements**
Guido F Pauli

**Dietary Supplements Admission
Evaluation & Labeling**
Tieraona Low Dog

Food Ingredients
Jon DeVries

GC Microbiology Expert Committee 2022-2025 Cycle



USP Volunteers

- Mark Schweitzer (Chair)
- Allison Scott
- Antje Hermelink
- Brandye Michaels
- Charles Taylor
- Christine Massaro
- David Roesti
- Edward Tidswell (Vice-Chair)
- Friederich von Wintzingerode
- Jay S. Bolden
- Jessica Vencill Hankins
- Liliana Gamboa
- Lynne Ensor
- Marianne Larsen
- Marsha Steed
- Meicheng Yang
- Peter Nissen
- Phil Duncanson
- Vanja Kastelic
- Victoria Abbott-Ozug

Government Liaisons

- Andrea Ottesen, FDA
- Colleen Thomas, FDA
- Marla Stevens-Riley, FDA
- Peter Bryk, FDA
- Poulomi Nandy, FDA
- Shannon Ruelle, FDA
- Simleen Kaur, FDA
- Anna Lau, NIH

USP Liaisons

- Huiping Tu; Sr. Principal Scientist
- Leslie Furr; Sr. Scientist II

EC Manager

- Kimberly McKinney



Focus Areas

- **Rapid Microbiological Methods**
- Endotoxin and Pyrogens
- Microbial Control and Sterility Assurance
- Bioburden
- Sterilization
- Aseptic Processing
- Cell and Gene Therapy Products
Microbial Control



Why Rapid Microbial Methods?



- ▶ The absence of adventitious agent (bacteria, mycoplasma, virus etc.) is critical for the quality of pharmaceuticals, where contamination event can arise from a contaminated starting materials or during production (e.g., cell line, cell substrates, equipment, facilities and/or operators).
- ▶ Determination of sterility of final product: 14 days of incubation; USP GC<71>; EP 2.6.1 & JP 4.06
- ▶ Determination of mycoplasma in cell culture: 28 days of incubation; USP GC<63>; EP 2.6.7
- ▶ Products with a **short life, limited supply, and urgent needs**, are usually infused into patients before the completion of the test
 - Advanced therapies (cell and gene therapies)
- ▶ Rapid microbial methods offer alternatives to traditional compendial methods: reduced time for testing, advanced technologies and possible automation, increased sensitivity and accuracy

Moving Toward Rapid Microbial Testing: US Regulatory Guidance and Regulations



- ▶ 21 CFR 610.12: Biologics sterility testing
 - ***Microbiological Testing*** required for cell banks, in-process intermediates, and final product.
- ▶ FDA (2008): Guidance for FDA Reviewers & Sponsors: Content and Review of CMC Information for Human Somatic Cell Therapy INDs
- ▶ FDA, (2020): Guidance for Industry: Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)
 - Recommends in-process testing 48 to 72 hours prior to final harvest or after the last re-feeding of the cell cultures
 - Recommends a rapid microbial detection test on the final formulated product

Compendial and Other Recommendations for Rapid Microbial Methods (RMMs)



▶ USP

- <1223>: Validation of alternative microbiological methods
- <1071>: Rapid microbial test for release of sterile short life products: a risk-based approach

▶ EP

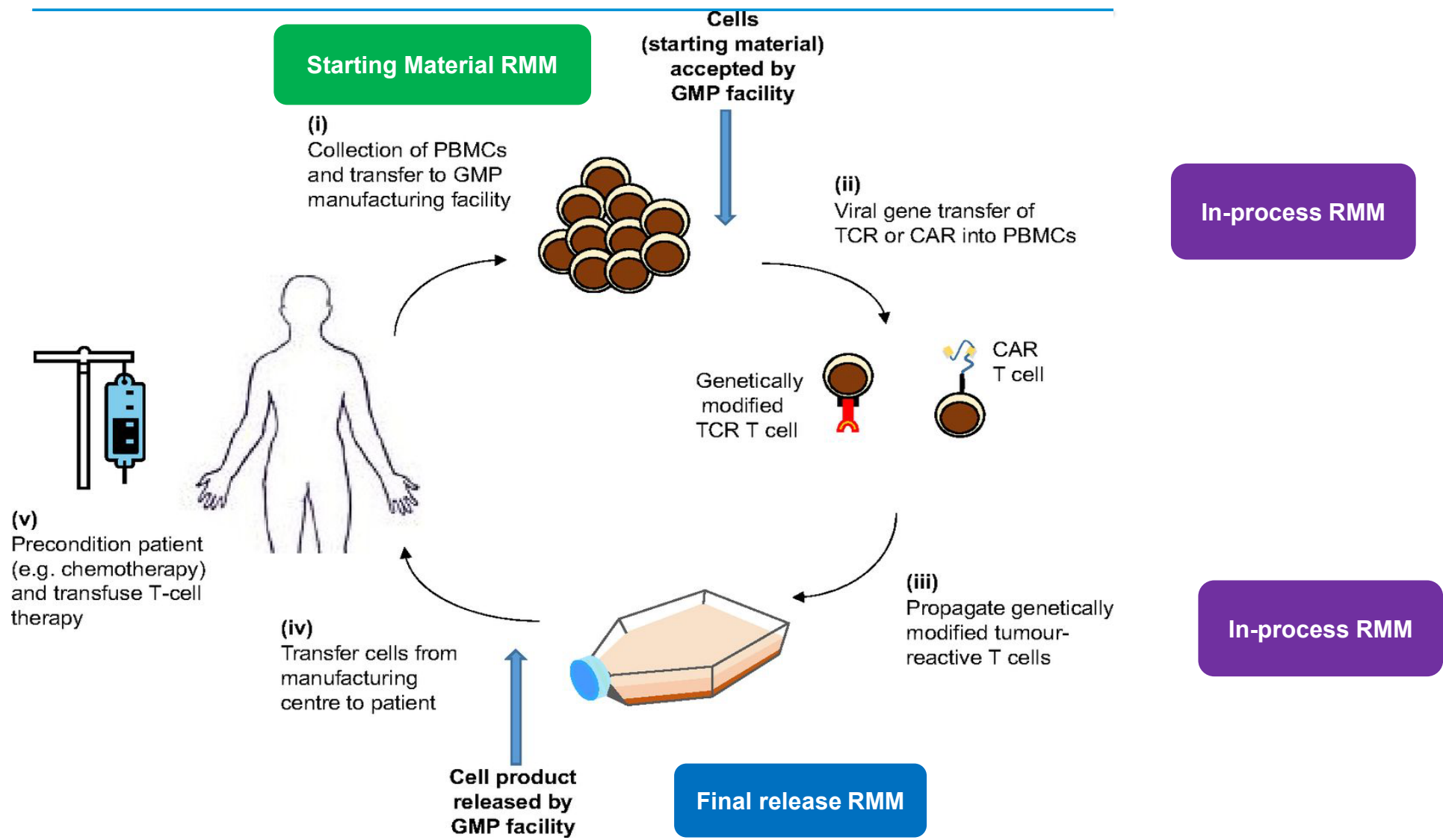
- 5.1.6: Alternative Methods for Control of Microbiological Quality
- 2.6.27: Microbial contamination for cell therapy products

▶ JP: G4 5.2: Rapid Microbial Methods

▶ PDA Technical Report #33: Evaluation, Validation and Implementation of New Microbiological Testing Methods

▶ Annex 1 “Manufacture of Sterile Products” : The use of appropriate technologies (e.g. .. rapid microbial testing and monitoring systems) should be considered to increase the protection of the product.

Use of RMM in Ex Vivo Cell Therapies



USP General Notices for Alternative Methods



The USP allows for alternative methods:

- ▶ General Notices 6.30 *Alternative and Harmonized Methods and Procedures* allows for the use of an alternative to the compendial test method provided that it is validated according USP <1225> *Validation of Compendial Methods* and produce comparable results to the compendial method.
- ▶ To address the specific requirement of microbial testing, USP <1223> *Validation of Microbiological Methods* was written and became official in 2008.
- ▶ The revised chapter <1223> providing more flexibility to the implementation of alternative methods was published online in the July-August 2015 Pharmacopeial Forum with an official date of December 1, 2015.

- ▶ The USP is open to the inclusion of new / rapid test methods (see USP General Notices and Requirements 6.30).
- ▶ Any new method:
 - must be broad in application, i.e., suitable for use with the vast majority of monographed products.
 - must not be single source, patented technology.
 - must be open source and able to be applied in any laboratory.
- ▶ Evaluation of candidate methods that might supplant existing referee method is in progress and will continue in the current 2020-2025 cycle.

- ▶ The USP Microbiology EC recommended a **risk-based approach** to rapid sterility testing where a compromise between time-to-result, limit of detection, and sample size would promote patient safety by providing results prior to the administration of the product
- ▶ Products with a **short life, limited supply, prepared for immediate use and urgent needs**, are usually infused into patients before the completion of the test
- ▶ Based on the 2017 stimulus article, USP published a general informational chapter <1071> entitled “Rapid Sterility Testing of Short-life Products: A **Risk-Based Approach**” official in the Second Supplement to USP 42/NF 37 on December 1, 2019.
- ▶ ATP bioluminescence, flow cytometry, isothermal micro-calorimetry, nucleic acid amplification, respiration, and solid phase cytometry were recommended to advance as candidates for USP General Test Methods

Rapid Microbial Methods Chapters Under Development



- ▶ The USP Microbiology EC are working to draft a series of official rapid microbial contamination tests based on the validation data from the peer-reviewed literature, submission from sponsor and, if necessary, collaborative proof of concept and validation studies

General Chapters	Update	
<72> Respiration-Based Microbial Methods for the Detection of Contamination in Short Life Products	• PF 46(6)	• Ongoing major revision of <72> & <73> based on the comments received from PF, EC members and GLs • Revising <1071> to align with the content in <72>, <73> & <74> • All three revised chapters will be published in PF
<73> ATP Bioluminescence-Based Rapid Microbial Methods for the Detection of Contamination in Short Life Products		
<74> Solid Phase Cytometry-Based Microbial Method for the Detection of Contamination in Short Life Products	• PF 48(5)	• Comments will be reviewed by the new MEC
<77> Mycoplasma Nucleic Acid Amplification Tests		

Future Directions for USP Microbiology EC

Consideration of Rapid Microbial Methods



- ▶ USP <75> nucleic acid amplification methods and USP <76> flow cytometry methods are in the plan to develop
- ▶ USP <xx> Nucleic Acid Amplification
Tests for Burkholderia cepacia complex is under development
- ▶ Explore the new technologies as alternative rapid microbial methods for determining the contamination and identification of microorganisms
- ▶ Apply the rapid microbial methods not limited to the short shelf-life products, but to the other sterile and non-sterile products where the control and reduction of microbial contamination is considered important

Opportunities for Stakeholder Participation



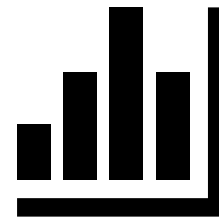
REACH OUT WITH YOUR



NEEDS



COMMENTS



DATA



EXPERTISE

hpt@usp.org

Questions



The standard of trust

Thank You



The standard of trust