



# Current Activities of the USP General Chapters -Microbiology Expert Committee

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## **Mission:**

USP's mission is to improve global health through public standards and related programs that help ensure the quality, safety, and benefit of medicines and foods.

# Role of the USP



- ▶ Non-government Pharmacopeia established in 1826
- ▶ Independent, not-for-profit, self-supporting (no external funding)
- ▶ Generates revenue from the sale of:
  - Reference Standards
  - USP publications and related products
- ▶ Standards recognized in several countries
- ▶ Volunteers from industry, academia, and government agencies are involved in setting standards
- ▶ Multinational participation in standard setting (Council of Experts)

# International Recognition

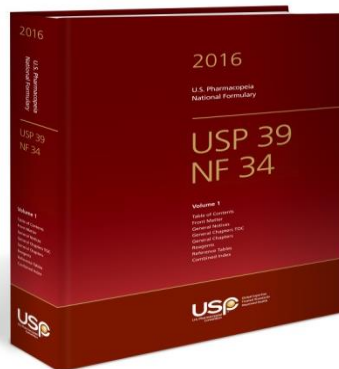


International regulatory authorities and governments have incorporated USP standards into their laws and regulatory provisions

- USP-NF is recognized in 39 countries
- FCC is recognized in 8 countries



USP Documentary Standard  
USP40/NF35 with the second supplement  
is official through May 1, 2018



***USP–NF* contains:**

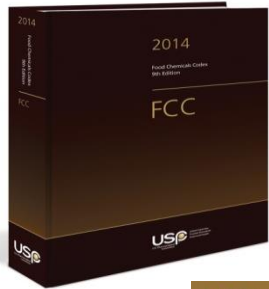
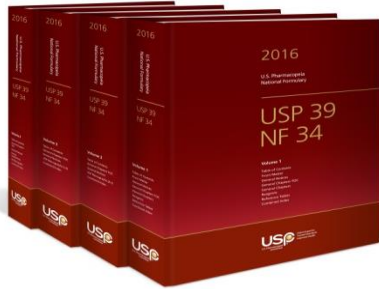
- ▶ Over 4,500 monographs
- ▶ Over 230 General Chapters

# Documentary Standards



- ▶ **Monographs**
  - Contain acceptance criteria to address quality, purity, strength, and potency of an article
  
- ▶ **General Test Chapters**
  - Standardized tests for assessing pharmaceutical quality of compendial articles and referenced in drug substances, excipient and drug product monographs and regulatory submissions
  
- ▶ **General Information Chapters**
  - Guidance to assist compendial users on relevant topics

# Documentary Standards Drivers for Official USP Reference Standards



# Reference Standards



## Reference Standards

Over 3,500 actual substances to characterize drugs, biologics, excipients, nutritional and dietary supplements





# How does USP set Standards?



- ▶ Pharmacopeial Forum Published Bi-monthly
  - Jan/Feb, Mar/Apr, May/Jun, Jul/Aug, Sep/Oct, Nov/Dec
- ▶ Established 1975
- ▶ **Available Free and Online only from Jan 2011**
- ▶ Contents
  - Policies and Announcements
  - Pharmacopeial Previews
  - In-process Revisions
  - Stimuli to the Revision Process
  - Nomenclature
  - Interim Revision Announcements
  - Harmonization with JP and Ph. Eur.

# Pharmacopeial Forum



“Pharmacopeial Forum is published to provide an opportunity for public review of and comment on revision activities affecting the United States Pharmacopeia and the National Formulary. It also provides a forum for the exchange of ideas and information relating to the development and revision of standards and analytical methods.”

# Development and Revision of Official USP Standards



Proposal is published *on-line* in *Pharmacopeial Forum* (PF) for public review and comment



Comments on PF proposal reviewed by USP Scientific Staff and Expert Committee



If **major** revisions to the proposal are needed, the **comments, responses, and, the revised proposal** are published in *PF* for additional public review.

If no further revisions or **minor revisions** are needed, Expert Committee recommends for official adoption and the **comments and responses are published in the *Commentary Section*** (<http://www.usp.org/usp-nf/official-text/proposal-statuscommentary>)



Board of Trustees approves for official adoption

## Objectives

Compatible with its overall mission, the role of USP in Microbiology is to develop public standards pertaining to microbiology, that, along with other requirements, ensure the consistent quality of products –dosage forms, drug substances, excipients, food ingredients, dietary supplements.

# USP GC-Microbiology EC 2015-2020 Members



- ▶ David Hussong, Chair
  - ▶ Edward Tidswell, Vice-Chair
  - ▶ James Akers
  - ▶ James Agalloco
  - ▶ Dilip Ashtekar
  - ▶ Tony Cundell
  - ▶ Dennis Guilfoyle
- Rajesh Gupta
  - Russell Madsen
  - Karen McCullough
  - Robert Mello
  - David Roesti
  - Paul Stinavage
  - Donald Singer



# USP GC-Microbiology EC 2015-2020 Liaisons



- ▶ Radhakrishna Tirumalai, USP Staff Liaison
- ▶ Randa Melhem, (FDA /CBER)
- ▶ Marla Stevens-Riley, ( FDA/CDER)
- ▶ Richard Friedman, (FDA/CDER)
- ▶ David Lau (FDA/ORA)
- ▶ Laura Huffman (FDA/CVM)
- ▶ Andrea Ottesen (FDA/CFSAN)
- ▶ Colleen Thomas (FDA/CDER)



# Areas of Responsibility for the Microbiology EC



- ▶ Microbiological Tests
- ▶ Microbiological Monitoring
- ▶ Not Responsible for:
  - Water
  - Monographs (other than recommendation of Microbial Limits, Sterility and Bacterial Endotoxin Specifications)
  - Antibiotic Assays

# General Test and Informational Chapters



- ▶ General test method chapters are assigned chapter numbers 1 through 999
- ▶ General informational chapters are assigned chapter numbers 1000 through 1999
- ▶ Dietary supplement chapters 2000 through 3000



# USP Microbiology Chapters - 1



- <51> Antimicrobial Effectiveness Test
- <55> Biological Indicators – Resistance Performance Tests
- <61> Microbiological Examination of Non-sterile Products: Microbial Enumeration Tests
- <62> Microbiological Examination of Non-sterile Products Absence of Specified Microorganisms
- <63> Mycoplasma Tests
- <71> Sterility Tests
- <85> Bacterial Endotoxins Test
- <151> Pyrogen Test
- <161> Medical Devices- Bacterial Endotoxin and Pyrogen Tests
- <610> Alternative Sampling Methods for Non-sterile Inhaled and Nasal Products

# USP Microbiology Chapters - 2



- <1035> Biological Indicators for Sterilization
- <1072> Disinfectants and Antiseptics
- <1111> Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical use
- <1112> Applications of Water Activity
- <1113> Microbial Identification, Characterization and Strain Typing
- <1115> Bioburden Control of Non-sterile Drug Substances and Products
- <1116> Microbiological Control and Monitoring of Aseptic Processing Environments
- <1117> Microbiological Best Laboratory Practices
- <<1208> Sterility Testing – Validation of Isolator Systems



<1207> Package Integrity Evaluation – Sterile Products

<1207.1> Package Integrity and Test Method Selection

<1207.2> Package Integrity Leak Test Technologies

<1207.3> Package Seal Quality Test Methods

# USP Microbiology Chapters - 4



## <1229> Sterilization of Compendial Articles-General Concepts

- <1229.1> Steam Sterilization by Direct Contact
- <1229.2> Moist Heat Sterilization of Aqueous Liquids
- <1229.3> Monitoring of Bioburden
- <1229.4> Sterilizing Filtration of Liquids
- <1229.6> Liquid Phase Sterilization
- <1229.7> Gaseous Sterilization
- <1229.8> Dry Heat Sterilization
- <1229.10> Radiation Sterilization
- <1229.11> Physicochemical Integrators and Indicators
- <1229.12> New Sterilization Methods
- <1229.13> Sterilization-in-Place
- <1229.14> Sterilization Cycle Development
- <1229.15> Sterilizing Filtration of Gases

# USP Microbiology Chapters - 5



- <1223> Validation of Alternative Microbiological Methods
- <1227> Validation of Microbial Recovery from Pharmacopeial Articles
  
- <2021> Microbial Enumeration Tests – Nutritional and Dietary Supplements
- <2022> Microbiological Procedures for Absence of Specified Microorganisms – Nutritional and Dietary Supplements
- <2023> Microbiological Attributes of Non-sterile Nutritional and Dietary Supplements

# <1228> Depyrogenation



The production of parenteral products requires not only that products be sterile, but that they are also free from harmful levels of pyrogens.

The most common pyrogen are bacterial endotoxins derived from the cell walls of Gram-negative bacteria

Depyrogenation is defined as the direct and validated destruction or removal of pyrogens. For the purposes of this chapter series, the term *depyrogenation* refers to the destruction or removal of bacterial endotoxins, the most prevalent and quantifiable pyrogen.

# <1228> Depyrogenation Series



## <1228> *Depyrogenation*

- ▶ <1228.1> *Dry Heat Depyrogenation*
- ▶ <1228.2> *Chemical Depyrogenation*
- ▶ <1228.3> *Depyrogenation by Filtration*
- ▶ <1228.4> *Depyrogenation by Rinsing*
- ▶ <1228.5> *Endotoxin Indicators for Depyrogenation*
- ▶ <1228.6> *Endotoxin Control*

# Purified LPS or Naturally Occurring Endotoxin (NOE)



When parenteral products are contaminated with endotoxin, the contaminant is not purified LPS, but rather whole cells or cell wall fragments where the LPS is bound to other cell wall components (NOE). Purified LPS and native endotoxin are dissimilar in many respects.

Because the LPS molecule in natural endotoxin is embedded in cell wall components, it is much less prone to aggregation and stickiness that may cause recovery problems and variability in depyrogenation studies.



# Key Activities in Progress



New and revised chapter proposals (in PF 43.5, September-October 2017 Issue)

- <1211> Sterility Assurance – Complete Revision with focus on Sterility Assurance
- <1222> Terminally Sterilized Pharmaceutical Products—Parametric release- Complete revision
- <1228.4> Depyrogenation by Washing (new proposal)



The definition of a suitable sterility assurance program for a product requires preliminary information regarding the formulation, manufacturing process and primary container.

An initial determination should be made regarding the potential for terminal sterilization of the drug product in its primary container applying the principles defined in Sterilization <1229>.

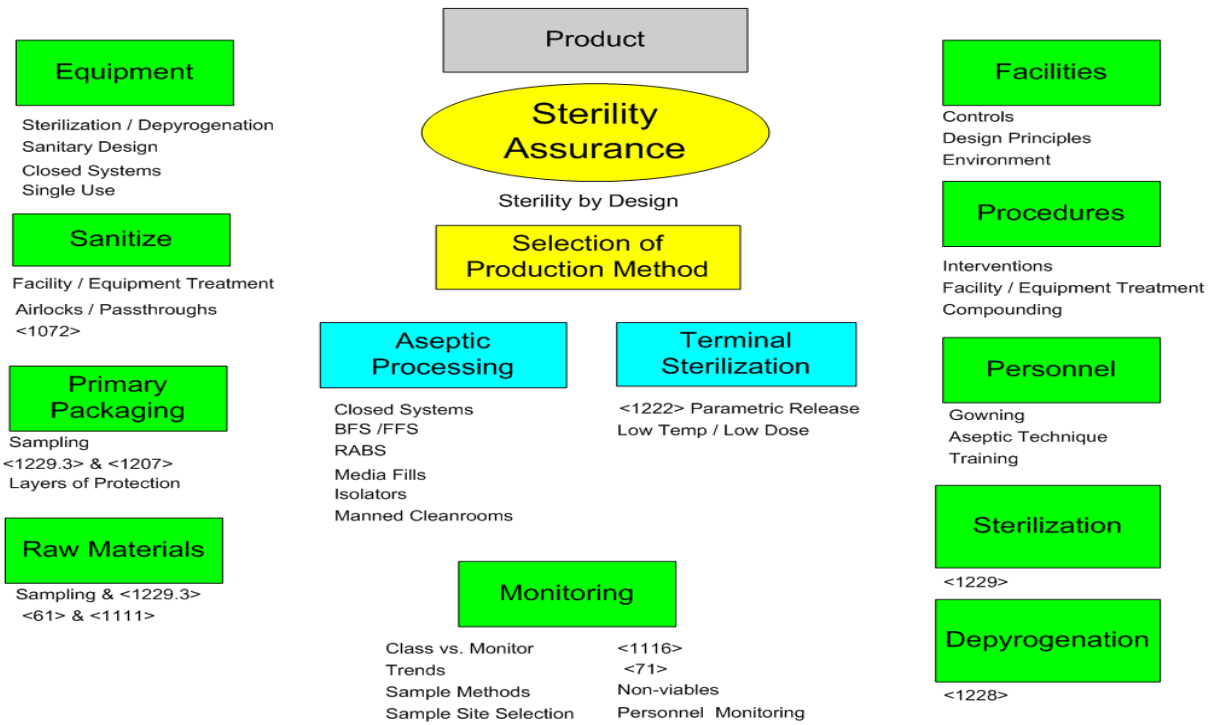
As described in <1229> the appropriate process provides a balance between conditions that are lethal to potential bioburden present in/on the drug product and those that preserve the essential quality attributes of it.



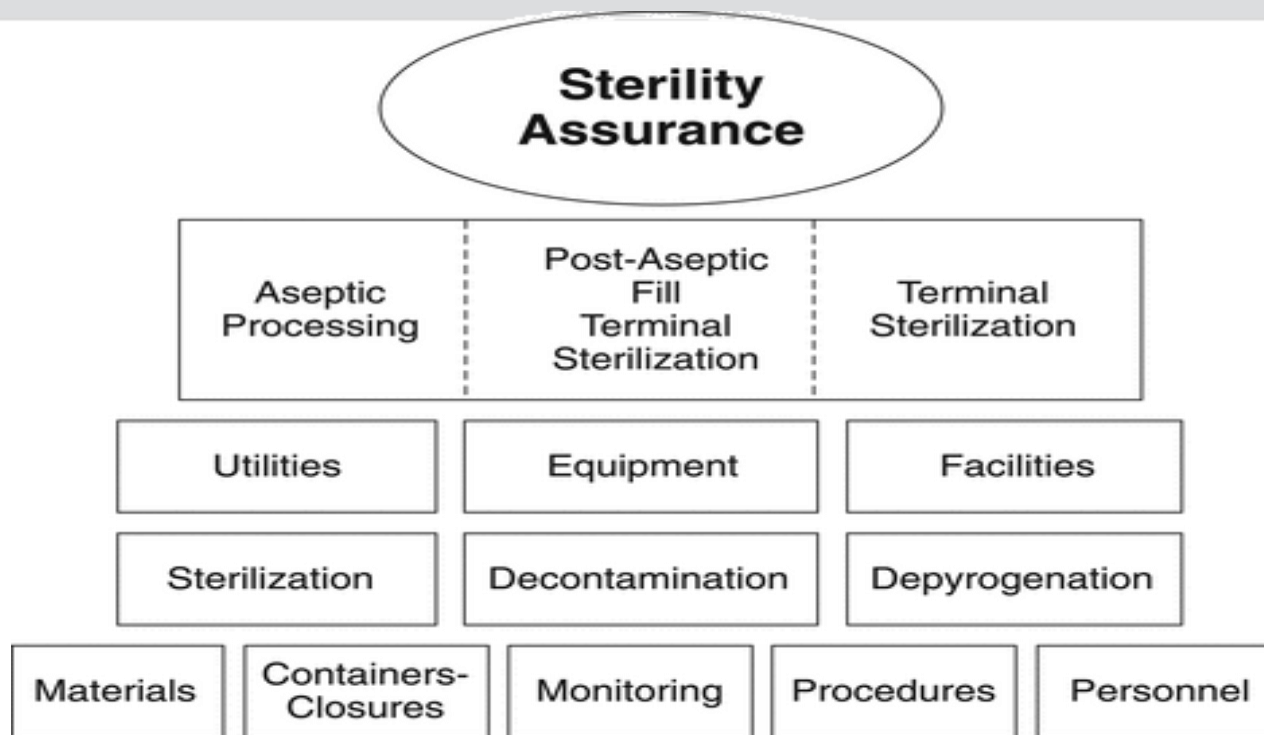
This informational chapter will provide a general description of the concepts and principles involved in the preparation of articles that must be sterile. Any modifications of or variations in the practices from those described herein should be considered in the context of the overall sterility assurance program

The sterility of an item is delivered through the implementation of interrelated controls that in combination provide confidence that the items are sterile. It is the controls that provide the assurance rather than the results of any in-process or finished goods testing.

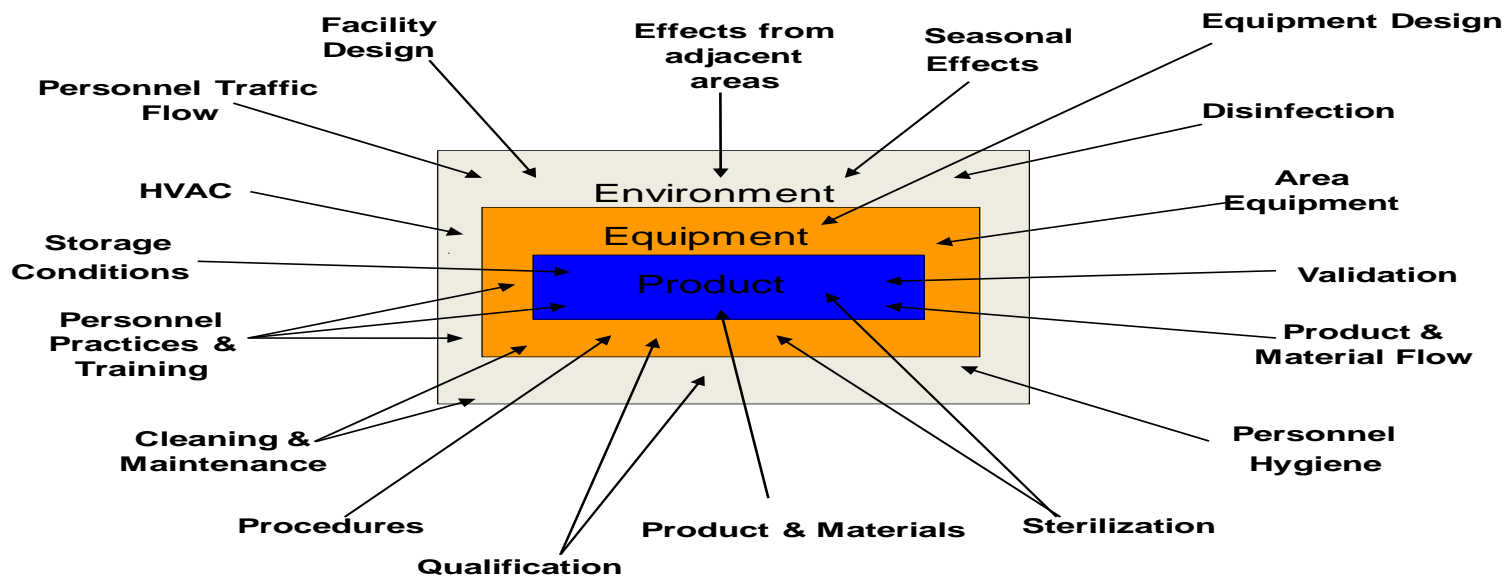
# Proposed New <1211> Sterility Assurance – Concept



# Elements Contributing to Sterility Assurance



# Influences on Sterile Products



# Key Activities in Progress



New chapter proposal <1085> Guidelines on Endotoxin Tests

With the retirement of FDA's 1987 endotoxin guideline lots of useful guidance were lost on topics such as:

- Endotoxin Limit Calculation
- Training
- To pool or not to pool
- Out-of-Specification
- RSE:CSE standardization
- Endotoxin limits for non-compendial articles
- Standard curve controls

**USP <1085> proposal expected to plug that gap.**

# Key Activities in Progress



- The USP is open to the inclusion of new / modern referee microbial test methods.
- However, any new referee method must be:
  - broad in application, i.e., suitable for use with the vast majority of monographed products.
  - not a single source, patented technology.
  - open source and able to be applied in any laboratory.
- Evaluation of candidate analytical methods that might supplant or supplement existing referee methods is planned in the current 2015-2020 cycle.



# Rapid Sterility Testing - 1



- ▶ Our stakeholders who manufacture, test and release short-lived cell-based biologicals, sterile compounded and Positron Emission Tomography (PET) injectable products find that the current USP <71> growth-based sterility test, with at least a 14 day incubation, is not suitable for their needs.
- ▶ Many of these products are administered to patients before a growth-based sterility test is complete.
- ▶ An expert panel comprised of such stakeholders and technology experts to evaluate user requirements and technologies for such a compendial test was constituted under the leadership of Drs. Cundell and Tidswell has prepared recommendations for user needs and technological appropriateness.

# Key User Requirement Specifications



- ▶ Limit of detection
- ▶ Ability to detect a wide range of viable microorganisms, i.e., specificity
- ▶ Time to result
- ▶ Availability of instruments and reagents from multiple vendors
- ▶ Availability of Reference Standards
- ▶ Sample quantity i.e., minimum number of articles tested and quantity per container tested
- ▶ Ease of use/simplicity of test and data interpretation
- ▶ Low false positive and negative rates

# Key User Requirement Specifications



- ▶ Method suitability
- ▶ Improved patient safety
- ▶ Regulatory acceptance
- ▶ Robustness and reliability of equipment
- ▶ Sample preparation
- ▶ Data integrity
- ▶ Aseptic test material handling, i.e., open vs. closed systems

# Candidate Technologies for Rapid Sterility Testing



The Expert Panel selected the following six analytical platforms, listed alphabetically as candidates for compendial rapid sterility testing:

- ▶ Adenosine triphosphate (ATP) bioluminescence
- ▶ Flow cytometry
- ▶ Isothermal microcalorimetry
- ▶ Nucleic acid amplification
- ▶ Respiration
- ▶ Solid phase cytometry

# Candidate Rapid Sterility Tests



Most commonly used rapid sterility tests and their technologies include:

- ▶ Scan RDI Microbial Detection System (Solid Phase LASER Scanning Cytometry)
- ▶ BacT/ALERT Microbial Detection System (CO<sub>2</sub> sensor)
- ▶ Milliflex Rapid System (ATP Bioluminescence)

# Rapid Sterility Testing - 2



- ▶ The Expert Panel recommendations were submitted and accepted by the USP Microbiology Expert Committee
- ▶ A stimulus article on this topic entitled *Development of Compendial Rapid Sterility Tests* has been published in in PF 43(5) September-October 2017 issue
- ▶ Next steps are the publication of USP general informational chapter, conduct proof of concept studies on candidate technologies, validate the most promising methods, and publish a general test method chapter on risk-based sterility tests.

# Key Activities in Progress



- ▶ *In response to stakeholders requests, the USP intends to publish a test for absence of Burkholderia cepacia complex in raw materials and aqueous dosage forms- oral, nasal, and topical solutions.*

# *Burkholderia cepacia* complex



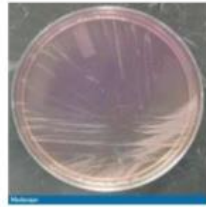
- ▶ In May 2017: In response to multiple infection outbreaks, the FDA advises drug manufacturers that *Burkholderia cepacia* complex poses a contamination risk in non-sterile, water-based drug products.



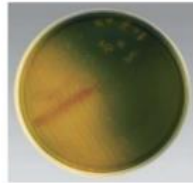
# Burkholderia cepacia



## Burkholderia cepacia



BCSA



OFPBL



# Why is *B. cepacia* a bad actor?



- *B. cepacia* complex (BCC) species are gram-negative, rod-shaped bacteria, including opportunistic pathogens, that have potential for overcoming antimicrobial preservative systems and antiseptics, and growing in aqueous oral liquids and topical products.
- BCC exhibit high metabolic versatility and variable virulence due in part to their large genomic size, i.e., 8 million base pairs, and wide-spread distribution.
- BCC may cause serious infections in individuals with cystitis fibrosis and chronic granulomatous disease
- BCC are often opportunistic pathogens among mechanically ventilated patients, the immunosuppressed and those with serious underlying disease.

# Burkholderia cepacia complex



- ▶ BCC were described by Belgium clinical microbiologist Peter Vandamme and his co-workers.
  - Associated with cystic fibrosis infection and consisting of nine genomovars with the most prevalent pathogens being *Burkholderia cenocepacia* and *Burkholderia multivorans* accounting for >85% of the BCC CF infections.
- ▶ To date 15 genomovars have been identified from clinical and environmental isolates.

# Bcc Screening Methods



Two general strategies are possible to screen for BCC:

- ▶ Modification of methods USP <62> to ensure the isolation of BCC members.
- ▶ Addition of a new chapter describing a test for the absence of *B. cepacia* complex to the specified microorganism screening.
  - These screening methods include the use of selective media for BCC.

# Bcc Screening Methods



The following test for the absence of *B. cepacia* complex is proposed:

- ▶ Not less than 1 g of product is used to inoculate soybean-casein digest broth, which is mixed and incubated at 30-35° C for 18 to 24 hours.
- ▶ Burkholderia cepacia Selective Agar (BCSA) is inoculated by streaking out from the broth and the plate incubated 30-35° C for 48 to 72 hours.
- ▶ The product complies with the test, if there is no growth on the plate.



## 2 Supplement to USP 40 Official December 2017

- <1229.14> Sterilization Cycle Development (New)
- <1229.15> Sterilizing Filtration of Gases
- <161> Medical Devices--Bacterial Endotoxin and Pyrogen Tests (revision)

# Summary



- ▶ **The USP Microbiology Expert Committee is moving forward purposefully on several important fronts with careful prioritization.**
- ▶ **Are you aware of these activities and do they meeting with your approval?**