USP Microbiology – General Chapters and Dietary Supplements 18 November 2020

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Agenda

- Introduction to USP
- Utility of USP standards
- Compendial Hierarchy

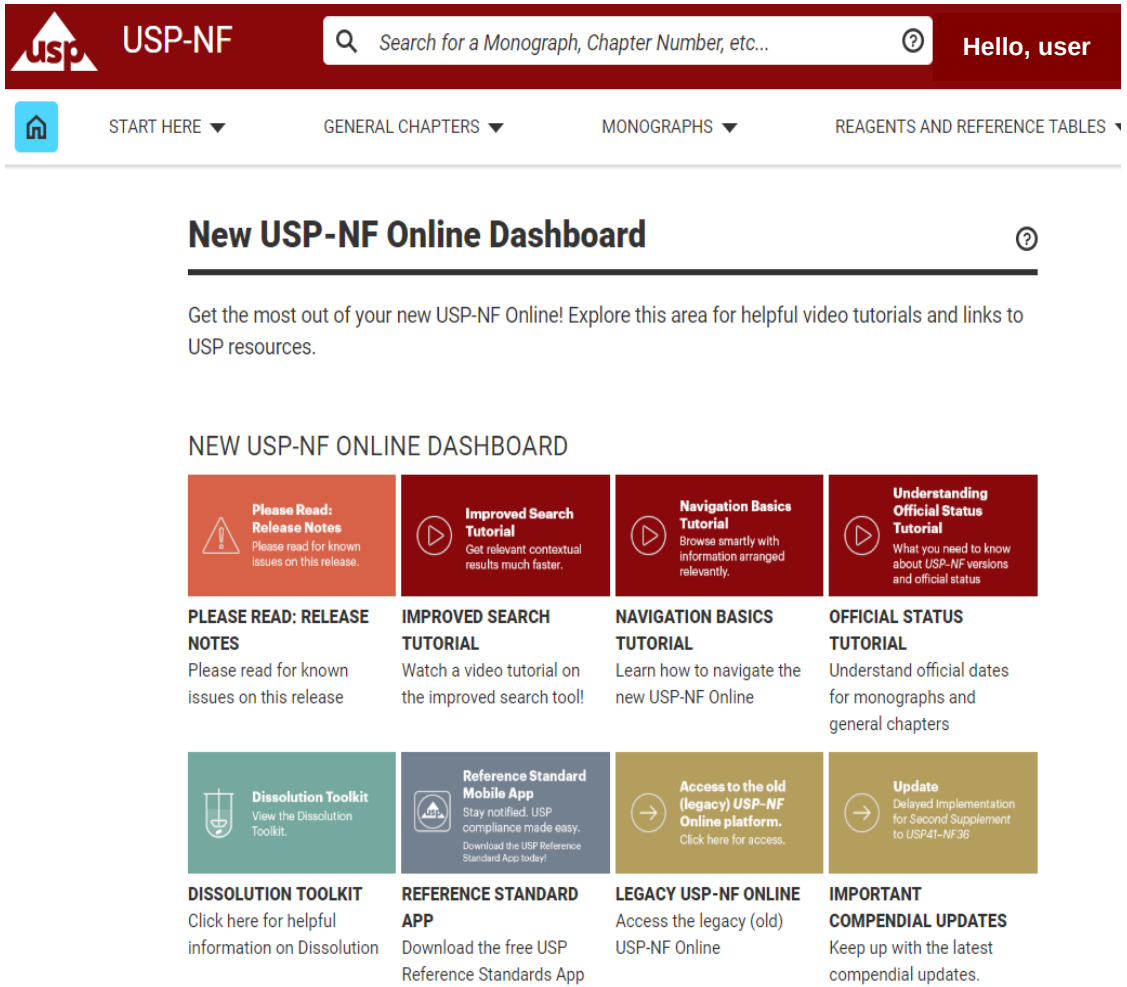
- USP microbiology chapters
- Suitability Testing
- New Chapter <60>

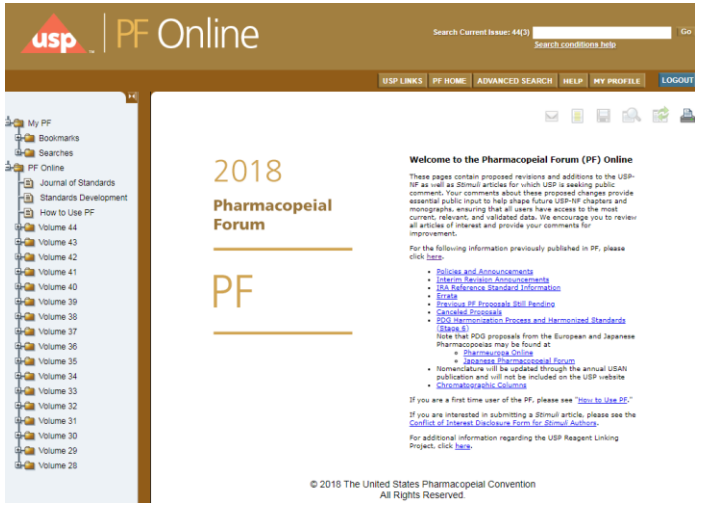
Who We Are?

Mission

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

USP COMPENDIA





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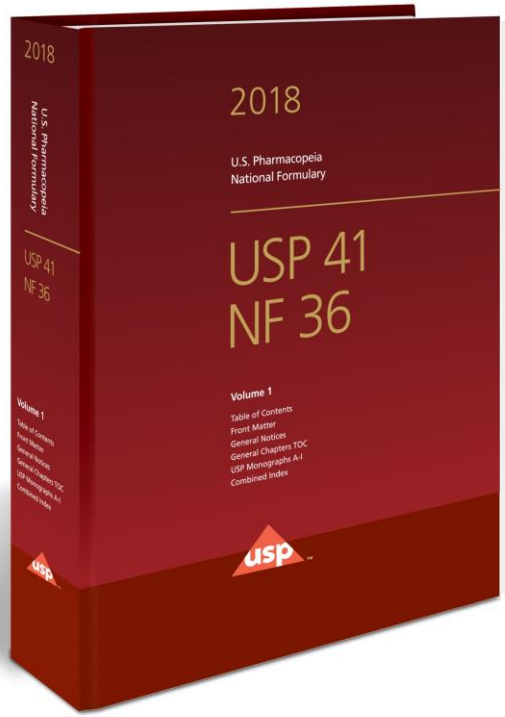
Reference Standards Directly Linked to Monographs



- ID Tests
- Related Compounds
- Impurity Tests
- Limit Tests
- Residual Solvents
- Dissolution
- Assay

The Value of Public Standards

- Provides scientific basis for decision making
- Ensures a consistent approach to quality
- Useful for monitoring of counterfeit and substandard products and quality

- Appropriate titles
- Useful definitions
- Validated methods
- Established limits

Value of public standards in DS&HM

Industry

Dietary supplement and ingredient manufactures produce quality products

Practitioner/Patient

Uphold practitioner and patient confidence in the quality of their supplements

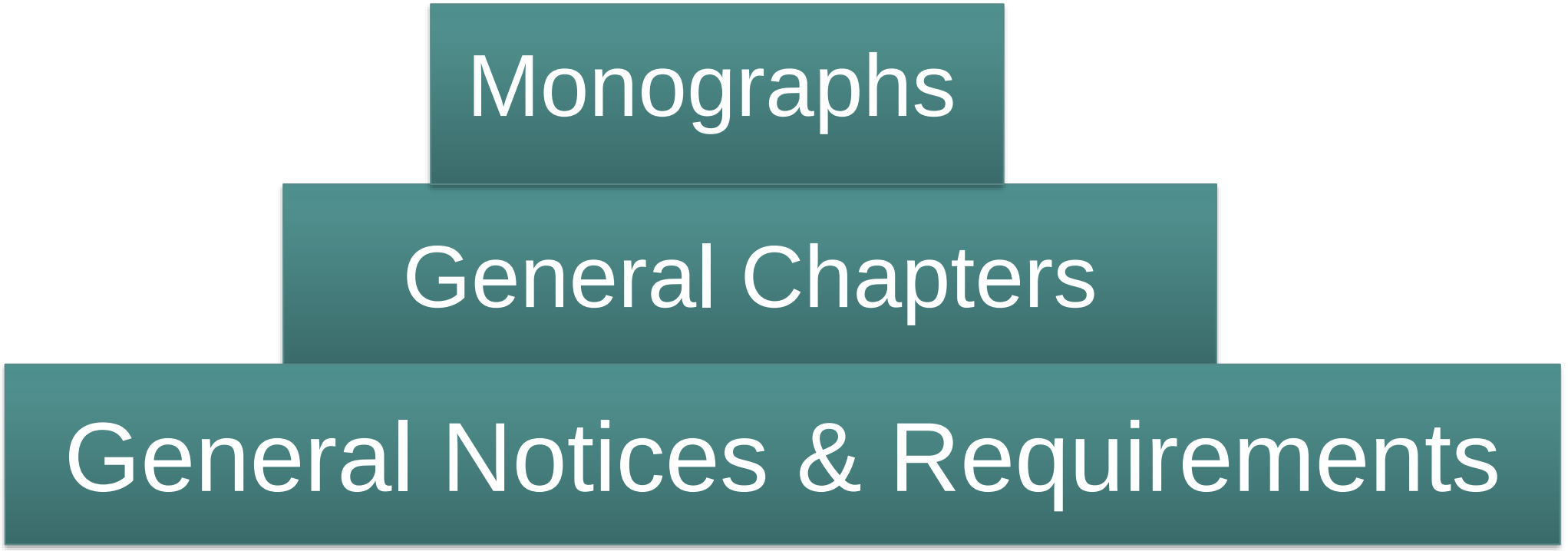
Government

Regulators ensure quality products reach consumers

Advantages to Compliance with USP Standards

- Supply Chain Transparency
  - Ingredient supplier and purchaser understand the quality of the materials purchased when using USP materials
  - Easier dispute resolution when both purchaser and supplier recognize the same test methods and specifications
- Ingredients that conform to USP may indicate USP in the ingredient table (must refer to the USP name used in the monograph, may also use another name) to indicate ingredient quality

USP Documentary Standards- Compendial Hierarchy



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General Chapters

- General chapters provide guidelines on activities related to tests and procedures in monographs
- General chapters may contain descriptions of tests and procedures, general information on interpretation of compendial requirements, or general guidance on official substances or official products
  - <1> to <999>: General tests & Assays
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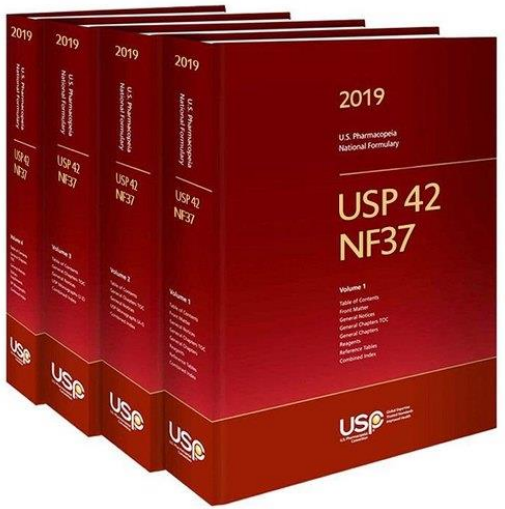
  - ≥<2000>: Dietary Supplements

USP Monographs: Dietary Supplement

- A list of official and validated tests
- Their analytical procedures
- Their acceptance criteria
- Together these define specifications for
  - *Identity*
  - *Purity/Limits for Contaminants*
  - *Content (Strength/Composition)*
  - *Quality (Performance and Other Requirements)*



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- <1000> - <1999> Informational Chapters
  - Provide information about standards, assays etc.
  - No compliance requirements associated
- Above <2000> - Dietary Supplement Chapters
  - Chapters specifically related to dietary supplement ingredients/products
  - Required if cited in monograph or General Notices when claiming compliance to USP
- Dietary Supplement monographs may also cite chapters below <2000>

USP Compendial Microbiology Tests

USP Microbiology

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

Commonly used USP Microbiological General Chapters

- <51> Antimicrobial Effectiveness Testing
- <61> Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests
- <62> Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms
- <64> Probiotic Tests
- <2021> Microbial Enumeration Tests—Nutritional and Dietary Supplements.
- <2022> Microbiological Procedures for Absence of Specified Microorganisms—Nutritional and Dietary Supplements
- <2023> Microbiological Attributes of Nonsterile Nutritional and Dietary Supplements

Microbiological quality of non sterile products

The topic is covered in two chapters:

⟨61⟩ Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests

⟨62⟩ Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms

Major Pharmacopeias ar Harmionized (USP; JP; and Eu.Ph)

These chapters applies to drug substances and drug products

DS has their equivalent test

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Comparison of <61>/<62> and <2021>/<2022>

- Differences
  - <61>/<62> Suitability of Test Method; <2021>/<2022> term Preparatory Testing
  - Difference in challenge organisms for Suitability/Preparatory Testing
  - Differences in specifications
  - <61>/<62> do not have option for retest, <2021></2022> do
- Differences between the chapters are shown in the following charts

Enumeration	<61>	<2021>
Preparatory Testing/Method Suitability		
Challenge organisms:	TAMC S. aureus P. aeruginosa B. subtilis C. albicans A. brasiliensis TYMC C. albicans A. brasiliensis	TAMC S. aureus E. coli B. subtilis TYMC C. albicans A. brasiliensis Enteric E. coli Salmonella spp.
Inoculum:	< 100 cfu	25 – 250 cfu
Recovery requirement:	NLT Factor of 2	> 70%
Test Method		
Incubation times:	TAMC: 3 – 5 days	TAMC: 48 – 72 h
Other:	See <62>	Enterobacterial count (Bile-tolerant Gram negative)
Retest:	Does not mention	Additional 10 g from original sample plus 10 g from another sample

Presence/absence	<62>	<2022>
Preparatory Testing/Method Suitability		
Inoculum:	< 100 cfu	25 – 250 cfu
Test Method		
Bile-tolerant gram negative	Absence/presence test Quantitative test	See <2021>
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Retest	Does not mention	Retest with 25 g sample but make allowances for sample size

Compendial Microbiology Tests

Validation or Method Suitability

Compendial microbiology test methods are growth-based methods which require that any microorganisms present be capable of growth in the presence of the article under test

According to 21 CFR 211.194(a)(2), laboratory records require a statement of the method used in testing the sample; that the method meet proper standards of accuracy and reliability as applied to the product tested. If the method used in testing the sample is in the current USP-NF, a statement indicating the method and reference will suffice.

Compendial Microbiology Tests

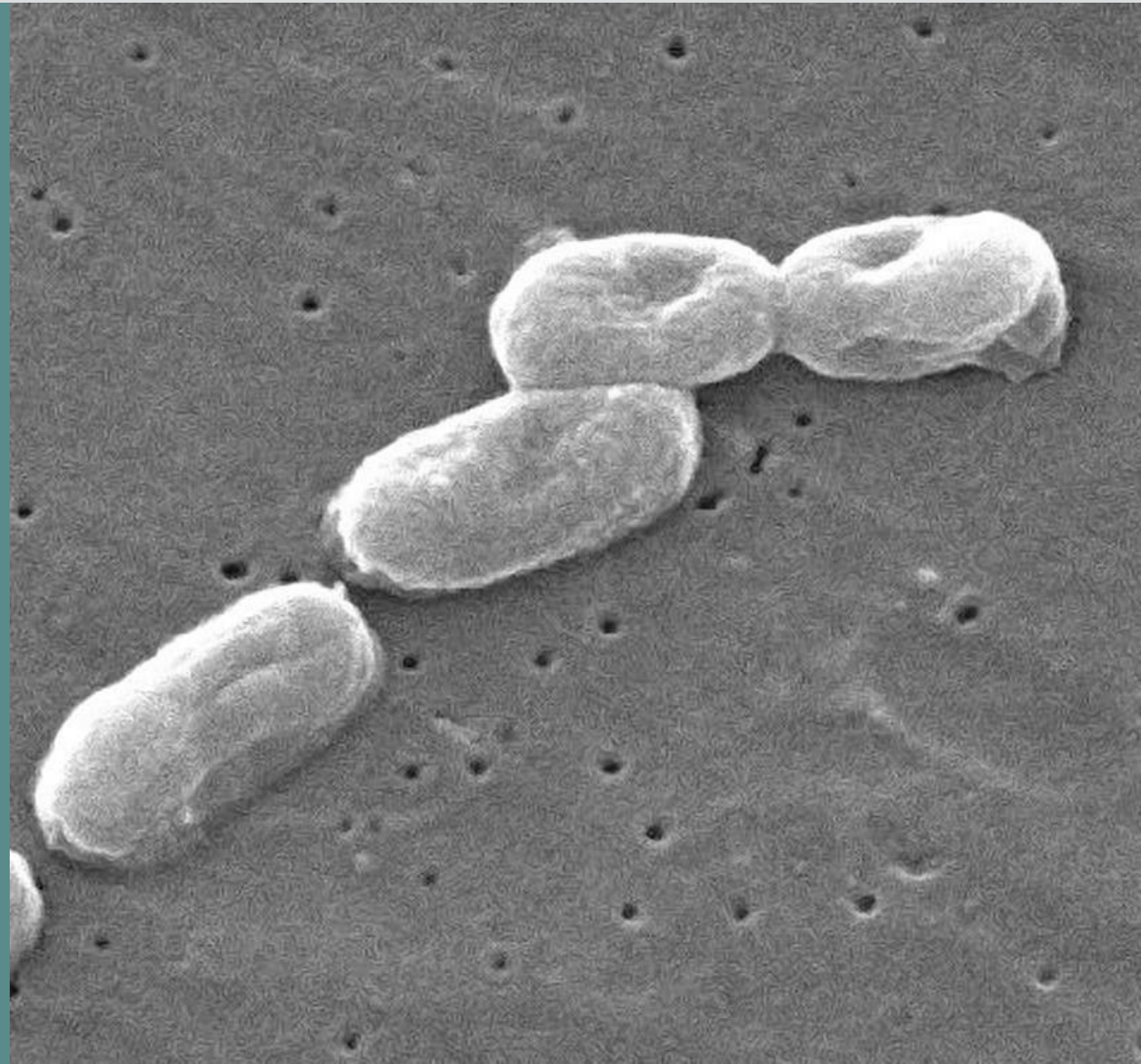
Validation or Method Suitability

- Methods that are official in the USP, such as, chapters <51>, <61>, <62> or <71> are considered to be already validated.
- If the microorganisms added during the test of the suitability of the method do not grow, it is necessary to eliminate the biostatic properties of the article
- *USP* <1227> *Validation of Microbial Recovery from Pharmacopeial Articles* presents information on how to accomplish this.
- Three common methods used to neutralize antimicrobial properties of a product:
  1. chemical neutralization, 2. dilution, and 3. filtration and washing

<60> Microbiological Examination of Non-sterile Products – Tests for *Burkholderia cepacia* Complex

Scope

The tests are designed to determine whether a substance or preparation complies with an established specification for microbiological quality and/or to evaluate whether products—especially those for inhalation use or aqueous preparations for oral, oromucosal, cutaneous, or nasal use—contain members of the Bcc



FDA Statement from May 2017

- Use scientifically sound and appropriate acceptance criteria (e.g., USP Chapter <1111> Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use) and test procedures (e.g., USP <61>/<62> Microbiological Examination of Non-sterile Products: Microbial Enumeration Tests and Tests for Specified Microorganisms, respectively) ***to assure that drug product components (including pharmaceutical water*) *and finished drug products conform to appropriate quality standards*** (21 CFR 211.160(b)).

- *FDA advises drug manufacturers that Burkholderia cepacia complex poses a contamination risk in non-sterile, water-based drug products 5/22/2017 (available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-drug-manufacturers-burkholderia-cepacia-complex-poses-contamination-risk-non-sterile)

PDA/FDA Conference 2018

Summary

- Water quality for sterile and non-sterile drug product manufacture will be checked as part of the overall quality, laboratory, materials, facility/equipment inspection
- Control and trending of microbiological water quality extremely important
- ***Manufacturers of liquid non-sterile products should be monitoring PW system for Bcc – preservatives often ineffective***
- **Control of Pharmaceutical Water Systems: A Regulatory Perspective Dr. S. Langille presentation at 2018 FDA/PDA Conference, September 26, 2018**

Additional points on <60>

- *B. cepacia* Selective Agar as it is widely used in clinical microbiology and its efficacy is supported in the peer-reviewed literature.
- Three species from the BCC most associated with patient infection are used for suitability testing.
- The option is available to use diluted soybean-casein digest broth to facilitate the recovery of BCC from product or purified water.
- The USP chapter is designated as <60> as <62> is a harmonized chapter.

Questions

Empowering a healthy tomorrow

Thank You

Empowering a healthy tomorrow

EML Madison Site

- Became part of Eurofins in 2018 Covance acquisition
- Designated as the Eurofins “Center of Excellence for Probiotics and Dietary Supplements”
- Current Offerings:
  - Probiotic enumeration by plate methods and flow cytometry
  - Probiotic identification
  - Full suite of USP testing including suitability

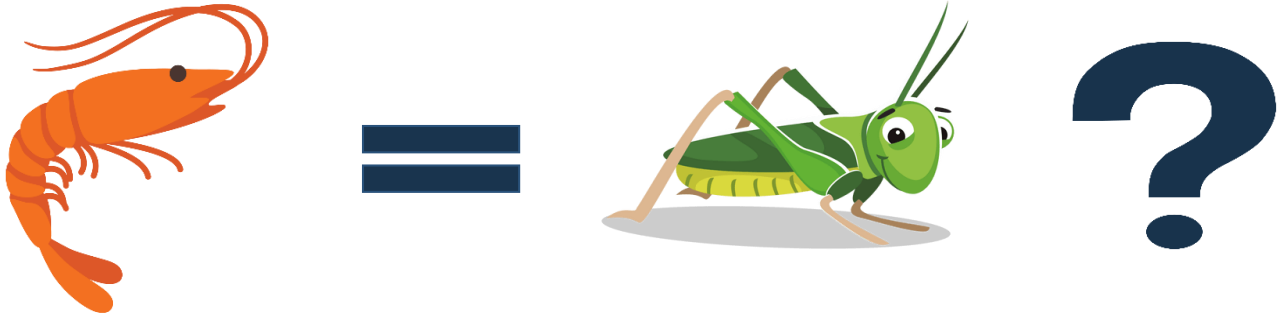
USP Applicable Products

- **Dietary Supplements/Supplement Ingredients**
  - Contain highly synthesized components with unknown antimicrobial properties
  - Contain dry/powdered botanicals with potentially high contamination and known antimicrobial/inhibitory properties
- **Probiotics**
  - Contain highly concentrated mainly gram positive organisms
- **Hemp/CBD**
  - Contain highly synthesized components and/or botanicals
- **Personal Care Products**
  - Contain highly synthesized components and/or antimicrobial preservation
  - Multiple use containers, risk contamination by user

Why is this important?

- **Antimicrobial/Competitive Inhibition can lead to False Negative results.**
- **USP require all product formulations to undergo a Preparatory/Suitability test to ensure resulting contamination testing is accurate.**
- **Antimicrobial/competitive inhibition could potentially be neutralized at the time of consumption/use putting the user at risk and a company's overall brand at risk.**

- **AOAC/BAM**
  - **Matrix Claims- Validation is by matrix category and subcategory, e.g. Category – Meat and poultry; subcategory – protein < 10 %, example – prepared foods with high carbohydrate e.g. frozen entrées**
    - **AOAC/BAM matrix claims are mainly specific to food and other food types. Dietary supplement, supplement ingredients, probiotics, cannabis and personal care products are difficult to fit into the current matrix categories and would need a new category validation.**
      - **Peanut Butter because of the high fat content mostly aligns with high-fat dairy (butter) but is not dairy.**
      - **Crickets mostly align with category Shrimp.**



USP vs AOAC/BAM cont.

- Validation for a new category requires comparison with reference method (BAM or OMA)
  - Qualitative methods:
    - Inoculated samples: 5 zero-level, 20 low-level, 5 high-level; low-level gives 25-75 % positive tests
    - No statistically significant difference between “new” method and reference method.
  - Quantitative methods
    - Three inoculated levels (high, medium, and low) and one uninoculated level.
    - For each level, analyze five test portions by both new and reference methods
    - Plot “new” method on Y axis vs. ref. method on X axis: look for major discrepancies
    - Report mean difference between “new” and ref. method and 95 % confidence intervals.
- **USP**
  - Option to follow compendial methods with suitability/preparatory test
  - Option to follow <1223> Validation of Alternative Microbiological methods

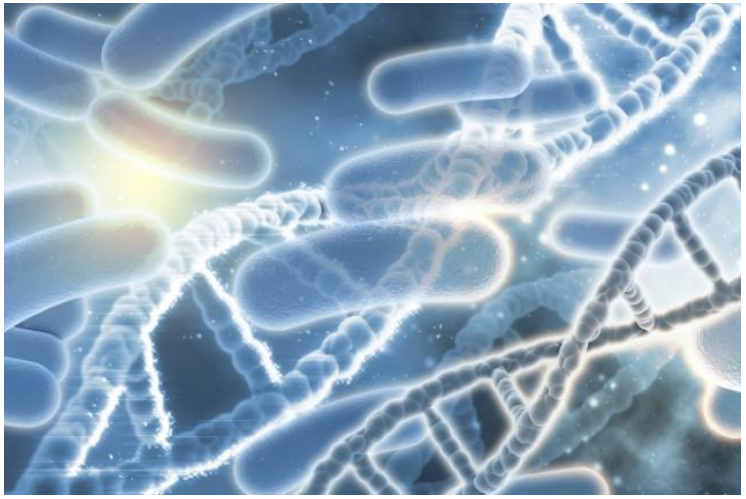
USP <2023> Specifications, sampling plans, test procedures

- **Setting Specifications**
  - Knowledge of material's origin, i.e. animal or botanical vs synthesized
  - Manufacturing process, i.e. drying, extraction, heat treatment, irradiation, or gaseous sterilization treatment
  - Contamination potential- components, processing, growth inhibiting or promoting properties.
- **USP Guidance**
  - Individual monographs provide guidance on definition, identification, performance, impurities/contamination and additional requirements needed to meet USP's standard.
  - If no guidance for contamination is listed under the individual monograph or if an individual monograph is not available then Chapter <2023> is used.
  - For Probiotics if an individual monograph is unavailable, Chapter <64> is used, it has grouped together classifications of probiotics to provide testing guidance.

USP Chapter <2023> Categories/Test Guidance

Category	USP Ch <2021> TAMC	USP Ch <2021> TCYM	USP Ch <2021> BTGN	USP Ch <2022> Salmonella	USP Ch <2022> E.coli
Dried/powdered botanicals	X	X	X	X	X
Powdered botanical extracts	X	X		X	X
Tinctures	X	X			
Fluidextracts	X	X			
Infusion/Decoctions	X	X			
Nutritional Supplement with Botanicals	X	X		X	X
Botanicals treated with boiling water before use	X	X	X	X	X
Dietary supplement ingredients/raw materials	X	X			X
Nutritional supplements with synthetic or highly refined ingredients	X	X			X

Probiotic Classifications



- Non-spore-forming bacteria
  - PCR identification, enumeration guidance
- Spore- forming bacteria
- Yeast and molds

Contamination

- Non-Lactic acid Bacteria (ISO 13559)- Non-spore-forming bacteria
- Yeast and Molds USP Ch <2021>- Non-spore and spore forming bacteria
- Total aerobic microbial count USP Ch <2021>- Yeast and Molds
- *Escherichia coli* and *Salmonella* USP Ch <2022>- all probiotic classifications
- *Listeria monocytogenes*, *Staphylococcus aureus*, or *Psueodomas aeruginosa* in additional to the listed above should be tested and confirmed if any ingredients poses a risk identified in a formal program such as HACCP
- *Clostridium perfringens* and *Cronobacter sakazakii* should be tested if a probiotic is intended for infant use

USP <51> What is it?

- **USP <51> Antimicrobial Effectiveness Testing is used to determine the effectiveness of preservatives added to products designed for multiple uses.**
  - **Provides information regarding the ability of a product to reduce and control the population of specific microorganisms called out in the USP.**
  - **Often also referred to as “Preservative Effectiveness Testing” or “Preservative Challenge Testing”**

Product Types

- **USP <51> provides a breakdown of the product types to be tested as follows:**
  - **Category 1- Injections; other parenterals including emulsions, OTC products, sterile nasal products, and ophthalmic products made with aqueous bases or vehicles**
  - **Category 2- Topically used products made with aqueous bases or vehicles; non-sterile nasal products and emulsions, including those applied to mucous membranes**
  - **Category 3- Oral products other than antacids, made with aqueous bases or vehicles**
  - **Category 4- Antacids made with an aqueous base**

Test Specifics

- Samples are inoculated with the following challenge organisms at a concentration specific to product category (10^3 to 10^6).
  - *Candida albicans (ATCC No. 10231)*
  - *Aspergillus brasiliensis* (ATCC No. 16404)
  - *Escherichia coli* (ATCC No. 8739)
  - *Pseudomonas aeruginosa* (ATCC No. 9027)
  - *Staphylococcus aureus* (ATCC No. 6538)
- Samples are tested at defined intervals (7, 14, 28 days) by category for the viable population of each inoculated organism and must meet USP specified acceptance criteria.
- Acceptance criteria is defined by the category type, but generally requires a decrease of the viable populations or no increase of the viable populations.

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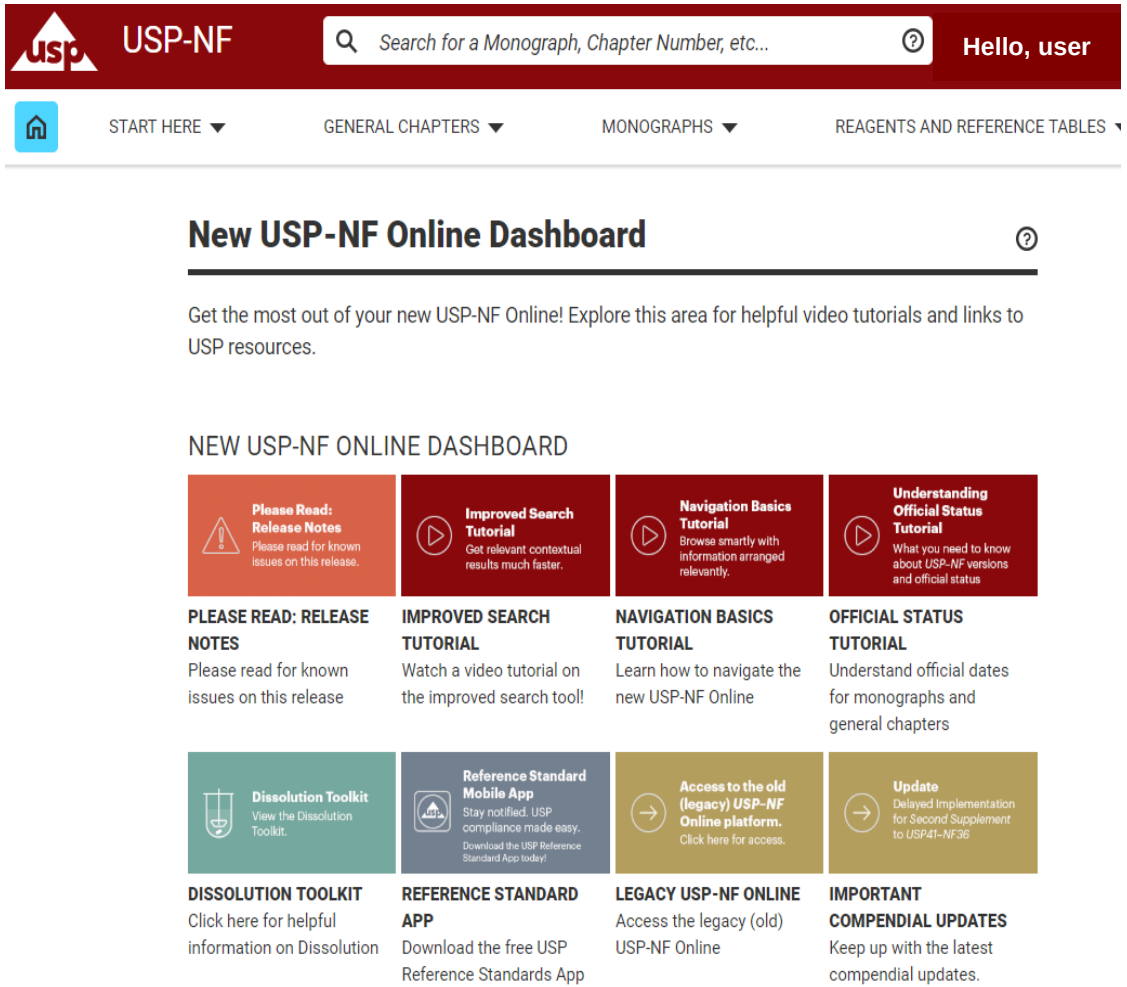

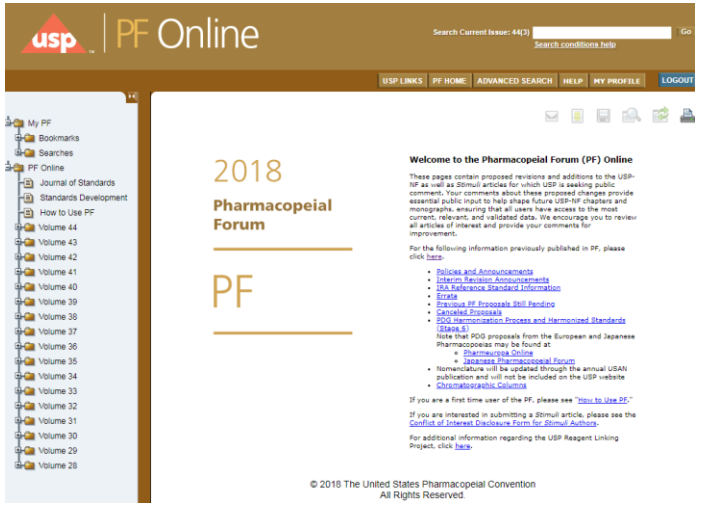

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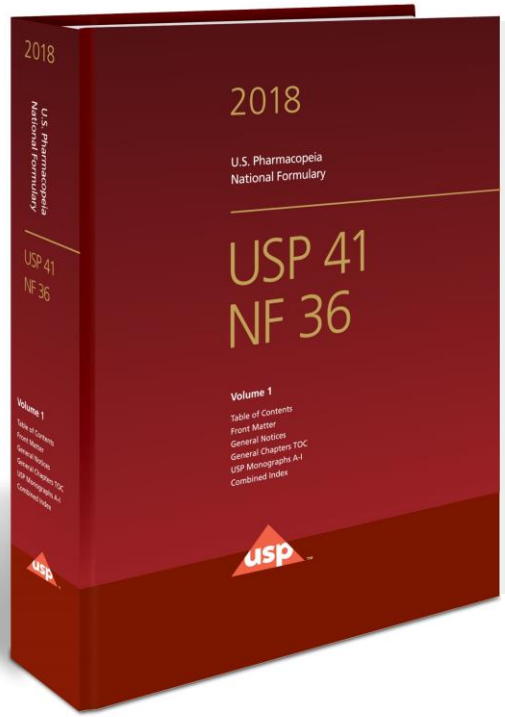

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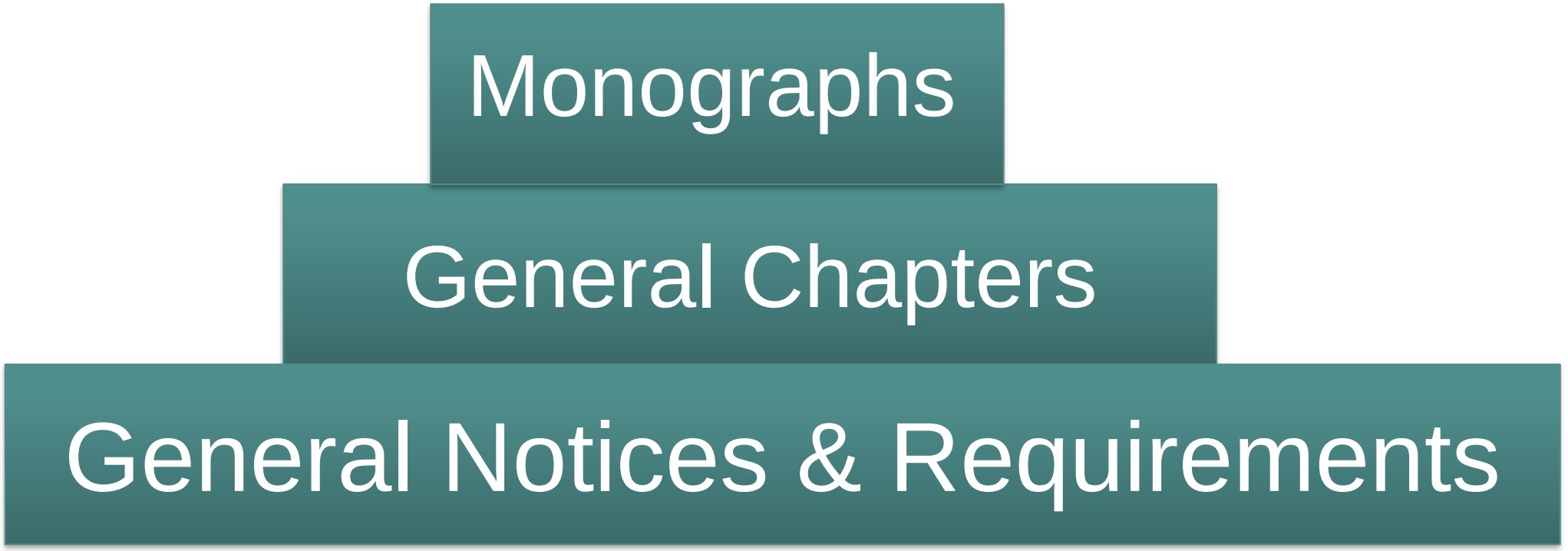

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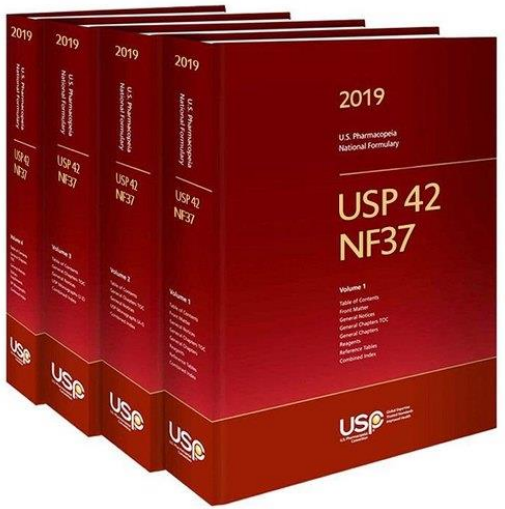

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Compendial microbiology test methods are growth-based methods which require that any microorganisms present be capable of growth in the presence of the article under test

According to 21 CFR 211.194(a)(2), laboratory records require a statement of the method used in testing the sample; that the method meet proper standards of accuracy and reliability as applied to the product tested. If the method used in testing the sample is in the current USP-NF, a statement indicating the method and reference will suffice.

Compendial Microbiology Tests

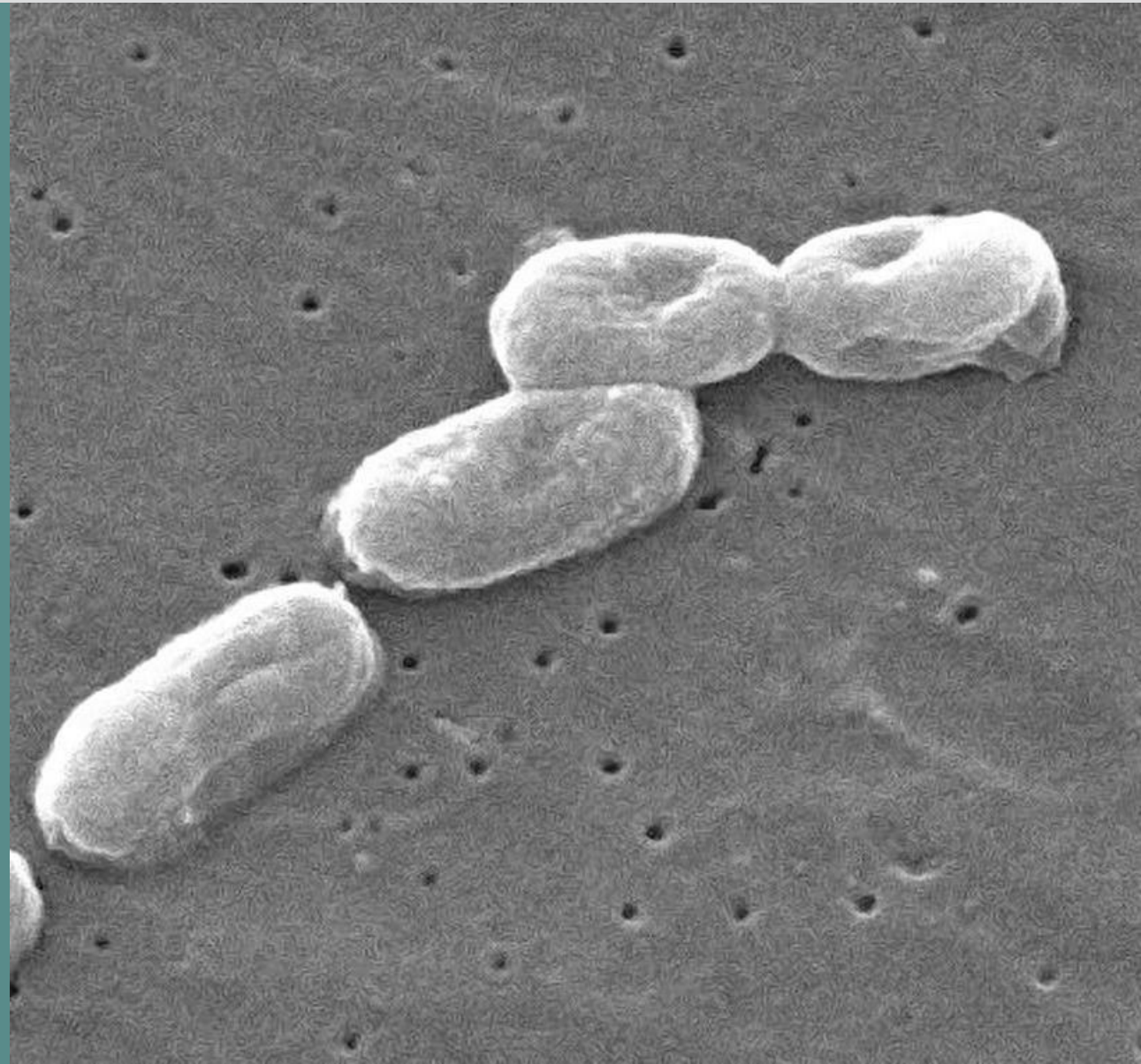
Validation or Method Suitability

- Methods that are official in the USP, such as, chapters <51>, <61>, <62> or <71> are considered to be already validated.
- If the microorganisms added during the test of the suitability of the method do not grow, it is necessary to eliminate the biostatic properties of the article
- *USP* <1227> *Validation of Microbial Recovery from Pharmacopeial Articles* presents information on how to accomplish this.
- Three common methods used to neutralize antimicrobial properties of a product:
  1. chemical neutralization, 2. dilution, and 3. filtration and washing

<60> Microbiological Examination of Non-sterile Products – Tests for *Burkholderia cepacia* Complex

Scope

The tests are designed to determine whether a substance or preparation complies with an established specification for microbiological quality and/or to evaluate whether products—especially those for inhalation use or aqueous preparations for oral, oromucosal, cutaneous, or nasal use—contain members of the Bcc



FDA Statement from May 2017

- Use scientifically sound and appropriate acceptance criteria (e.g., USP Chapter <1111> Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use) and test procedures (e.g., USP <61>/<62> Microbiological Examination of Non-sterile Products: Microbial Enumeration Tests and Tests for Specified Microorganisms, respectively) ***to assure that drug product components (including pharmaceutical water*) *and finished drug products conform to appropriate quality standards*** (21 CFR 211.160(b)).

- *FDA advises drug manufacturers that Burkholderia cepacia complex poses a contamination risk in non-sterile, water-based drug products 5/22/2017 (available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-drug-manufacturers-burkholderia-cepacia-complex-poses-contamination-risk-non-sterile)

PDA/FDA Conference 2018

Summary

- Water quality for sterile and non-sterile drug product manufacture will be checked as part of the overall quality, laboratory, materials, facility/equipment inspection
- Control and trending of microbiological water quality extremely important
- ***Manufacturers of liquid non-sterile products should be monitoring PW system for Bcc – preservatives often ineffective***
- **Control of Pharmaceutical Water Systems: A Regulatory Perspective Dr. S. Langille presentation at 2018 FDA/PDA Conference, September 26, 2018**

Additional points on <60>

- *B. cepacia* Selective Agar as it is widely used in clinical microbiology and its efficacy is supported in the peer-reviewed literature.
- Three species from the BCC most associated with patient infection are used for suitability testing.
- The option is available to use diluted soybean-casein digest broth to facilitate the recovery of BCC from product or purified water.
- The USP chapter is designated as <60> as <62> is a harmonized chapter.

Questions

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Thank You

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