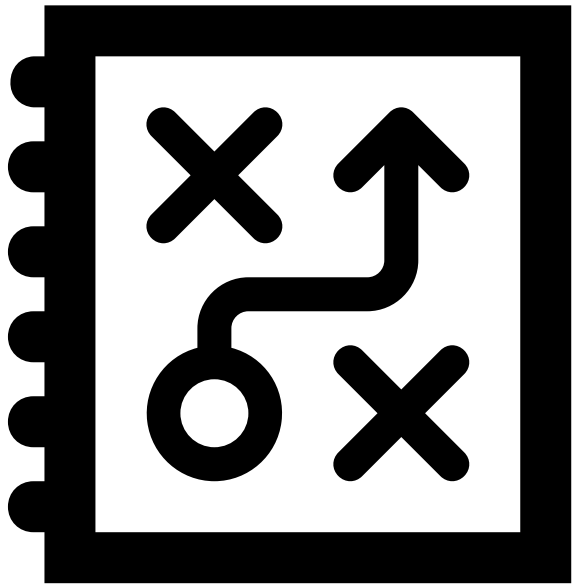
Standards Ecosystem

(The Alphabet Soup)

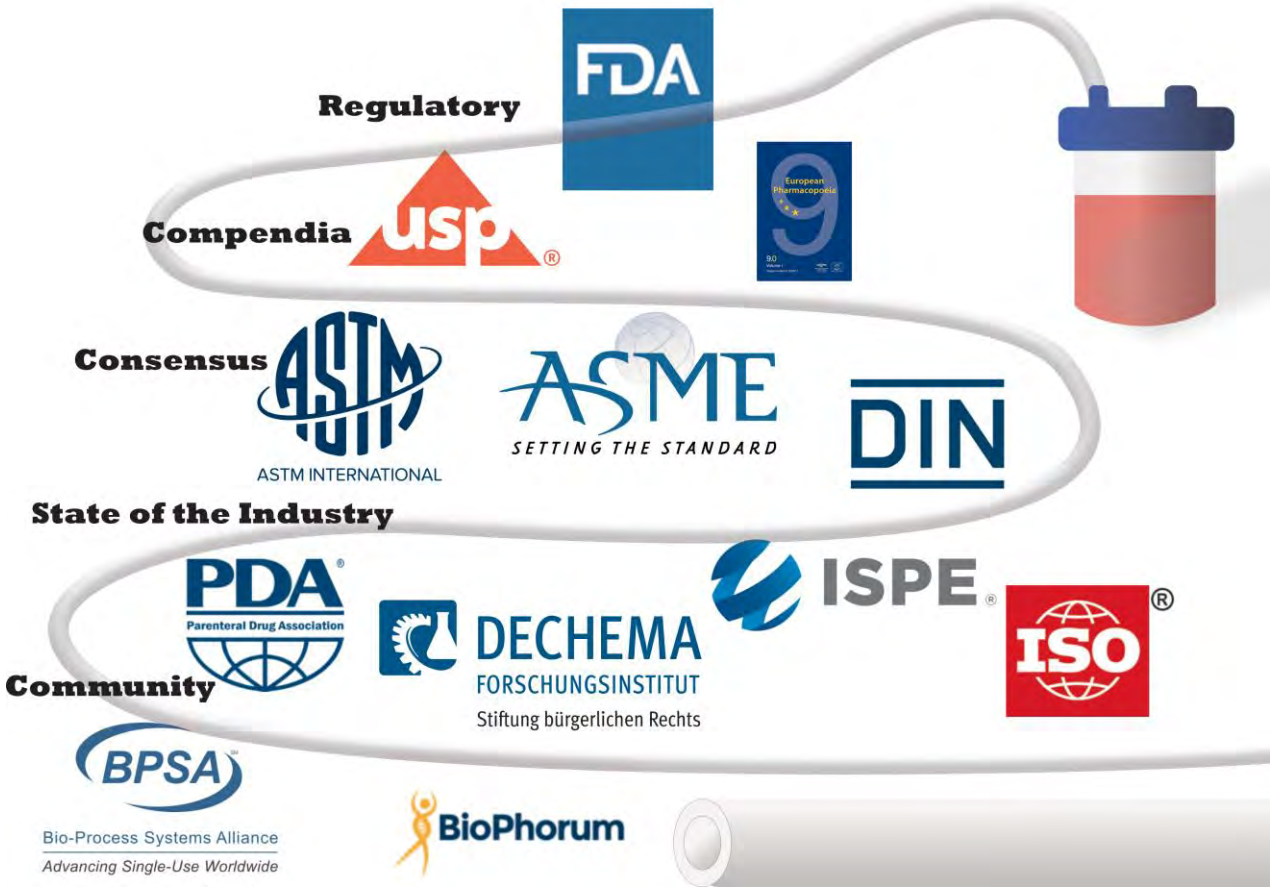
James Dean Vogel, P.E.
Founder and Director
The BioProcess Institute
13 July 2022

We are going to do Single Use?

- What is needed?
- What do we have to do?
- Are there rules?
- There is this Alphabet Soup?
- Is there a playbook?



Regulations *vs.* Compendia *vs.* Standards *vs.* Guidelines



The Road to Standardization

General Single-Use Guidance

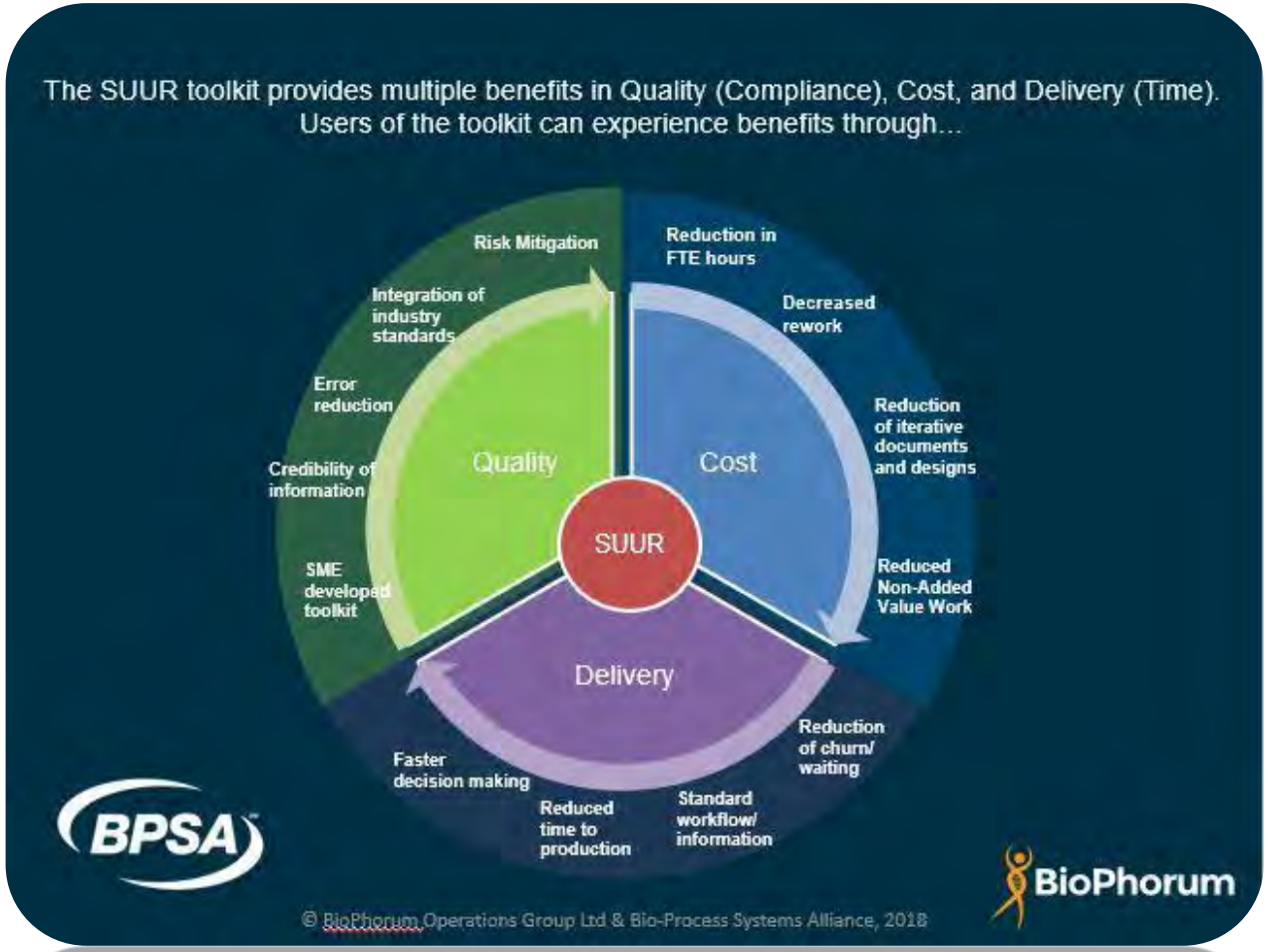
- BPSA-Many publications
- ISPE-Good Practice Guide for Single-Use Technology (2018)
- PDA-Technical Report No. 66: Application of Single-Use-Systems in Pharmaceutical Manufacturing (2014)

Single-Use Bioprocess Design

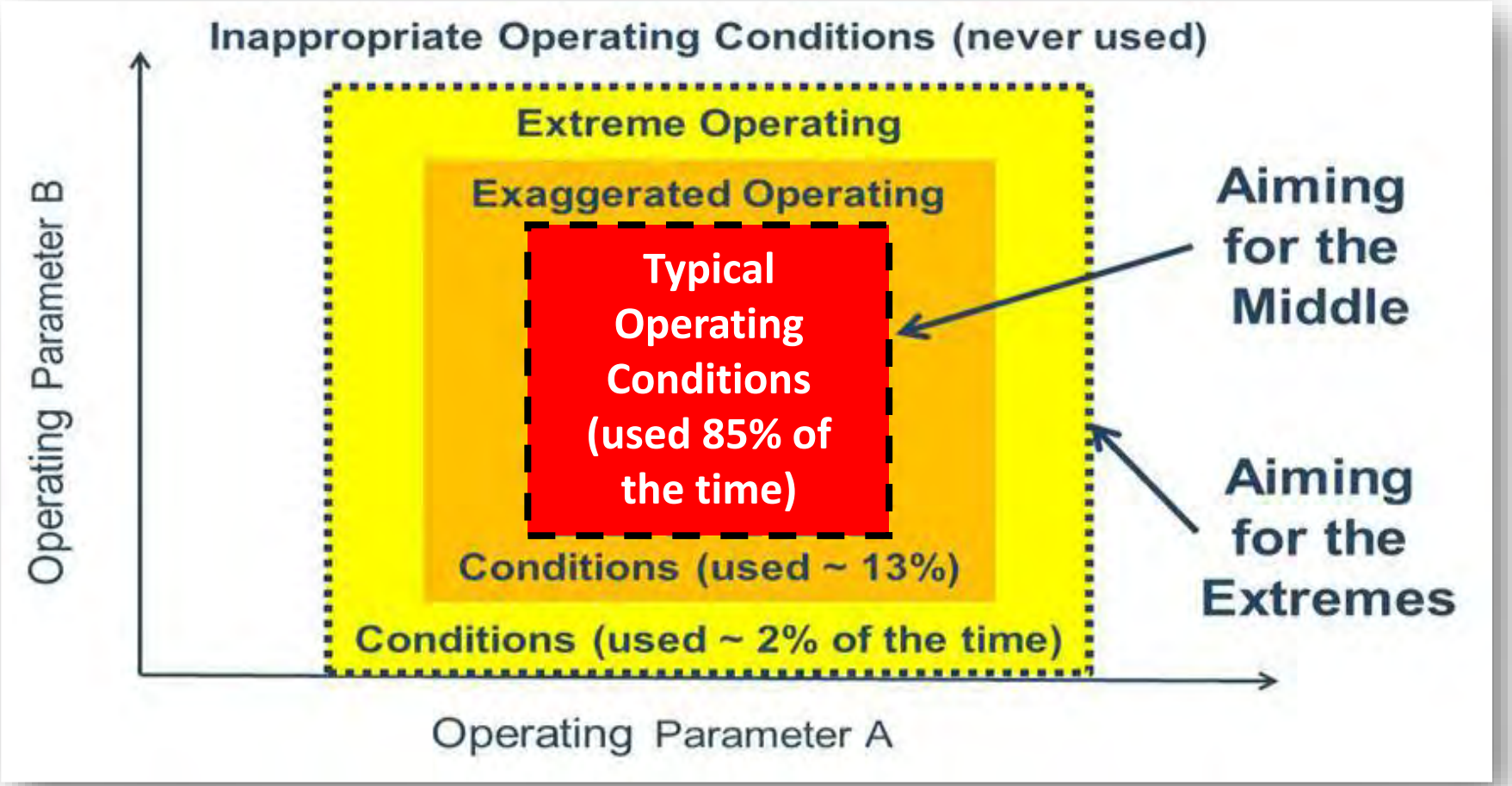
User Requirements

- Application Requirements
- Qualification Requirements
- Quality Requirements
- Supply Chain Requirements
- Expected information from the Supplier

User Requirements Toolkit



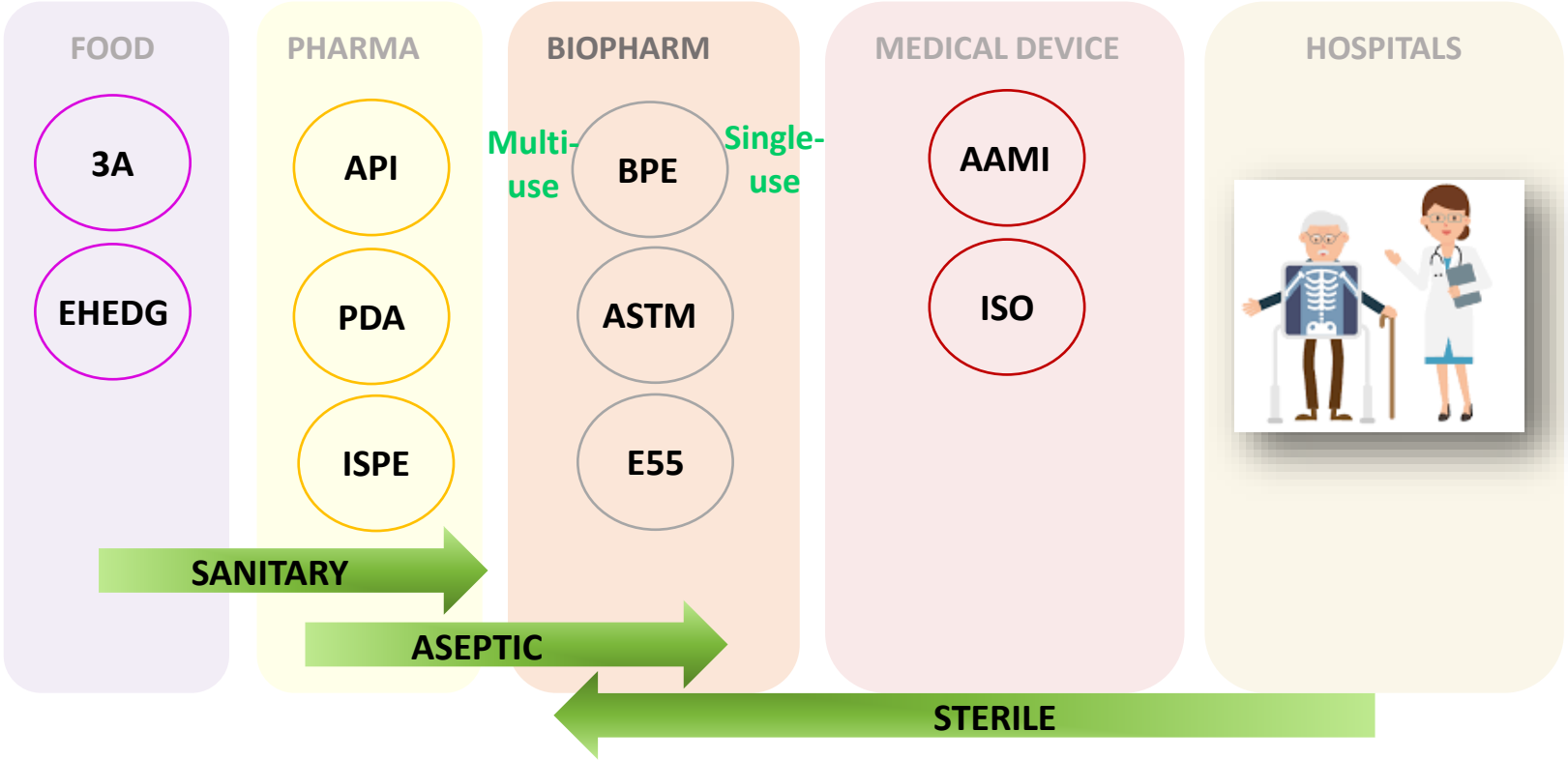
Process Ranges (USP)



Process Design Space

- The Design Space for each aspect considered are evaluated.
- The potential of the process to interact with the article/material is essential for this evaluation.

Food and Medical Device Lead into What BioPharm is Doing



Single-Use vs. Multi-Use

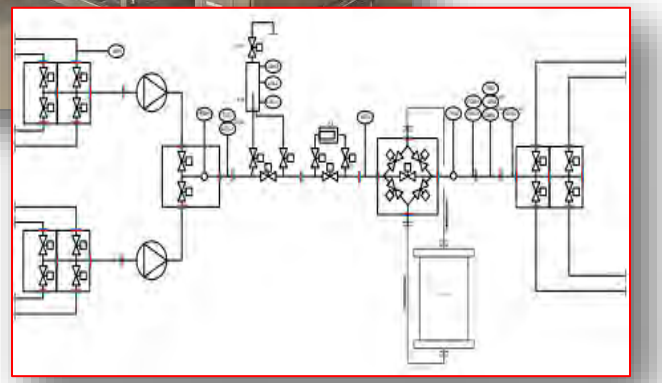
Same Process: The drug product is processed using similar operations in both cases (e.g. product is purified using affinity chromatography)

Same Goal: In both cases, the processing equipment ***shall not adulterate the product***. Both type systems need to provide a clean and sterile environment

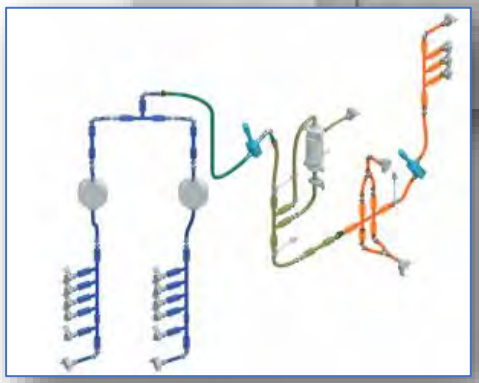
Different Approach: Multi-Use cleanability/sterility is validated by end-user. Single-Use cleanability/sterility is validated by manufacturer

Why is one approach used instead of the other?

Multi-Use Chromatography skid



Single-Use Chromatography skid



Requirements: Single-Use *vs.* Multi-Use

Single-Use Technologies live in two different universes

Medical Device Universe

1. **They are provided as 'ready-to-use', sterilized components, like Medical Devices**
2. **Govern by Medical Devices Standards: AAMI**

1. **They perform the functions of bioprocess equipment**
2. **Govern by equipment Standards: ASME BPE**

Bioprocess Equipment Universe

Medical Device: *Parallel Universe*

- Materials are mostly polymers
- Interaction directly with the patient and drugs
- Intravenous (IV) are Closed Process
- Different
  - Sales channels
  - Supplier Companies different
  - Supplier prepares product (Sterilization)
- Regulatory-risk
  - FDA branch - CDRH
  - Recognize standards
    - ISO 13485
    - AAMI

A Place for Standards

- **Standards are appropriate when**
  - A shared (industry)problem
  - That is not in competitive space
  - That leads to uncertainty/confusion/waste
  - That has a path to consensus
- **Why not just a white paper?**
  - Standards amplify the message.
  - Standards generally undergo periodic review for correctness and relevance.
  - Standards require formal consensus.
  - Standards have a higher level of impact.
  - US Law and FDA support use of standards.

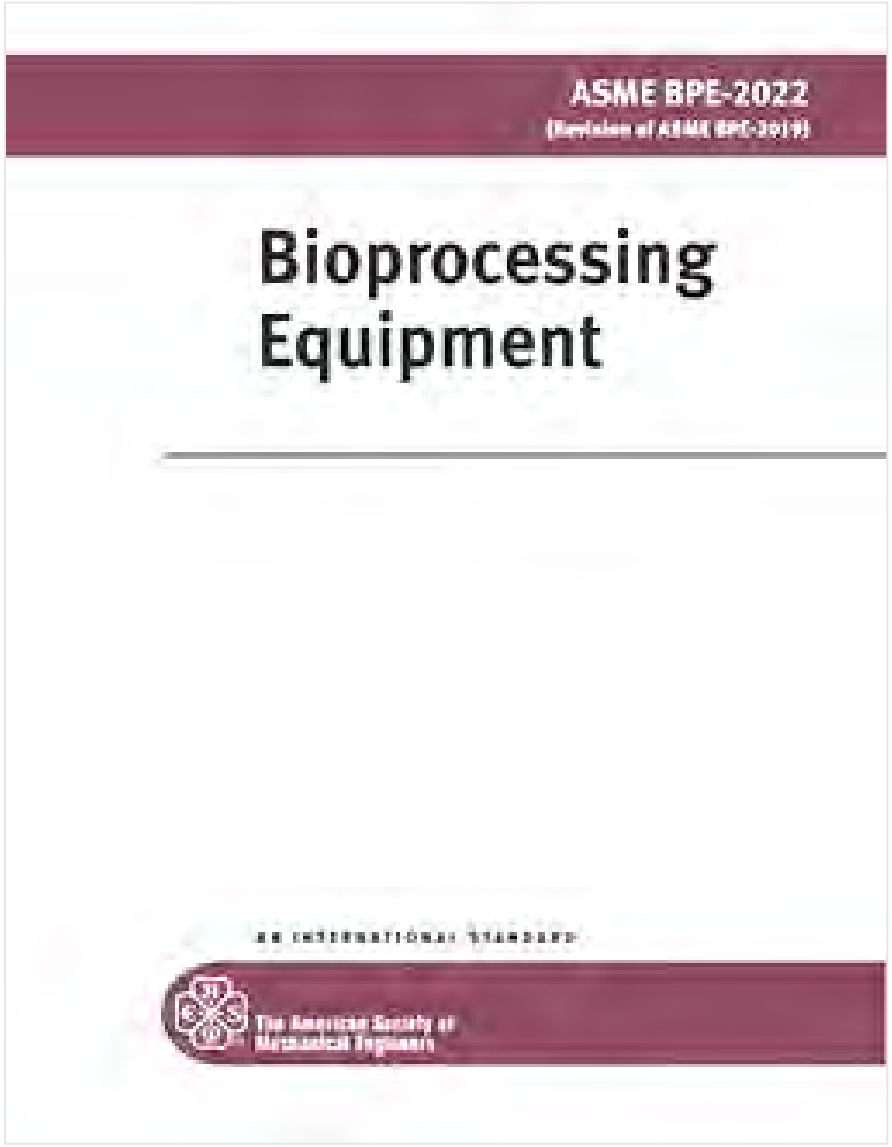
National Technology Transfer and Advancement Act of 1995

(d) UTILIZATION OF CONSENSUS TECHNICAL STANDARDS BY FEDERAL AGENCIES; REPORTS - (1) IN GENERAL- Except as provided in paragraph (3) of this subsection, all Federal agencies and departments shall use technical standards that are developed or adopted by voluntary consensus standards bodies, using such technical standards as a means to carry out policy objectives or activities determined by the agencies and departments.

Standards and Guidelines

- ASME BioProcessing Equipment (BPE)
- ASTM Committee E-55 on Manufacturing of Pharmaceutical and Biopharmaceutical Products
- United States Pharmocopedia (USP)
- Others


ASME
SETTING THE STANDARD



ASME
SETTING THE STANDARD

ASME-BPE (American Society of Mechanical Engineers - BioProcessing Equipment Standard) www.asme.org

The ASME BPE Standard provides requirements for systems and components that are subject to cleaning and sanitization and/or sterilization including systems that are cleaned in place (CIP'd) and/or steamed in place (SIP'd) and/or other suitable processes used in the manufacturing of biopharmaceuticals. **This Standard also provides requirements for single-use systems and components used in the above listed systems and components.** This standard may be used, in whole or in part, for other systems and components where bioburden risk is a concern.

Reorganized in 2022 to focus on Single-Use Systems!

Description

- The Standard provides requirements for systems and components where bioburden risk is a concern.
- It includes Mandatory and Nonmandatory Content:
  - Mandatory content are requirements (components, equipment and systems SHALL conform to it to be considered in conformance to ASME BPE)
  - Nonmandatory content is included in Nonmandatory Appendices (NMA) as clarification to requirements, standard test methods or recommendations.

There is a lot of useful information in the NMAs!

GR-2 SCOPE OF THE ASME BPE STANDARD

The ASME BPE Standard provides requirements for systems and components that are subject to cleaning and sanitization and/or sterilization including systems that are cleaned in place (CIP'd) and/or steamed in place (SIP'd) and/or other suitable processes used in the manufacturing of biopharmaceuticals. This Standard also provides requirements for single-use systems and components used in the above listed systems and components. This Standard may be used, in whole or in part, for other systems and components where bioburden risk is a concern.

A Brief History

- The first publication of the ASME BioProcess Equipment Standard was in 1997
- The initial goal was to standardize dimensions and tolerances, MOCs, surface finish and joining methods for bioprocess components (e.g., tubing, fittings, diaphragm valves)
- The Standard developed to include design and performance requirements for components, equipment and systems for multi-use applications (CIP/SIP able)

ASME BPE and Single-Use Requirements

- Single-use components were introduced in BPE under the Polymeric Materials (PM) section in 2009 (one page). By 2016, content grew to 3 pages.
- The PM sub-committee separated Single-use content into a Mandatory Appendix III in the 2019 edition (4 pages) to make it easier for users to find this content.
- In 2019, BPE's leadership recognized the importance of SUTs in the industry and established Project 2022 with the intention of re-organizing the Standard to address SUTs separate from multi-use. ***The 2022 Standard has now been published!***

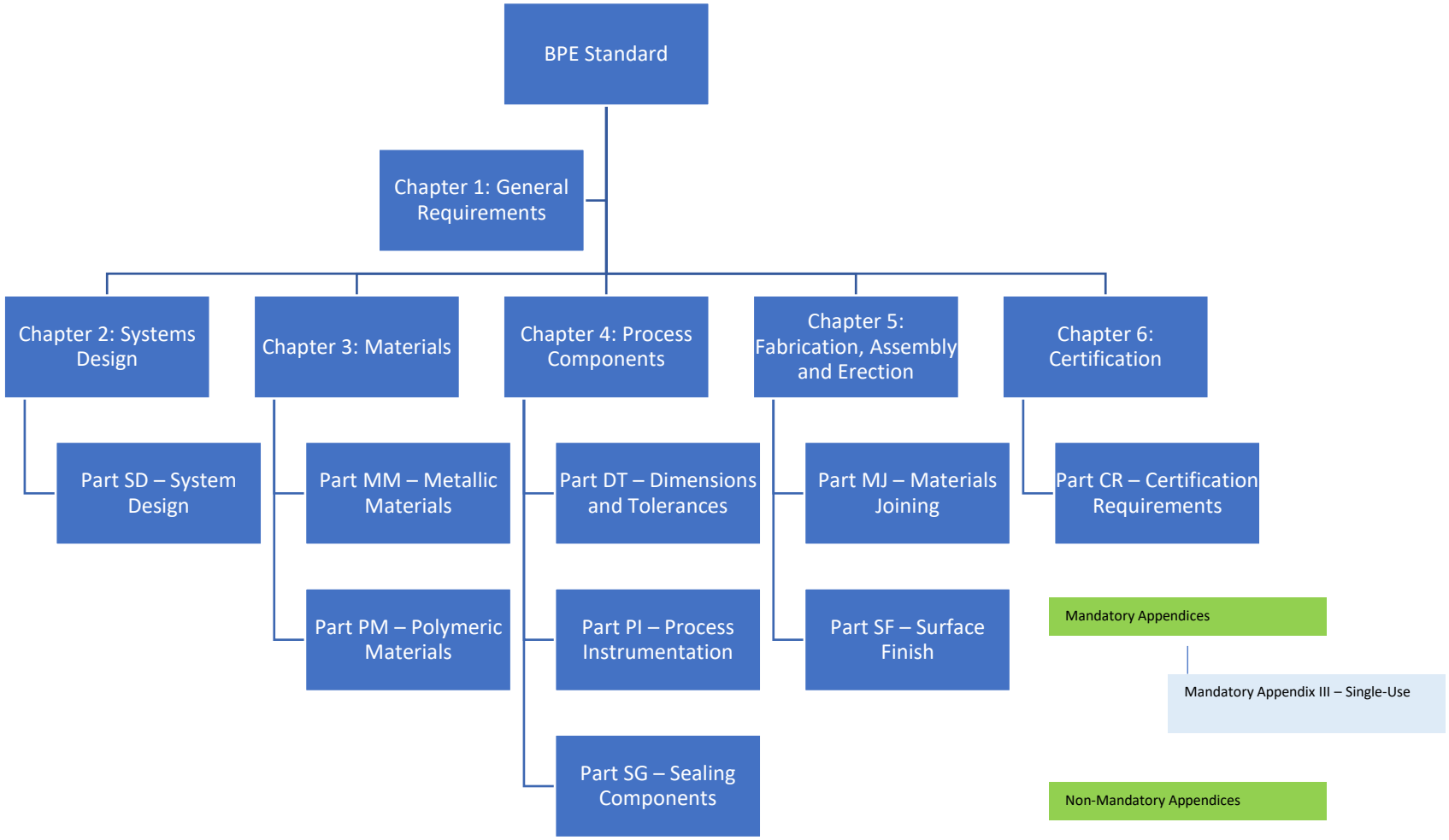
Design and performance requirements for multiuse vs single-use are vastly different!

Single-Use Content Task Groups (>13)

Task Group	Scope
PHU	Evaluate polymeric clamps to determine max ID required to contact a ferrule and not leak
SU Hose barb connections	Develop template to qualify a mechanical hose barb connection. Review current mandatory content and include more content around qualifying connections as a manufacturing process rather than component based
SU bags	Expand on the current content, including: -material standardized testing, - sizes, dimensions and volume definitions, -functional qualification requirements
SUT Particulate	Ensure alignment with the industry particulate monitoring and control practices and other Standards and guidance documents
SUT Integrity	Quality risk management and life-cycle approach to establish integrity assurance of single-use systems, such as but not limited to bag assemblies and liquid transfer sets for processing, storage, and shipping
Change Management	Review of PM-2.2.3.4 and PM-2.2.3.3
SU Tube Welds	Create acceptance criteria table and clarify responsibilities of the tube welding equipment manufacturer vs owner/user
SU Shelf Life	Review of existing content to add clarity regarding nonsterilized, gamma sterizable components that are incorporated into assemblies.
SU Valves	Address design and performance requirements specific to single-use applications for single-use valves (pinch valves, pinch clamps, etc.)
SU Design conformance	Develop new single-use design conformance and risk assessment content
SU Sterilization/Bioburden Control	Review and align content from SD and GR with Single-Use requirements. Include requirements on bioburden control and sterilization of single use assemblies and components
Irradiation	Irradiation terminology
Biocompatibility	Align Biocompatibility requirements throughout the Standard

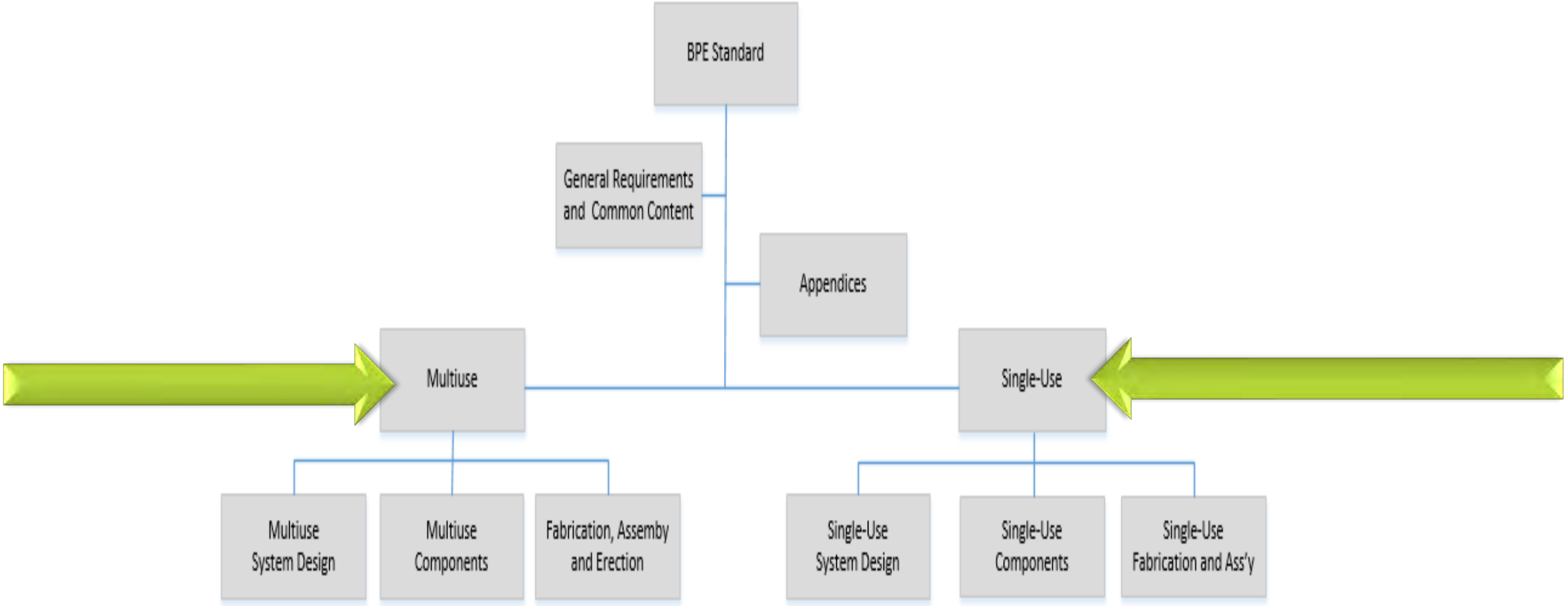
PROJECT 2022

2019 Structure



PROJECT 2022

New Structure



New Structure of 2022 Standard

MULTIUSE (CHAPTERS 1-6)

Part GR: General Requirements
Part CR: Certificate Requirements
Part MM: Metallic Materials
Part PM: Polymeric and Other Nonmetallic Materials
Part SD: Systems Design for Multiuse
Part DT: Dimensions and Tolerances for Process Components
Part PI: Process Instrumentation for Multiuse
Part MC: Components for Multiuse
Part MJ: Materials Joining for Multiuse

SINGLE-USE (CHAPTERS 7-9)

Part SU: Systems Design for Single-Use
Part SC: Components for Single-Use
Part SJ: Joining Methods for Single-Use

SINGLE-USE MANDATORY APPENDIX

III: Single-Use Components and Assemblies

SINGLE-USE NONMANDATORY APPENDICES

APPENDIX P: General Background/Useful information for Extractables and Leachables
APPENDIX FF: Leak Test Methods for Single-Use Components and Assemblies


ASTM
INTERNATIONAL
Standards Worldwide

ASTM International

www.astm.org

ASTM International develops international voluntary consensus standards similar to the ASME BPE. Twelve thousand ASTM standards are used around the world to improve product quality, enhance safety, facilitate market access and trade, and build consumer confidence. ASTM International includes more than 30,000 of the world's top technical experts and business professionals, representing 150 countries. Working in an open and transparent process and using ASTM's advanced electronic infrastructure, ASTM members deliver the test methods, specifications, guides, and practices which support industries and governments worldwide.

About ASTM International

- **ASTM International**
  - Founded in 1902. International not-for-profit organization that develops consensus standards – including test methods
  - Participation open to all - 32,000 technical experts from across the globe
- **ASTM's Objectives**
  - Promote public health and safety
  - Contribute to the reliability of materials, products, systems and services
  - Facilitate national, regional, and international commerce
- **ASTM Standards**
  - Known for high technical quality
  - Over 12,500 ASTM standards for more than 100 industry sectors
  - Over 5,000 ASTM standards used in regulation or adopted as national standards around the world in at least 75 countries

6,788

ASTM standards have been adopted, used as a reference, or used as the basis of national standards outside the USA

ASTM E55 Brief History

Committee E55 on Manufacture of Pharmaceutical and Biopharmaceutical Products

Staff Manager: Travis Murdock

ASTM Committee E55 on Manufacture of Pharmaceutical Products was formed in 2003. E55 meets twice each year, in May and November, with about 50 members attending three days of technical meetings (every 3rd to 4th meeting of E55 is held outside of the United States). This Committee addresses issues related to process control, design, and performance, as well as quality acceptance/assurance tests for the pharmaceutical manufacturing industry. Stakeholders include manufacturers of pharmaceuticals and pharmaceutical equipment, federal agencies, design professionals, professional societies, trade associations, financial organizations, and academia. The Committee, with a membership of approximately 200, currently has its standards published in the Annual Book of ASTM Standards, Volume 14.05. E55 has 3 technical subcommittees that maintain jurisdiction over these standards. Information on this subcommittee structure and E55's portfolio of approved standards and Work Items under construction are available from the List of Subcommittees, Standards and Work Items below.

ASTM E55 Main Committees

Each main committee in ASTM International is composed of subcommittees that address specific segments within the general subject area covered by the technical committee. Click on the subcommittee links below to see the title of existing standards for each subcommittee. Then, click on the resulting titles to see the standard's scope, referenced documents, and more.

- E55.01 Process Understanding and PAT System Management, Implementation and Practice
- E55.03 General Pharmaceutical Standards
- E55.04 General Biopharmaceutical Standards
- E55.05 Lyophilization
- E55.06 Microbial/Sterility Assurance for Pharmaceutical and Biopharmaceutical Products
- E55.90 Executive
- E55.91 Terminology
- E55.94 Outreach and Education
- E55.95 Roadmap for Standards Development

ASTM E55 Standards

Design, Verification and Application

E3051-16 Standard Guide for Specification, Design, Verification, and Application of Single-Use Systems in Pharmaceutical and Biopharmaceutical Manufacturing

E2500-20 Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment

Inspection

E3263-20 Standard Practice for Qualification of Visual Inspection of Pharmaceutical Manufacturing Equipment and Medical Devices for Residues

Cell Growth

E3231-19 Standard Guide for Cell Culture Growth Assessment of Single-Use Material

ASTM E55 Standards

Particulate

E3060-16 Standard Guide for Subvisible Particle Measurement in Biopharmaceutical Manufacturing Using Dynamic (Flow) Imaging Microscopy

E3230-20 Standard Practice for Extraction of Particulate Matter from the Surfaces of Single-Use Components and Assemblies Designed for Use in Biopharmaceutical Manufacturing

Integrity

E3244-20 Standard Practice for Integrity Assurance and Testing of Single-Use Systems

E3251-20 Standard Test Method for Microbial Ingress Testing on Single-Use Systems

E3336-22 Standard Test Method for Physical Integrity Testing of Single-Use Systems

Organization of ASTM E55
(Pharm. Manufacturing)

Continuous Processing

E2537-16 Standard Guide for Application of Continuous Process Verification to Pharmaceutical and Biopharmaceutical Manufacturing

E2968-14 Standard Guide for Application of Continuous Processing in the Pharmaceutical Industry

ASTM E55 Work Groups

(

WK65428 * Standard Standard Guide for Application of Continuous Manufacturing (BioCM) in the Biopharmaceutical Industry (Technical Contact:) Ballot E55 (21-04) Item 001; Ballot E55 (22-02) Item 003; Ballot E55.04 (20-01) Item 001;

WK65429 * Standard Standard Practice for Process to Remove Retrovirus by Small Virus Retentive Filters (Technical Contact:) Ballot E55 (20-03) Item 004; Ballot E55 (20-07) Item 002; Ballot E55.04 (19-04) Item 001;

WK73465 Standard Standard Guide for Accelerated CMC development, manufacture and supply of therapies and vaccines for use in pandemics such as COVID-19 (Technical Contact:) Ballot E55 (20-05) Item 002;

WK74514 * Standard Standard Practice for Measurement of Particulate Matter in Pharmaceuticals using Automated Membrane Microscopy (Technical Contact:)

WK78574 * Standard Standard Guide for Best Practices for Microbial Control for Cell Therapeutics (Technical Contact:)

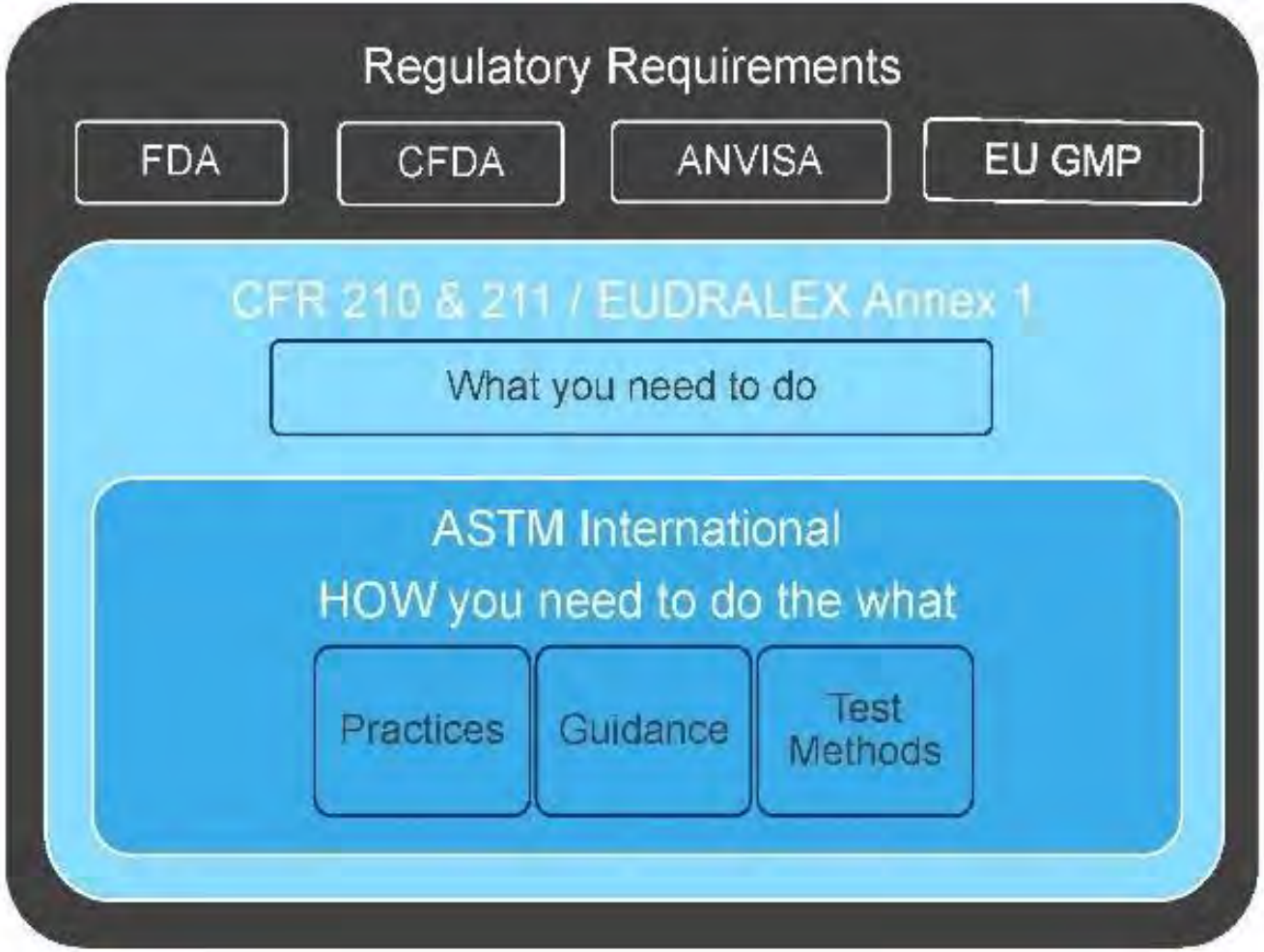
WK81610 * Standard Standard Practice for Development and validation of test methods to quantify particulate matter on the surfaces of single-use assemblies designed for use in biopharmaceutical manufacturing (Technical Contact:)

WK81999 * Standard Standard Guide for Establishment of a Microbiological Quality Level for Pharmaceutical and Biopharmaceutical Products and Processes (Technical Contact:)

ASTM E55 New Vision

- Socialize Roadmap and engage industry partners
- Evaluate Current Structure
- Training on how to use ASTM Standards
- Establish Strategic Liaisons

E55 Vision and Roadmap
Pharmaceutical Manufacturing



ASTM INTERNATIONAL
Standards Worldwide

ASTM and BioPhourm

- Memorandum of Understanding (MOU) signed in October 2021
- Two organizations work in tandem on Key priorities
- Meetings are scheduled.

ASTM Balance of Multi-Use and Single Use

Begin with Principles for “Multi-Use”

E2500 Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment

Translate to Principles for Single-Use

E2500-20 Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment (03)

E3051-16 Standard Guide for Specification, Design, Verification, and Application of Single-Use Systems in Pharmaceutical and Biopharmaceutical Manufacturing (02)

Multi-Use → Single-Use → The Details

E2500-20 Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment (03)

E3051-16 Standard Guide for Specification, Design, Verification, and Application of Single-Use Systems in Pharmaceutical and Biopharmaceutical Manufacturing (03)

Integrity Management

- E3244-20 Standard Practice for Integrity Assurance and Testing of Single-Use Systems (04)
- E3251-20 Standard Test Method for Microbial Ingress Testing on Single-Use Systems (04)
- WK74440/E3336-22 Physical Integrity Testing of Single-Use Systems (04)

Particulate Management

- E3060-16 Standard Guide for Subvisible Particle Measurement in Biopharmaceutical Manufacturing Using Dynamic (Flow) Imaging Microscopy (03)
- WK74514 Measurement of Particulate Matter in Pharmaceuticals using Automated Membrane Microscopy (03)
- E3230-20 Standard Practice for Extraction of Particulate Matter from the Surfaces of Single-Use Components and Assemblies Designed for Use in Biopharmaceutical Manufacturing (04)

Cell Culture Compatibility

- E3231-19 Standard Guide for Cell Culture Growth Assessment of Single-Use Material (04)

And friends → WK65428 the Application of Continuous Processing in the Biopharmaceutical Industry (04)

USP (U.S. Pharmacopeial Convention)

www.usp.org

The USP is a scientific nonprofit organization that sets standards for the quality, purity, strength, and identity of medicines, food ingredients, and supplements. USP's drug standards are enforceable in the United States by the Food and Drug Administration (FDA). These standards are also used in more than 140 other countries.

ASME-BPE Updates on Standards and Industry Groups

<87>,<88>,<1031> Biocompatibility of Materials Used in Drug Containers, Medical Devices, and Implants *(draft – not final)*

- Drafts published (2021). Comment period now closed.
- <88> Animal implantation removed for most applications (other <88> tests remain)
- <88> "Pharmaceutical grade polymeric material" to replace Class VI
- <1031> Implies significant shared knowledge around plastics formulation/ingredients
- <1031> Does not address single-use.

- **Singles-Use & Manufacturing Equipment Requirements:**
  - Out of scope. Additional clarity or consensus opinion from <88> on SUT unlikely.
  - If industry wants to draft guidance on expectations, that is encouraged

<665>,<1665> Extractables Requirements for Plastic Manufacturing Systems

- Official date to be May 1, 2026
- Provides industry time to implement
- Track outputs & alignment with ICH Q3E

<665>Plastic Components and Systems Used to Manufacture Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products

Type of Posting:
Posting Date:
Targeted Official Date:
Expert Committee:

May 18, 2022

ASME-BPE Updates on Standards and Industry Groups

Standards build trust

<383> Cured Silicone Elastomers for Pharmaceutical Packaging and Manufacturing Components

- Published in PF 48(3). Open for comment through July 31
- Aligns with EP 3.1.9

⟨ **383**⟩ **Cured Silicone Elastomers for Pharmaceutical Packaging and Manufacturing Components.** The General Chapters—Packaging and Distribution Expert Committee is proposing this new chapter, based on comments received from the *PF* 45(2) [March–Apr 2019] publication of *Plastic Materials, Components, and Systems Used in the Manufacturing of Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products* (665) and the *USP General Chapter Prospectus* (https://www.uspnf.com/notices/gc-prospectus-688-cured-silicone-elastomers-for-pharm-manufacturing-and-packaging-components).

This chapter would apply to cured silicone components such as tubing, gaskets, and O-rings that are used in manufacturing operations for drug substances and drug products, as well as silicone components for pharmaceutical packaging systems.

Due to the scope of the proposed new chapter, the Packaging and Distribution Expert Committee is proposing a 5-year delayed implementation to allow industry adequate time to implement.

(GCPD: D. Hunt)

Correspondence Number—C266457

<788>, Particulates

- USP closely following activity by PDA, then will evaluate next steps
- Unlikely to be any focus on single-use

May 18, 2022

Standards build trust

<382> Elastomeric Component Functional Suitability in Parenteral Product Packaging/Delivery Systems PF 48(3) *(in process revision)*

New Advancements in Product Performance testing (stimulus PF 48(3))

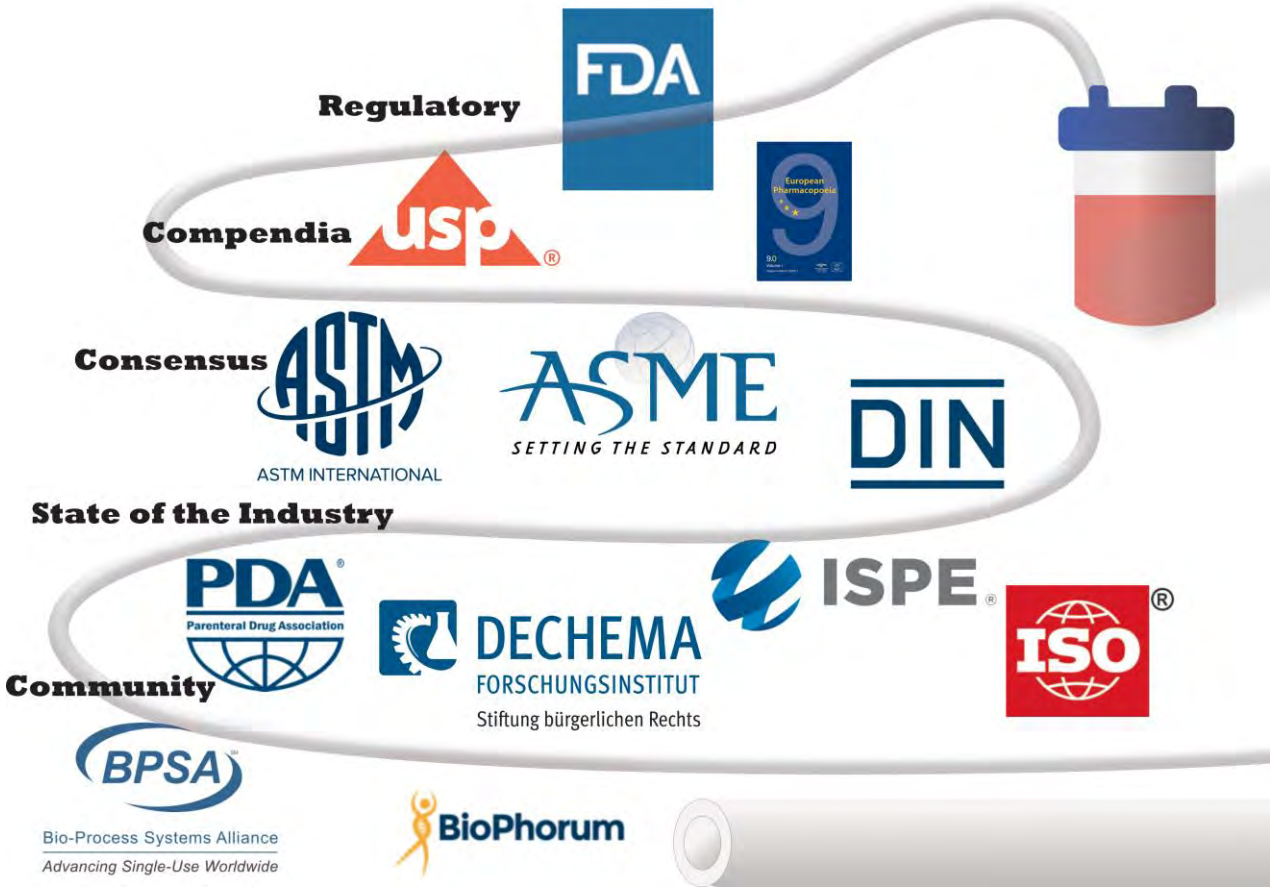
- 5 working groups to conduct gap analysis and generate stimulus article
- Nanomaterials PF 47(6)
- Continuous Manufacturing PF 48(4)(July 2022)

<1079> Risk and Mitigation Strategies for the Storage and Transportation of Finished Drug Products *(in process revision)*

May 18, 2022

Other Organizations

Regulations *vs.* Compendia *vs.* Standards *vs.* Guidelines

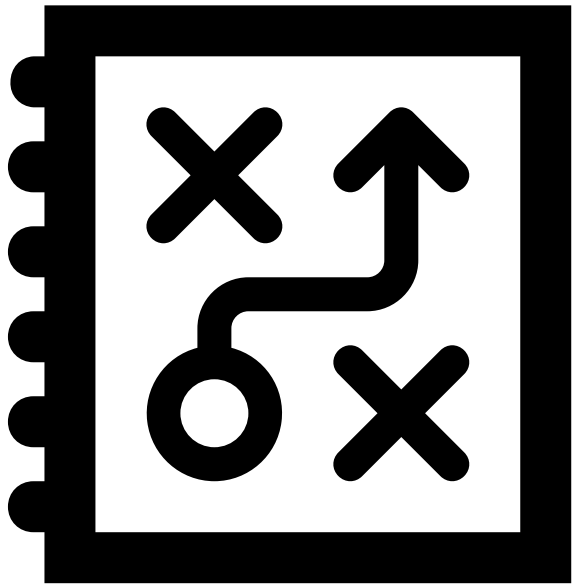


Other Organizations' Activities

- AAMI: Association for the Advancement of Medical Instrumentation® TIR104:2022-Guidance on transferring health care products between radiation sterilization sources
- DECHEMA: Technical State-of-the-Art and Risk Analysis on Single-Use Equipment in Continuous Processing Steps-March 2020
- ISPE-Ongoing efforts
- BioPhorum –Ongoing efforts
- PDA-Ongoing efforts

We know what to do with Single Use!

- There are Playbooks!
- Thanks to BPSA and many of you!
- We need more help!



Single-Use Playbooks

- BPSA- https://bpsalliance.org/
- ASME BPE- https://www.asme.org/codes-standards/find-codes-standards/bpe-bioprocessing-equipment-(1)
- ASTM E55- https://www.astm.org/get-involved/technical-committees/committee-e55
- USP- https://www.usp.org/
- AAMI- https://www.aami.org/home
- DECHEMA- https://dechema.de/en/
- ISPE- https://ispe.org/
- PDA- https://www.pda.org/
- BioPhorum- https://www.biophorum.com/

Upcoming Meetings

ASME
SETTING THE STANDARD

September 26-26, 2022
Scottsdale, AZ

January 30-Feb 2, 2023
San Juan, PR

ASTM INTERNATIONAL
Standards Worldwide

October 17, 2022
Scotland

Thank you

- Jeff Carter-Cytiva-ASTM
- James Hathcock-Pall-USP
- Milena McFeeters-The BioProcess Institute-ASME

Questions

The BioProcess Institute

We help the bioprocessing industry make better medicines.

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