



Standard Guide for Specification, Design, Verification, and Application of Single-Use Systems in Pharmaceutical and Biopharmaceutical Manufacturing¹

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1. Scope

1.1 This guide is intended as a complement to Guide [E2500](#).

1.2 This guide is applicable to the range of manufacturing systems described in Guide [E2500](#), specifically all elements of single-use systems, or hybrids of single-use and traditional components, used for the manufacturing of pharmaceutical and biopharmaceutical products, including: materials of construction, components, assembly, manifolds, supporting utilities, associated process monitoring and control systems, automation systems, and controlled environment that have the potential to affect product quality and patient safety.

1.3 This guide is applicable for the implementation of changes to manufacturing system design for existing systems. It may be used for continuous improvement and changes in operation from clinical through to commercial scale.

1.4 For brevity, single-use systems are referred to as SUS throughout the rest of this guide.

1.5 The approach may be applied by the end user, the supplier of SUS, and raw materials sub-suppliers further back in the supply chain.

1.6 This guide is not intended to apply to the use of single-use technology for packaging, primary containers, combination products (products composed of any combination of a drug, device, or biological product) or devices.

1.7 This guide does not address specific local requirements, which remain the responsibility of the end user.

1.8 *This guide does not address employee health and safety, environmental, nor other good engineering and manufacturing practices (GXP) requirements. This standard does not purport to address all of the safety concerns, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate safety and health practices and determine the applicability of regulatory limitations prior to use.*

¹ This guide is under the jurisdiction of ASTM Committee [E55](#) on Manufacture of Pharmaceutical and Biopharmaceutical Products and is the direct responsibility of Subcommittee [E55.03](#) on General Pharmaceutical Standards.

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2. Referenced Documents

2.1 *ASTM Standards*:²

[D4169 Practice for Performance Testing of Shipping Containers and Systems](#)

[E2363 Terminology Relating to Process Analytical Technology in the Pharmaceutical Industry](#)

[E2500 Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment](#)

2.2 *United States Pharmacopeia*:³

[USP<788> Particulate Matter in Injections](#)

[USP<790> Visible Particulates in Injections](#)

2.3 *International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)*:⁴

[ICH Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients](#)

[ICH Q8 \(R2\) Pharmaceutical Development](#)

[ICH Q9 Quality Risk Management](#)

[ICH Q10 Pharmaceutical Quality System](#)

2.4 *ISO Standards*:⁵

[ISO 13485:2003 Medical Devices—Quality Management Systems—Requirements for Regulatory Purposes](#)

[ISO 14644 Cleanrooms and Associated Controlled Environments](#)

[ISTA 3A General Simulation Performance tests](#)

2.5 *U.S. Food and Drug Administration (USFDA)*:⁶

[Guidance for Industry Process Validation: General Principles and Practices](#)

² For referenced ASTM standards, visit the ASTM website, www.astm.org, or contact ASTM Customer Service at service@astm.org. For *Annual Book of ASTM Standards* volume information, refer to the standard's Document Summary page on the ASTM website.

³ Available from U.S. Pharmacopeial Convention (USP), 12601 Twinbrook Pkwy., Rockville, MD 20852-1790, <http://www.usp.org>.

⁴ Available from International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), ICH Secretariat, 9, chemin des Mines, P.O. Box 195, 1211 Geneva 20, Switzerland, <http://www.ich.org>.

⁵ Available from American National Standards Institute (ANSI), 25 W. 43rd St., 4th Floor, New York, NY 10036, <http://www.ansi.org>.

⁶ Available from U.S. Food and Drug Administration (FDA), 10903 New Hampshire Ave., Silver Spring, MD 20993, <http://www.fda.gov>.

Pharmaceutical cGMPs for the 21st Century, A Risk-Based Approach

2.6 European Medicine Agency:

Commission Directive 2003/94/EC of 8 October 2003

2.7 Other Publications:

PDA Technical Report No. 66 Application of Single-Use Systems in Pharmaceutical Manufacturing

Consensus Quality Agreement Template for Single-Use Biopharmaceutical Manufacturing Products BioProcess Systems Alliance⁷

TAPPI Standard Practice T 564 sp-11

3. Terminology

3.1 Definitions:

3.1.1 For definitions of terms used in this guide, refer to Terminology E2363, Guide E2500, and PDA Technical Report No. 66. Terms requiring special consideration as they relate to SUS are detailed below.

3.1.2 *design reviews, n*—purpose of design reviews is still to evaluate design against standards and requirements, identify problems, and propose corrective actions.

3.1.2.1 *Discussion*—However, the scope of the review may differ depending on whether the end user is considering a standard design, configured variants of standard designs which maintain adherence to the supplier's design space, or customized designs, which incorporate one or more features that are outside of the supplier's design space. Such features may include components, design layout, design dimensions, or materials of construction. The end-user should first consider the requirements for any given SUS based on the application (for example, product or process contact, temperature, volumes, flow rates, mixing, requirements for sensors and controls etc. as applicable) and define them clearly in a document such as a user requirement specification (URS). In the case of standard or configured designs, the review will address the supplier's criteria for selection of materials, components, and functional design and align these against the URS. In the case of end-user-specified custom designs, the design review should affirm that the combination of supplier- and user-derived design attributes aligns with the URS. Additionally, the review should evaluate the risk taken in deviating from the supplier design space, and the possible need for risk mitigation, which generally will be the end user's responsibility. The risk assessment should be retained as part of the development history. Conditions and expectations should be covered in a quality agreement. The quality agreement should outline the responsibilities of the supplier and the end user with respect to the quality assurance of the system manufactured or supplied or both by the supplier to the end user. Quality agreement templates are available from various industry groups (for example, Consensus Quality Agreement Template for Single-Use Biopharmaceutical Manufacturing Products BioProcess Systems Alliance).

3.1.3 *modular, adj*—SUS can consist of assemblies of components or subassemblies that can be built or reconfigured or

both in a modular manner provided that connectors are compatible with each other.

3.1.4 *subject matter experts, n*—individuals with expertise in a particular area or field, which will include, but are not limited to, material sciences, plastics and molding technologies, sterilization, particulate assessment, and leachables and extractables.

3.1.5 *verification, n*—verification is a systematic approach to verify that SUS, acting singly or in combination, are fit for intended use, have been properly installed, and are operating correctly.

3.1.5.1 *Discussion*—The manufacturing process for an SUS consists of multiple steps and verification activities should be appropriate for the stage of the SUS design and manufacturing process (for example, material selection versus component dimensions versus configuration) and the intended purpose of the component or finished assembly or both. Verification is an umbrella term that encompasses all types of approaches to assuring systems are fit for use including qualification, commissioning and qualification, verification, system validation, or other and extends across the supply chain as materials and components are integrated into the completed SUS. Given that each system is partially or completely replaced after use, it is important to confirm that components have been assembled correctly, none of the critical attributes of the assembly are damaged during installation, and no leaks that may compromise the SUS are evident before use. Suppliers of SUS and their materials and components should apply similar rigor and change control procedures to their sub-suppliers to ensure consistent quality over the lifetime of the SUS (see also 8.2, Change Management).

4. Summary of Guide

4.1 This guide is based on a similar risk-based and science-based approach taken in Guide E2500 and is similar in purpose, content, and organization.

4.2 The objective of this guide is to provide additional information to support defined and controlled processes relevant to SUS, or hybrid traditional SUS to enable the production of products that consistently meet defined quality requirements. A further objective is to support supplier manufacturing capability that meets quality requirements of SUS or User Requirement Specifications (URS) or both as applicable.

4.3 The approach described within this guide supports continuous process capability improvements and facilitates incorporation of new capabilities as technology evolves.

4.4 The main elements of this guide are:

4.4.1 The underlying key concepts,

4.4.2 A description of the specification, design, and verification process, and

4.4.3 A description of the required supporting processes.

5. Significance and Use

5.1 Application of the approach described within this guide is intended to satisfy international regulatory expectations in ensuring that SUS are fit for their intended use and safety.

⁷ Available from BioProcess Systems Alliance, <http://www.bpsalliance.org>.

requirements for sourcing, supply, design, specification, installation, operation, and performance.

5.2 The approach described in this guide applies concepts and principles introduced in the FDA initiative, Pharmaceutical cGMP's for the 21st Century – A Risk-Based Approach. It supports and is consistent with the framework described in FDA Guidance for Industry, Process Validation: General Principles and Practices, in ICH Q7, ICH Q8 (R2), ICH Q9, and ICH Q10.

5.3 This guide includes concepts developed in the PDA Technical Report No. 66.

5.4 This guide may be used independently or in conjunction with other ASTM Committee E55 proposed standards to be published by ASTM International.

5.5 Specific standard practices about extractables, leachables, particulate matter, and integrity testing/leak detection, biocompatibility, and raw materials as available should be used by suppliers and end users and applied to their own manufacturing process facilities.

6. Key Concepts

6.1 This guide follows similar key concepts to those covered by Guide **E2500** focusing on clarification and discussion of SUS, good engineering practice, good manufacturing practice, and use of supplier and end user documentation. The concepts are listed in the following:

- 6.1.1 Risk-based approach,
- 6.1.2 Science-based approach,
- 6.1.3 Critical aspects of SUS,
- 6.1.4 Quality by design,
- 6.1.5 Good engineering/manufacturing/distribution/documentation practices,
- 6.1.6 Subject matter expert,
- 6.1.7 Use of supplier documentation,
- 6.1.8 Continuous improvement and change management, and
- 6.1.9 Supply chain.

6.2 *Risk-Based Approach:*

6.2.1 The underlying principle of risk management focuses on the issues which have the highest probability of occurring or have the greatest effect on the product quality and consequently patient safety.

6.2.2 Risk management underpins the specification, design, verification, and documentation activities as described in Guide **E2500** and in ICH Q9.

6.2.3 SUS are an integral part of the drug manufacturing process and it is critical that SUS suppliers provide SUS in a timely manner. Special consideration should be given to mitigating the risk of an interruption of the supply chain of SUS, which may have an impact on the security of supply of drug to patients.

6.3 *Science-Based Approach:*

6.3.1 Product and process information, as it relates to product quality and patient safety, remain the basis for making science- and risk-based decision that ensure that the SUS are designed and verified to be fit for their intended use.

6.3.2 Examples of end-user product and process information to consider include: critical quality attributes (CQAs), critical process parameters (CPPs), process control strategy information, and prior production experience. For SUS, these can include extractables information, certificates of analysis, sterilization records, change control documents, and product design specifications.

6.3.3 Additional information to consider is the processing parameters and materials for the SUS themselves. Materials and designs should be selected and developed based on the intended use of the SUS (for example, cell culture, buffer bag, and product container) using quality by design approaches, such that sources of variability are understood and are managed such that they do not impact the performance of the end user's process or product quality.

6.3.4 Special consideration should be given to the supplier's evaluation and selection of materials of construction (for example, films, tubing, and connectors) as related to their fitness for intended use based on parameters such as physico-chemical properties, mechanical strength, optical properties, and anticipated operating temperature. Materials should be robust and compatible with product and process fluids and should not be excessively prone to damage, which compromises structural integrity. The shedding of any materials, either as solid particles or soluble leachables, that impact product quality or process performance should be well characterized. For SUS, this is particularly important since changes may be made in the construction materials, production and sterilization processes, additives such as anti-oxidants and dyes, and material origin based on their availability over the lifetime of a given process. Such changes should be evaluated with the appropriate diligence based on the risk to the product or the process.

6.3.5 Consideration should be given to the possible impact of materials of construction or in-process leachables from materials of construction, or both, on product quality or process performance.

6.4 *Critical Aspects of SUS:*

6.4.1 Critical aspects of SUS are typically functions, features, abilities, and performance or characteristics necessary for the manufacturing process and systems to ensure consistent product quality and patient safety. They should be identified and documented based on scientific product and process understanding for both the SUS manufacturing process and the end-user process.

6.4.2 SUS often consist of multiple combinations of individual components. Often, multiple design configurations can be considered with varied materials and components, each of which can be demonstrated as capable of meeting the critical performance requirements for a given system such as volume, compatibility, low bioburden, freedom from leaks, and mixing if required.

6.4.3 Adopting a modular design approach allows for the interchangeable use of functionally equivalent components and provides flexibility, which can be used to the advantage of both end user and supplier to manage the risk to supply continuity, subject to the appropriate qualification of the components.