Designation: E3244 – 23

Standard Practice for Integrity Assurance and Testing of Single-Use Systems[1]

This standard is issued under the fixed designation E3244; the number immediately following the designation indicates the year of original adoption or, in the case of revision, the year of last revision. A number in parentheses indicates the year of last reapproval. A superscript epsilon (ε) indicates an editorial change since the last revision or reapproval.

1. Scope

1.1 This practice uses quality risk management (QRM) and life-cycle approach to establish integrity assurance of single-use systems (SUSs), such as but not limited to bag assemblies and liquid transfer sets for processing, storage, and shipping of (bio)pharmaceutical products. It gives recommendations to identify failure modes and risks associated with such systems and their use-cases and how to identify the relevant leak(s) of concern. Integrity assurance in this context is limited to the barrier properties of the SUS, linked to microbial integrity and bioburden control (product quality) and liquid product loss (operator and environmental contamination). The required level of integrity assurance will depend on how critical the application is and can be interpreted in different ways. It can also vary between processes and applications used for different modalities (for example, advanced therapies). Other package barrier properties different from that, such as but not limited to gas barrier properties for gas headspace preservation, as well as porous barrier packages are not considered. Specific aspects how to address the contamination control strategy (CCS) for SUS are also described in chapters 8.131ff of the new Revision of Annex 1 (**1**),[2] including chapter 8.137 regarding SUS integrity.

1.2 The test method overview provides descriptions that focus on the standard test setup and the identification of challenges in combination with SUSs. Details, including specific test setups, test parameter, and result interpretation, are not discussed. For more detailed information refer to Test Method E3251 for microbial test methods, and to Test Method E3336 for physical test methods.

1.3 This practice is not intended to apply to the use of single-use technology for primary containers, combination products (products composed of any combination of a drug, device, or biological product), or devices. Appropriate procedures related to these products are discussed in documents covering the integrity assurance for primary containers (**2**) or medical products (**1, 3**).

1.4 Techniques and procedures for complaint management and root cause analysis related to integrity failures are also not discussed.

1.5 The values stated in SI units are to be regarded as standard. No other units of measurement are included in this standard.

1.6 *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, health, and environmental practices and determine the applicability of regulatory limitations prior to use.*

1.7 *This international standard was developed in accordance with internationally recognized principles on standardization established in the Decision on Principles for the Development of International Standards, Guides and Recommendations issued by the World Trade Organization Technical Barriers to Trade (TBT) Committee.*

2. Referenced Documents

2.1 *ASTM Standards:*[3]

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

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

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

2.2 *ICH Documents:*[4]

ICH Q9(R1) Quality Risk Management

3. Terminology

3.1 *Definitions:*

[1] This practice is under the jurisdiction of ASTM Committee E55 on Manufacture of Pharmaceutical and Biopharmaceutical Products and is the direct responsibility of Subcommittee E55.04 on General Biopharmaceutical Standards.

Current edition approved June 1, 2023. Published August 2023. Originally approved in 2020. Last previous edition approved in 2020 as E3244 – 20. DOI: 10.1520/E3244-23.

[2] The boldface numbers in parentheses refer to a list of references at the end of this standard.

[3] 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.

[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.

3.1.1 *bioprocess container (biocontainer), n*—a container (bag, bottle, tank, etc.) used primarily for liquid (or frozen liquid) storage during various stages of biopharmaceutical manufacturing processing.

3.1.2 *calibrated leak, n*—a hole which is characterized by its size (for example, artificially created into a SUS, a SUS's material, or component and used for creating positive controls).

3.1.2.1 *Discussion*—Often, the size is a nominal size which is equivalent to a gas flow through an idealized geometry (**2**). A commonly used idealized geometry is the "nominal diameter orifice size", corresponding to the size of a perfect circular hole of negligible length that would give the same gas flow in the calibration conditions (for example, dry air flow rate measured at 25 °C, with 1 barg inlet pressure and 1 atm outlet pressure).

3.1.3 *destructive test method, n*—a test method that will alter the intended use of the tested SUS during the test and not allow further use (see also *non-destructive test method*).

3.1.4 *end user, n*—a company processing (bio)pharmaceutical products.

3.1.5 *integrity assurance, n*—a holistic approach of risk analysis and mitigation by means of product and process robustness, quality, and process control and integrity testing to assure that a SUS maintains its integrity prior to and during use.

3.1.6 *integrity test, n*—a test used to confirm the defined barrier properties of a SUS.

3.1.7 *leak, n*—a breach in a SUS's material or a gap between SUS's components through which there is a break-down of the barrier property of interest.

3.1.8 *leak test, n*—a test used to identify leaks not correlated to the defined barrier properties of a SUS.

3.1.9 *maximum allowable leakage limit (MALL), n*—the greatest leakage rate (or leak size) tolerable for a given product package to maintain its barrier properties under its use-case conditions (for example, prevent any risk to product safety, product quality, or operator and environmental safety).

3.1.9.1 *Discussion*—In this document's context, the product package is a SUS containing a (bio)pharmaceutical product, but not a final dosage form.

3.1.10 *non-destructive test method, n*—a test method that maintains the test article in a condition for further use, without impacting its quality attributes (see also *destructive test method*).

3.1.11 *single-use components, n*—parts used in single-use systems, most commonly, but not limited to, bioprocess containers, tubing, connectors, clamps, valves, sensors, and filters.

3.1.12 *single-use system (SUS), n*—process equipment used in (bio)pharmaceutical manufacturing, disposed of after use and usually constructed of polymer-based materials.

3.1.13 *SUS supplier, n*—a manufacturer that produces and/or assembles single-use systems, also known as a system integrator.

3.1.14 *tracer gas, n*—a gas to be detected against the background of all other gases.

3.2 *Abbreviations:*

3.2.1 *BPOG*—Biophorum

3.2.2 *BPSA*—Bio Process Systems Alliance

3.2.3 *cGMP*—current Good Manufacturing Practice

3.2.4 *ICH*—International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

3.2.5 *LoD*—limit of detection

3.2.6 *MALL*—maximum allowable leakage limit

3.2.7 *QbD*—quality by design

3.2.8 *QRM*—quality risk management

3.2.9 *SUS*—single-use system

3.2.10 *SUSI(T)*—single-use system integrity (testing)

3.2.11 *SUT*—single-use technologies

4. Significance and Use

4.1 This practice provides:

4.1.1 A holistic approach to evaluate risks associated with an integrity breach in a SUS, considering its life cycle from development to disposal.

4.1.2 An overview of physical and microbial test methods that could be applicable to SUS testing, for qualification and validation purposes, as well as for routine testing.

4.1.3 Information on the main challenges faced when testing SUSs for integrity.

4.2 This practice can be used by SUS suppliers and SUS end users to define an integrity assurance strategy for SUSs, with the relevant tests when appropriate.

5. Procedure

5.1 *Quality Risk Management (QRM) and Life-Cycle Approach:*

5.1.1 *Introduction of Quality Risk Management (QRM):*

5.1.1.1 QRM, as defined in ICH Q9, is a methodology to assess potential risk to product quality within a process. Potential risks are managed based on their occurrence and severity in the process/product and are reviewed throughout the life cycle of the process/product. When discussing a SUS, its integrity can be a critical attribute for maintaining product quality or protecting the operator or environment from exposure, or both. There must be necessary controls, monitoring, and testing in place to ensure that the integrity of the SUS is maintained throughout its life cycle. To accomplish this, the SUS supplier and end user can adopt a life-cycle approach, where the integrity assurance of the SUS is considered from the design and production process at the SUS supplier to its final application in the end user's manufacturing process. Within the life cycle, the risks to SUS integrity (SUSI) can be proactively identified and the necessary controls and testing put in place. These risks can be different for both the SUS supplier and end user, which can necessitate differences in the test methods, testing frequency and sensitivity utilized for ensuring SUSI.

5.1.1.2 The general approach of identifying and mitigating risks is the same regardless of the modality and the manufacturing process for which the SUS is used, but risk rating and