Designation: E3336 – 22

# Standard Test Method for Physical Integrity Testing of Single-Use Systems[1]

This standard is issued under the fixed designation E3336; 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 The test methods described in this standard are applicable for single-use manufacturing equipment, further called Single-use Systems (SUSs), used for (bio)pharmaceutical products.

1.2 The test methods described in this standard are not intended to be used on 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 (**1**)[2] or medical products (**2-4**).

1.3 The test methods and their validation are described to only cover testing of empty and dry SUSs. Residual liquid in the SUS can impact the test reliability and reproducibility.

1.4 The test methods are intended to be used to confirm the barrier properties of the test article, further called integrity testing, or test the SUS for leaks of certain sizes, further called leak testing.

NOTE 1—To verify that an integrity test can confirm the intended barrier properties of the SUS, its detection limit must be equal or better than the respective maximum allowable leakage limit.

1.5 The physical test methods covered by this standard are:

1.5.1 Pressure-based test methods.

1.5.2 Tracer gas-based test methods.

1.6 The physical test methods described are in general non-destructive and allow further use of the SUS.

NOTE 2—Some variations can be used in a destructive way, for example, to perform root cause analysis of the leak.

1.7 The standard describes the test apparatuses, operation procedures, environment requirements, and discusses specific challenges with testing SUSs, as well as how to perform robust validation of the test method.

1.8 This standard does not include methods to determine the maximum allowable leakage limit for maintaining the barrier properties of the SUS. For that, refer to Practice E3244 and Test Method E3251.

1.9 This standard does not describe how to select the appropriate test method. For that, refer to Practice E3244.

1.10 Furthermore, it does not discuss whether an integrity test should be conducted, at what frequency and where in the life cycle of a SUS. For that refer to Practice E3244.

1.11 Filter membrane integrity testing that additionally tests the integrity of the SUS is excluded from the scope. Certain components of the SUS may require additional testing.

1.12 *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.*

1.13 *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]

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

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

F2095 Test Methods for Pressure Decay Leak Test for Flexible Packages With and Without Restraining Plates

F2338 Test Method for Nondestructive Detection of Leaks in Packages by Vacuum Decay Method

F2391 Test Method for Measuring Package and Seal Integrity Using Helium as the Tracer Gas

[1] This test method 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.

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[2] The boldface numbers in parentheses refer to the 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.

2.2 *Other Documents:*

USP <1207> Sterile Product Packaging Integrity Evaluation, United States Pharmacopeia (USP), 2016

EU GMP, Annex 1 Manufacture of Sterile Products, European Commission, 2009

EU GMP, Annex 2 Manufacture of Biological Medicinal Products for Human Use, European Commission, 2018

USP <1> Injections and Implanted Drug Products (Parenterals) – Product Quality Tests, United States Pharmocopeia (USP), 2020

## 3. Terminology

3.1 *Definitions:*

3.1.1 *apparatus, n*—a technical equipment or machinery needed for leak or integrity testing purposes.

3.1.2 *balanced pressure drop, n*—the pressure drop of positive control articles balanced against the pressure drop of negative control articles; for analyzing the validation results, once this value turns into positive it means that a defective test article can be differentiated from a non-defective one.

3.1.2.1 *Discussion*—The pressure drop values are mean values of all test articles used for the validation, and include, depending on the quality requirements of the test validation, a defined number of standard deviations. In addition, the accuracy of the measurement instrument should be taken into consideration.

3.1.3 *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.

3.1.4 *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).

3.1.4.1 *Discussion*—Often, the size is a nominal size which is equivalent to a gas flow through an idealized geometry (**1**). 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 $bar_g$ inlet pressure and 1 atm outlet pressure).

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

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

3.1.7 *family approach, n*—an approach to validate only one set of test parameters for a combination of several test article designs.

3.1.8 *hardware support structure, n*—a hardware that mechanically supports the SUS.

3.1.8.1 *Discussion*—This can be a restraining hardware, for example, a pair of plates or grids of rigid material, for example, aluminum or stainless steel, that are used to restrict the inflation of the SUS, or a hardware that does not restrict the inflation of the SUS to its nominal volume.

3.1.9 *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.

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

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

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

3.1.13 *maximum allowable leakage limit, 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).

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

3.1.14 *negative controls, n*—the negative control articles are intact, under intended use-case conditions non-leaking SUS (see also *positive control*).

3.1.15 *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*).

3.1.16 *positive controls, n*—the positive control articles are test articles of the exact same design as the negative control articles, equipped with a calibrated leak of known size (see also *negative control*).

3.1.16.1 *Discussion*—Positive controls can be manufactured by including a calibrated leak into the SUS or by attaching it using an appropriate connection.

3.1.17 *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.

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

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

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

3.1.21 *tracer gas calibrated leak standard, n*—element emitting a known flow of tracer gas, used to calibrate tracer gas leak detectors. It is an assembly of a pressurized reservoir with an isolation valve and an orifice.

3.2 *Abbreviations:*

3.2.1 *BPOG*—Biophorum

3.2.2 *BPSA*—Bio Process Systems Alliance

3.2.3 *cGMP*—current Good Manufacturing Practice