Bio-Process Systems Alliance Component Quality Test Matrices

BPSA Guidelines and Standards Committee

Incorporation of single-use bioprocess manufacturing systems has emerged in recent years as a significant trend in the biopharmaceutical industry. In response to the growing demand for single-use systems in biotech and pharmaceutical manufacturing and the challenges of the emerging single-use bioprocessing industry, providers of single-use components, systems, and related services formed an industry organization, the Bio-Process Systems Alliance (BPSA), in early 2006. This alliance was established under The Society of the Plastics Industry, Inc. (SPI) to give greater visibility and a united voice in promoting benefits of single-use manufacturing.

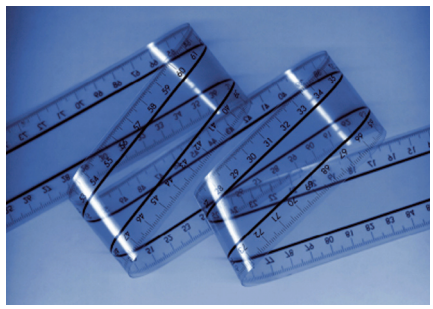
One of BPSA's core activities is to educate and to develop guides that safeguard the quality of drugs produced using this technology. As manufacturers of components and systems, BPSA members can offer extensive expertise and leadership in setting the direction for industry best practices. As one of its first initiatives, the BPSA Guidelines and Standards Committee conducted an initial review of referenced quality test methods and specifications currently applied to common components of single-use systems: filter capsules, films and containers, tubing, and connectors and fittings.

Recognizing Best Practices: BSPA serves as a forum for commercial members to recognize common best practices for quality testing of materials and functionality. Recognition of consensus quality test methods, referenced to established industry standards and regulatory bodies, can help guide users when making their selections and can facilitate qualification, validation, and use of single-use products. Ultimately they can serve to elevate and maintain the level of excellence across the single-use industry.

Component Quality Test Matrices

For each single-use system subcomponent class — whether filter capsules, films and containers, tubing, and connectors and fittings — BPSA member manufacturers identified consensus quality tests. The matrices describe test methods in common language and list consensus reference documents along with testing frequency: at initial qualification, periodically, on sample lots, or (in the case of filter integrity testing) continually. The matrices also compare different test references used for specific test methods.

In many cases individual component manufacturers may conduct tests that go beyond these consensus methods or apply them with greater frequency. The methods here are intended to highlight common industry practices. You should also consider additional test data provided by component manufacturers or systems integrators when making your selections. In some cases, if your company requires conformance to standards such as in the international pharmacopoeia not listed in this document, you should contact the system or specific component supplier directly.



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As more single-use systems become available, BPSA is confident that adoption of this technology will gain even further momentum. The members hope that these quality test matrices will serve as a guide to maintain suitable component quality for operation of single-use systems in pharmaceutical GMP environments.

These matrices are the first in a series of guides that BPSA is developing for its constituents. Future guides will address issues including other single-use system components, sterility claims, extractables and leachables, and system-based issues. BPSA's continuing focus is on educating users about single-use systems both independently and in conjunction with other organizations as

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Process Focus: Production and processing, storage

Who Should Read: Process development and manufacturing

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Level: Basic

appropriate. The alliance looks forward to continuing to enhance the visibility and understanding of such systems.

Part 1, containing matrices for films and containers and for connectors and fittings, appeared in BPI's April 2007 issue; Part 2, with matrices for filters and tubing, appeared in BPI's May 2007 supplement issue.

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Reference Standards Listed in the BPSA Matrices

AAMI TIR27 Vd_{max}, Fluid Path (www.aami.org)

ANSI/AAMI BF7 (http://marketplace.aami.org)

ANSI/AAMI/ISO 11137 (http://marketplace.aami.org)

ASTM (www.astm.org): D395, D412, D543-06, D624, D746, D792, D882, D1003, D1004, D1434, D1599-99 (2005), D1709, D1790, D2240, D3418, D3985, D4169, D4728-95, D4991-94 (1999), E515, E1640, F88, F392-93 (2004), F838-05, F838-83, F1249, F1927, F1980

DIN EN 554 (http://webstore.ansi.org)

DIN ISO 2872 (www.iso.org)

EN 12266-1 and EN 30993-1, -5, -12 (www.cenorm.be/catweb/cwen.htm)

European Pharmacopoeia (http://online.pheur.org/entry.htm): EP 2.6.1, 2.6.14, 2.9.19, 3.1.5, 3.1.9, 3.2.2.1, 3.2.9

ISO (www.iso.org): ISO 527-3, 3968, 7241-2, 7765-2, 8570, 10993, 11134, 11137, 11357-2, 11359-2, 15105-1, 15105-2, 15106-1, 15106-2, 15106-3

ISTA, ISTA 2A (www.ista.org)

21 CFR 177 (www.gpoaccess.gov/fr/index.html): 177.1350, -.1520, -.1550, -.2400, -.2510, -.2600

United States Pharmacopeia (www.uspnf.com/uspnf/login): <71>, <85>, <87>, <88>, <381>, <643>, <645>, <661>, <788>, <791>

Acronyms and Terms Appearing in the Matrices

AAMI	Association for the Advancement of Medical Instrumentation
ANSI	American National Standards Institute
ASTM	ASTM International (formerly named American Society for Testing and Materials)
BP	*British Pharmacopoeia*
CFR	*Code of Federal Regulations*
CPM	cycles per minute
DIN	Deutsches Institut für Normung e. V.
EN/CEN	European Committee for Standardization
EP	*European Pharmacopoeia*; set of physicochemical tests that include appearance, acidity, alkalinity, absorbance, reducing substances and transparency.
FEP	fluorinated ethylene-propylene
FFKM	ASTM designation for a perfluoroelastomer
FTIR	Fourier transform infrared spectroscopy
GTR	gas transmission rate
HPLC	high performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ISO	International Organization for Standardization
ISTA	International Safe Transit Association
iv	intravenous
NVR	nonvolatile residue
O2GTR	oxygen gas transmission rate
PFA	perfluoroalkoxyethylene
PFTE	polytetrafluoroethylene
PP	polypropylene
PVDF	polyvinylidene fluoride
RH	relative humidity
SAL	sterility assurance level
USP	*United States Pharmacopeia*

Arrhenius Method: predicts that materials age in a predictable manner relative to temperature. Testing at elevated temperatures is used to predict room temperature material deterioration.

Extractables: compounds that can be extracted from a component under extreme conditions such as the presence of harsh solvents or elevated temperatures. These compounds can contaminate the drug product. (from Kauffman J. Identification and Risk-Assessment of Extractables and Leachables. *Pharm. Technol.,* supplement February 2006.)

Leachables: compounds that are present in the drug formulation as a result of direct contact with the component under normal conditions. Leachables are typically a subset of extractables but may also include reaction products. (from Kauffman J. Identification and Risk-Assessment of Extractables and Leachables. *Pharm. Technol.,* supplement February 2006.)

Lot release: Representative sampling from the lot is tested as a requirement for lot release.

Periodic: Testing that is done on some frequency less than every lot but more than initial qualification.

Qualification: This test frequency includes material, process or design qualification as appropriate.

Resilience: A measure of durability from repeated use; for example, from repeated bending of the tubing or pressure from rollers in a peristaltic pump. Resilience is often characterized through a hysteresis measurement.

TABLE 1A–C: SINGLE-USE PRODUCT QUALIFICATION TEST METHODS, FILMS AND CONTAINERS (*CONTINUES ON THE FOLLOWING THREE PAGES*)

1A Test Type and General Description	Test References	Test Frequency	Summary Description of Test Reference
Physical — Mechanical			
Puncture Puncture resistance testing predicts the durability of the film while in use. Films with high puncture resistance correspond with materials that can absorb the energy of an impact by both resistance to deformation and increased elongation. Puncture resistance, measured in energy units, evaluates the film strength and extensibility properties. Puncture resistance is similar to tensile toughness.	ASTM D1709	Qualification	Two testing methods depending on the size of the striker, which are determined by the impact resistance of the material, are described. The standard technique is a staircase method to drop a weight and increase or decrease depending on pass or fail. Standard apparatus and striker have been described. Test conditions are 23 °C ± 2 °C and 50% RH ± 5%.
	ISO 7765-2	Qualification	The test is an instrumented force deformation test for specimens less than 1 mm thick. The specimen is tested for impact-penetration forces, biaxial deformation, and energy-absorption capabilities. Test specimen is penetrated by a striker at a uniform velocity. The data are then computer recorded. Each test should be repeated five times. This test is dependent on temperature and RH.
Tear Determines the tear resistance of flexible plastic film and sheeting at very low rates of loading	ASTM D1004	Qualification	Tear resistance at low rates of loading, 51 mm/2 min. Test is designed to measure the force to initiate tearing, with measurement taken from a constant-rate-of-grip separation machine. The force initiated to tear is calculated by the load-time. This test method is used to compare different materials. Test apparatus is described.
Tensile Strength A measure of the force required to stretch a material to its breaking point	ASTM D882	Qualification	Used for thin sheets of plastic, including film, less than 1.0 mm (0.04 in.) thick. Performed at 23 °C ± 2 °C at RH of 50% ± 5%. Speeds are determined by the material in question and a reference table provided by the standard. One type of specimen design.
	ISO 527-3	Qualification	Used for tensile properties on thin sheets or film less than 1 mm thick. This test calls for the specimen to be cut in one of four distinct manners and pulled in an apparatus at the following five rates: 5, 50, 100, 200, and 300 mm/min.
Physical — Permeability			
O_2 and CO_2 Determines the steady-state rate of transmission of O_2 or CO_2 gases through material	ASTM D3985	Qualification	Test method to evaluate steady-state 02GTR. The specimen is to be conditioned in a dry environment less than 1% RH. Then it separates two chambers at ambient pressure. The chambers are then purged — one with N_2 and the other with O_2. O_2 permeation is measured with a coulometric detector. No operating conditions specified.
	ASTM F1927	Qualification	This test method measures O2GTR across a specimen that is used to separate two chambers. This is measured by controlling temperature and RH% in O_2 on one side of the chamber and the temperature and RH% in N_2 on the other side of the chamber. The electrical output of the O_2 in N_2 is then measured. No standard operating conditions specified.
	ASTM D3985/D1434	Qualification	This test covers steady-state GTR, permeance, and permeability of plastic films. Two test methods, M and V, are provided. Test Method M evacuates the gas on the nontested side and measures the pressure increase. Test Method V maintains pressure on the lower side and measures the volume increase. Materials should be conditioned in a desiccant at 23 °C. RH and temperature need to be controlled. This test is used to measure multiple materials.
	ISO 15105-1	Qualification	Plastics — film and sheeting — determination of gas-transmission rate, Part 1: Differential-pressure method.
	ISO 15105-2	Qualification	Plastics — film and sheeting — determination of gas-transmission rate, Part 2: Equal-pressure method.
WVTR **(water vapor transmission rate)**	ASTM F1249	Qualification	Uses a modulated infrared sensor to measure water vapor permeability at 5 °C and 23 °C with 0% RH on the outside and 100% RH on the inside to simulate worst-case use conditions for a fluid storage container. This is a diffusion cell procedure with a dry gas chamber with controlled temperature and RH and a wet cell controlling the same variables. The WVTR is calculated from an infrared pressure sensor that compares WVTR to known value.
	ISO 15106-1	Qualification	Plastics — film and sheeting — determination of water vapor transmission rate, Part 1: Humidity detection sensor method.
	ISO 15106-2	Qualification	Plastics — film and sheeting — determination of water vapor transmission rate, Part 2: Infrared detection sensor method.
	ISO 15106-3	Qualification	Plastics — film and sheeting— determination of water vapor transmission rate, Part 3: Electrolytic detection sensor method.

Table 1A (CONTINUED): Single-use product qualification test methods, films and containers

Test Type and General Description	Test References	Test Frequency	Summary Description of Test Reference
Chemical and Biological			
Bacterial Endotoxin Evaluates the presence of bacterial endotoxins in or on a sample	USP <85> EP 2.6.14	Periodic	*Limulus* amebocyte lysate (LAL) testing is used to detect or quantify bacterial endotoxins that may be present in or on the sample of the article.
Biological Reactivity — In Vitro Evaluates the response of mammalian cell cultures to extracts of polymeric materials	USP <87>	Qualification	Extracts are obtained by placing the test and control materials in separate cell culture media under standard conditions. Cells are observed for visible signs of toxicity (such as a change in the size or appearance of cellular components or a disruption in their configuration) in response to the test and control materials.
Biological Reactivity — In Vivo Evaluates the response in animals to exposure of polymeric materials	USP <88>	Qualification	USP Biological Reactivity Test — In Vivo for Class VI Plastics, is a series of three tests: systemic toxicity, intracutaneous reactivity, and implantation. The first two are designed to determine the systemic and local, respectively, biological responses of animals to plastics and other polymers by the single dose injection of specific extracts prepared from a sample. The implantation test is designed to evaluate the reaction of living tissue to the plastic and other polymers by the implantation of the sample itself into animal tissue.
	ISO 10993	Qualification	The biological tests are designed to determine the biological response of animals to plastic material or by the injection of specific extracts prepared from the material under test.
Physicochemical — Containers Evaluates the physical and chemical properties of plastics and their extracts	USP <661>	Qualification	Material dependent: measures the properties of impurities extracted from plastics when leached with extraction medium (such as purified water and isopropanol) over a specified period and temperature. Includes the following: heavy metals, buffer capacity and nonvolatile residue.
Functional			
Accelerated Aging Provides information for developing accelerated aging protocols to rapidly determine the effects, if any, due to the passage of time and environmental effects on the sterile integrity of packages and the physical properties of their component packaging materials	ASTM F1980	Qualification	To determine the effects of time and environmental conditions on maintaining the sterility and physical properties of a packaging material. These data can be used to define or support shelf-life. They address the primary package as a whole and do not address the package/product interaction. Real time studies should be completed to confirm accelerated aging test results.
Chamber Integrity Used to measure manufactured product and seal barrier performance of a variety of package types and forms, as well as seal and/or closure types	Helium leak	Qualification	Used to measure manufactured product and seal barrier performance of a variety of package types and forms, as well as seal/closure types. Helium is injected into the package, and the package is sealed. Loss of pressure occurs when helium escapes. Helium can be used to detect leaks in many other methods (such as bubble test, helium mass spectrometry, vacuum/pressure retention).
	Pressure decay	Periodic	A pressure differential is applied to a package, and the change in pressure is measured either inside the package itself or outside in a sealed package test chamber. The change in test chamber pressure can be determined by absolute pressure measurement, or it can be determined using a differential pressure manometer in which the test chamber pressure change is compared with that of a control package. Several gases can be used: air, nitrogen (when stored products are sensitive to O_2), and helium, for example.
Seal Integrity-Peel Performed to ensure that functional strength requirements are met	ASTM F88	Lot release	This test method covers the measurement of the strength of seals in flexible barrier materials. It measures the force required to separate a test strip of material containing the seal and identifies the mode of specimen failure.
Sterility-Bacterial Ingress Test to determine whether a batch contains contaminated units	USP <71>	Qualification	This test is applied to substances, preparations, or articles that, according to the pharmacopeia, are required to be sterile.
	EP 2.6.1	Qualification	This test is applied to substances, preparations, or articles that, according to the pharmacopoeia, are required to be sterile. This is confirmed by inoculating articles with media and monitoring for 14 days to determine that no growth occurs.

Table 1A (CONTINUED): Single-use product qualification test methods, films and containers

Test Type and General Description	Test References	Test Frequency	Summary Description of Test Reference
Functional (*continued*)			
Transportation/Shipping Integrity Standard practice for performance testing of shipping containers and systems to provide a uniform basis of evaluating, in a laboratory, the ability of shipping units to withstand the distribution environment	ISTA	Qualification	ISTA (International Safe Transit Association) dedicated to the specific concerns of packaged-product distribution. Recommends guidelines and test protocols to challenge the strength and robustness of product and package combination. Test protocols are classified into categories called *series*. "Non-Simulation Integrity Performance Tests" (ISTA 1 Series); "Partial Simulation Performance Tests" (ISTA 2 Series); "General Simulation Performance Tests" (ISTA 3 Series); "Enhanced Simulation Performance Tests" (ISTA 4 Series:); "Focused Simulation Performance Tests" (ISTA 5 Series); and "Development Tests" (ISTA 7 Series).
	ASTM D4169	Qualification	Used to ensure that the identified shipping unit can protect the integrity of the product during transit. This is accomplished by mimicking actual shipping conditions encountered during product distribution.
Sterilization Validation			
Irradiation Validation Sterilization of healthcare products	ANSI/AAMI/ISO 11137 Method 1, Fluid Path	Qualification, followed by quarterly dose audits	Validates the minimum gamma irradiation dosage necessary to claim sterility at 10^{-6} sterility assurance level (SAL), based on the bioburden level of the fluid path of the finished product.
	AAMI TIR27 VD_{max}, Fluid Path	Qualification, followed by quarterly dose audits	Validates a specific minimum gamma irradiation dosage to claim sterility at 10^{-6} sterility assurance level (SAL), based on the bioburden level of the fluid path of the finished product.
Sterilization Process Compatibility Confirmation of manufacturer's specified performance claims after sterilization process	Manufacturer defined	Qualification	Manufacturer's supporting documents (poststerilization); outlines the claims of a product.

Table 1B: Single-use product qualification test methods, films and containers — application-dependent tests

Application-Dependent Test Type and General Description	Test References	Test Frequency	Summary Description of Test Reference
Brittleness Temperature Determines the temperature at which plastics and elastomers exhibit brittle failure	ASTM D1709	Qualification	Described are two testing methods depending on the size of the striker, which are determined by the impact resistance of the material. The standard technique is a staircase method to drop a weight and increase or decrease depending on pass or fail. Standard apparatus and striker have been described. Test conditions are 23 °C ± 2 °C and 50% RH ± 5%.
	ASTM D746	Qualification	Covers determination of the temperature at which plastics and elastomers exhibit brittle failure under specified impact conditions.
	ASTM D1790	Qualification	Covers determination of the temperature at which plastic sheeting 1.00 mm (0.040 in.) or less in thickness exhibits a brittle failure under specified impact conditions.
	ISO 8570	Qualification	Plastics — film and sheeting — determination of cold-crack temperature.
Chemical Resistance Standard test method for resistance of plastic to chemical reagent	ASTM D543-06	Qualification	Primary container or containers/components for storage of bulk substances or intermediate solutions have the potential to interact with the stored solutions. The chemical resistance test demonstrates that the bag/single-use components are compatible with the tested solution and that the material's initial specification remains within the limits after the contact time. These tests could be inspired from the ASTM D543-06, "Standard Practices for Evaluating the Resistance of Plastics to Chemical Reagents." Standard reagents are specified to establish comparable results. The type of conditioning depends on the end-use of the material. These practices include provisions for reporting changes in weight, dimensions, appearance, and strength properties. A comparison is done before and after contact with the plastic material. A general compatibility status is given upon testing results classified between "excellent compatibility" and "not recommended use."

Table 1B (CONTINUED): Single-use product qualification test methods, films and containers — application-dependent tests

Test Type and General Description	Test References	Test Frequency	Summary Description of Test Reference
Dart Drop Test method covers the determination of the energy as part of mechanical properties that causes plastic film to fail under specified conditions of impact of a free-falling dart	ASTM D1709	Qualification	Described are two testing methods depending on the size of the striker, which are determined by the impact resistance of the material. The standard technique is a staircase method to drop a weight and increase or decrease depending on pass or fail. Standard apparatus and striker has been described. Test conditions are 23 °C ± 2 °C and 50% RH ± 5%.
Gelbo Determines the flex resistance of materials by the formation of pinholes	ASTM F392-93 (2004)	Qualification	This test covers the flex resistance of materials by the formation of pinholes. Specimens are twisted and horizontally folded at a 45-cpm constant rate. A turpentine stain method is used to measure pinholes, but it can also be determined by the measure of GTR. Permeation is a good measure for multilayer films. Five different criteria levels are 2,700 cycles (1 hour), 900 cycles (20 min), 270 cycles (6 min), 20 cycles, and 20 partial cycles.
Glass Transition Temperature Determines the glass transition temperature (T_g) of materials. The T_g is the temperature where the polymer goes from a hard, rigid state to a rubber-like, flexible state.	ASTM E1640	Qualification	Applies to thermoplastic polymers, thermoset polymers, and partially crystalline materials that are thermally stable in the glass transition region and have an elastic modulus in the range of 0.5 MPa to 100 GPa.
	ASTM D3418	Qualification	Standard test method for transition temperatures and enthalpies of fusion and crystallization of polymers by differential scanning calorimetry.
	ISO 11357-2	Qualification	Plastics — differential scanning calorimetry, Part 2: Determination of glass transition temperature.
	ISO 11359-2	Qualification	Plastics — thermomechanical analysis, Part 2: Determination of coefficient of linear thermal expansion and glass transition temperature.
Haze and Transmittance Evaluation of specific light transmitting and wide-angle-light-scattering properties of materials	ASTM D1003	Qualification	Applies to essentially transparent plastic materials; performed on planar sections of materials.
Particulate Matter Evaluates the presence of particulates in or on a sample	USP <788>	Periodic	The light obscuration particle count test (LOPCT) is done to evaluate the presence of particulates. Particulate matter consists of mobile, randomly sourced, extraneous substances and cannot be quantified by chemical analysis due to the small amount of material that it represents and to its heterogeneous composition.
	EP 2.9.19	Periodic	This test is applicable to iv injection. By extension, this standard is used for processing containers manufactured under the same conditions as iv containers. Particulate contamination consists of extraneous, mobile undissolved particles, other than gas bubbles, unintentionally present in the solutions. For the determination of particulate contamination two procedures, Method 1 (light obscuration particle count test) and Method 2 (microscopic particle count test), are specified in the EP monograph.

Table 1C: Single-use product qualification test methods, films and containers — material-dependent tests

Material-Dependent Test Type and General Description	Test References	Test Frequency	Summary Description of Test Reference
Plastic Containers Qualification of Parenteral/Ophthalmic — Aqueous Solutions Tests of plastic materials for use as containers for drug solutions. Tests ensure that the plastics do not change/degrade under conditions of normal use. They look for changes in physical characteristics, pH, or other changes associated with light, or chemicals.	EP 3.2.2.1	Qualification	Tests only physical changes.
	21 CFR 177.1520	Qualification	Olefin polymers (polyethylene, polypropylene)
	21 CFR 177.1350	Qualification	Ethylene vinyl acetate copolymers
	EP 3.1.5	Qualification	Tests for the presence of several types of extractable substances in addition to physical changes. Tests for physical conditions of PE with additives.

Table 2A–C: Tests common to connectors and fittings

2A Test Type and General Description	Test References	Test Frequency	Summary Description of Test Reference
Burst Test Maximum pressure component will withstand at a given temperature. Burst resistance is typically reported in units of bar or psi.	ISO 7241-2	Qualification	Specifies different test methods which could be applied to quick-action couplings. Burst test is Section 21.
	ASTM D1599-99 (2005)	Qualification	"Short-Time Hydraulic Failure Pressure of Plastic Pipe, Tubing and Fittings." Procedure A is used to determine burst pressure of a specimen if the mode of failure is to be determined. Procedure B is used to determine that a specimen complies with a minimum burst requirement. Burst resistance is typically reported in units of bar or psi.
	EN 12266-1	Qualification	Industrial valves — testing of valves — part 1: pressure tests, test procedures and acceptance criteria.
Integrity (Leak) Test To confirm seal or assembly integrity; to confirm integrity of product.	ASTM E515 modified	Qualification	Bubble leak test/time vs. pressure; criteria based on number of bubbles allowed at a specific temperature, pressure and time.
	Pressure hold	Qualification	Minimum delta pressure over time.
	ASTM D4991-94 (1999) Vacuum leak test	Qualification	After gamma irradiation; after autoclave.

Table 2B: Additional tests common to connectors (*continues on next page*)

Test Type and General Description	Test References	Test Frequency	Summary Description of Test Reference
Bacterial Challenge/Soiling Test Identification of bacteria's ability to breach a seal.	Product manufacturer dependent	Qualification	Product dependent. A model organism is used to challenge the bacterial seal integrity of the component. Protocol commonly includes extended incubation of growth media.
Biological Reactivity — In Vitro Evaluates the response of mammalian cell cultures to extracts of polymeric materials.	ISO Elution Method; USP <87> Biological Reactivity (in vitro); USP <88>.	Qualification	Extracts are obtained by placing the test and control materials in separate cell culture media under standard conditions. Cells are observed for visible signs of toxicity (such as a change in the size or appearance of cellular components or a disruption in their configuration) in response to the test and control materials.
	Alternatives: ISO 10993-1, -5, and -12; EN 30993-1, -5, and -12		
Biological Reactivity — In Vivo Evaluates the interaction of medical devices with blood or the biological reactivity of animals to polymeric material.	ISO 10993-1	Qualification	"Biological Evaluation of Medical Devices — Part 1: Evaluation and Testing." Specifies the general principles governing the biological evaluation of medical devices; the categorization of medical devices based on the nature and duration of their contact with the body; and the selection of appropriate tests.
	USP <88>	Qualification and/or lot release	USP Biological Reactivity Test — In Vivo for Class VI Plastics, is a series of three tests: systemic toxicity, intracutaneous reactivity, and implantation. The first two are designed to determine the systemic and local, respectively, biological responses of animals to plastics and other polymers by the single dose injection of specific extracts prepared from a sample. The implantation test is designed to evaluate the reaction of living tissue to the plastic and other polymers by the implantation of the sample itself into animal tissue.
Particulate Matter Evaluates the presence of particulates in or on a sample.	USP <788>	Qualification and/or lot release	Evaluation for the presence of particulates in a flush effluent. Particulate matter consists of mobile, randomly sourced, extraneous substances and cannot be quantified by chemical analysis due to the small amount of material that it represents and to its heterogeneous composition.
	ANSI/AAMI BF7	Qualification and/or lot release	Addresses labeling requirements, performance requirements, test methods and terminology for disposable blood transfusion microfilters for use with adult populations to remove microaggregates from blood or blood products during transfusion.

Table 2B (CONTINUED): Additional tests common to connectors

Test Type and General Description	Test References	Test Frequency	Summary Description of Test Reference
Physicochemical Test with and without Alternative Extract Evaluates the physical and chemical properties of plastics and their extracts	USP <661>	Qualification	Material dependent. Measures the properties of impurities extracted from plastics when leached with extraction medium (such as purified water and isopropanol) over a specified period and temperature. Includes the following: heavy metals, buffer capacity, nonvolatile residue and residue on ignition.
Water Flow Rate and Pressure Drop Test Measuring flow through the connector at differential pressure	ISO 7241-2	Qualification	This test is conducted to determine the flow rate at a given temperature. Components are evaluated for pressure drop across the connector using a pressure gauge placed upstream from the test sample, a pressure gauge downstream from the test sample and a flow meter placed in the flow path of the test sample (compensated for temperature).
	ISO 3968	Qualification	Evaluation of differential pressure versus flow characteristics.

Table 2c: Tests common to connectors, sterilization validation

Test Type and General Description	Test References	Test Frequency	Summary Description of Test Reference
Sterilization Process Compatibility Confirmation of manufacturer's specified performance claims after sterilization process	Manufacturer defined	Qualification	Manufacturer's supporting documents (poststerilization); outlines the claims of the product.

TABLE 3: TESTS COMMON TO FILTERS (*CONTINUES ON THE FOLLOWING PAGES*)

Test Type and General Description	Test References	Test Frequency	Summary Description of Test Reference
Physical			
Burst Test Maximum pressure filter capsule shell will withstand at a given temperature. Burst resistance is typically reported in units of bar or psi.	Proprietary methods	Qualification	The purpose of this test is to determine the integrity of the housing and maximal level of resistance to pressure. The filter units are mounted to a manifold, and the downstream fittings are plugged. The units are pressurized with air until they burst.
Fiber Release Evaluate the presence of fibers shed from the filter or membrane.	USP <788> Particulates in Injectables	Varies by filter supplier	Meets "non–fiber-releasing" per 21 CFR 210.3 (b)(6); analysis of flush effluent.
Hydraulic Test Measure of robustness or filter capsules resistance to elevated pressure conditions; pressure pulsations.	Proprietary methods	Qualification	No reference standard.
Package Testing "Drop and Ship" testing for product integrity per any of the test references listed (those used by vendors may vary).	ISTA 2A ASTM D4169 ASTM D4728-95 DIN ISO 2872	Qualification	Packaging design, materials selection, and evaluation under shipping extremes.
Particle Release Evaluate the presence of particulates shed from the filter or membrane.	USP <788> Particulates in Large Volume Injections	Varies by filter supplier	Evaluation for the presence of particulates in a flush effluent. Particulate matter consists of mobile, randomly sourced, extraneous substances and cannot be quantified by chemical analysis due to the small amount of material that it represents and to its heterogeneous composition.
Water Flow Rate and Pressure Drop Test measuring flow through the device/filter at differential pressure.	Proprietary methods	Lot release	No reference standard.

Table 3 (CONTINUED): Tests common to filters

Test Type and General Description	Test References	Test Frequency	Summary Description of Test Reference
Chemical/Biological			
Bacterial Endotoxin Evaluates the presence of bacterial endotoxins in or on a sample.	USP <85>	Lot release	*Limulus* amebocyte lysate (LAL) testing is used to detect or quantify bacterial endotoxins that may be present in or on the sample of the article.
Bacterial Retention Test (sterilizing grade filters) Bacterial challenge and effluent sterility test based on standard methodology.	ASTM F838-05 ASTM F838-83	Membrane filter element or lot release (varies by filter supplier)	Confirms correlation of integrity test performed on 100% release basis.
Biological Reactivity — In Vitro Evaluates the response of mammalian cell cultures to extracts of polymeric materials.	ISO Elution Method; USP <87> Biological Reactivity (in vitro); USP <88>. Alternatives: ISO 10993-1, -5, -12; EN 30993-1, -5, -12	Qualification	Extracts are obtained by placing the test and control materials in separate cell culture media under standard conditions. Cells are observed for visible signs of toxicity (such as a change in the size or appearance of cellular components or a disruption in their configuration) in response to the test and control materials.
Biological Reactivity — In Vivo Evaluates the response in animals to exposure of polymeric materials.	USP <88> Biological Reactivity in Vivo	Qualification	USP Biological Reactivity Test — In Vivo for Class VI Plastics, is a series of three tests: systemic toxicity, intracutaneous reactivity, and implantation. The first two are designed to determine the systemic and local, respectively, biological responses of animals to plastics and other polymers by the single dose injection of specific extracts prepared from a sample. The implantation test is designed to evaluate the reaction of living tissue to the plastic and other polymers by the implantation of the sample itself into animal tissue.
Conductivity Test Qualification of flush effluent for hydrophilic filters.	USP <645>	Varies by filter supplier	Meets USP limit after proprietary flush.
Extractables and Extraction Quantitative and qualitative characterizations of filter extractables in model solvents.	Proprietary methods	Qualification	Extraction in a minimum volume, typically in water and ethanol. Quantitation by gravimetric nonvolatile residue. Qualification by FTIR, HPLC, or other applicable methods
Gravimetric Extractables (NVR) Quantitative measurement of extractables in water.	USP <661>	Qualification	After proprietary dynamic extraction in minimal volume.
Oxidizable Substances Qualification of flush effluent for hydrophobic filters.	USP Sterile Water for Injection; USP Oxidizable test	Varies by filter supplier	Meets USP limit after proprietary flush.
pH Shift Test Qualification of flush effluent for hydrophilic filters.	USP <791>	Varies by filter supplier	Meets USP limit after proprietary flush.
Total Organic Carbon (TOC) Qualification of flush effluent for hydrophilic filters.	USP <643>	Varies by filter supplier	Meets USP limit after proprietary flush.

Table 3 (CONTINUED): Tests common to filters

Test Type and General Description	Test References	Test Frequency	Summary Description of Test Reference
Functional			
Integrity Test (Sterilizing Grade and Virus Filters) Confirms retention capability.	Proprietary methods	100%	No reference standard
Sterilization Validation			
Irradiation Validation Sterilization of healthcare products.	ANSI/AAMI/ ISO 11137 Method 1, Fluid Path	Qualification, followed by quarterly dose audits	Validates the minimum gamma irradiation dosage necessary to claim sterility at 10^{-6} sterility assurance level (SAL), based on the bioburden level of the fluid path in the finished product.
	AAMI TIR27 VD_{max}, Fluid Path	Qualification, followed by quarterly dose audits	Validates a specific gamma irradiation dosage necessary to claim sterility at 10^{-6} sterility assurance level (SAL), based on the bioburden level of the fluid path in the finished product.
Sterilization Process Compatibility Confirmation of manufacturer's specified performance claims after sterilization process.	Manufacturer defined	Qualification	Manufacturer's supporting documents (poststerilization); outlines the claims of the product.

TABLE 4: TESTS COMMON TO TUBING (*CONTINUES ON THE FOLLOWING PAGES*)

Test Type and General Description	Test References	Test Frequency	Summary Description of Test Reference
Physical			
Compression Set Test Compression set measures the residual deformation after compressive loading under specified conditions.	ASTM D395	Qualification	Covers the testing of rubber intended for use in applications in which the rubber will be subjected to compressive stresses in air or liquid media.
Durometer A measurement of the hardness of a material.	ASTM D2240	Lot release	Durometer is based on the resistance to penetration of a specific indenter into the material under controlled conditions (force, material thickness, etc.). It is reported using the Shore scale, with Shore A hardness being typical for silicone rubber and thermoplastic elastomers.
Elongation A measure of material ductility	ASTM D412	Lot release	Indicates how far tubing can be stretched prior to break. Results are determined by comparing the distance tubing was stretched at the time of break to its original state and are reported in units of percent elongation.
Modulus at 100%, 200% Elongation *Elastic modulus* or *modulus of elasticity* is a measure of a material's tendency to deform when a force is applied.	ASTM D412	Based on customer requirements	Measurement is performed as a part of tensile and elongation measurement and is the stress at the noted strain (elongation). Results are reported as force per unit area.
Specific Gravity Density relative to water	ASTM D792	Qualification	Also referred to as *relative density*, specific gravity is a dimensionless property determined by dividing the density of the material by a reference density — typically water for solids.
Tear Resistance Tear strength measures the resistance to propagation of a rip or tear once the rip has been initiated.	ASTM D624	Qualification	Measurement is performed by inducing a tear in the specimen in a controlled manner and applying a force to pull the specimen apart.
Tensile Strength A measure of the force (stress) required to stretch a material to its breaking point.	ASTM D412	Lot release	Performed by placing a specimen of known dimensions into test equipment (tensiometer) and stretching the sample to its breaking point at a defined pull rate. The load (force) required to stretch the material to its breaking point is measured. Results are typically reported as the maximum load divided by the original cross-sectional area of the specimen using units of MPa or psi.

Table 4 (continued): Tests common to tubing

Test Type and General Description	Test References	Test Frequency	Summary Description of Test Reference
Chemical/Biological			
Bacterial Endotoxin Evaluates the presence of bacterial endotoxins in or on a sample.	USP <85>	Qualification	*Limulus* amebocyte lysate (LAL) testing is used to detect or quantify bacterial endotoxins that may be present in or on the sample of the article.
Biological Reactivity — In Vitro Evaluates the response of mammalian cell cultures to extracts of polymeric materials.	ISO Elution Method; USP <87> Biological Reactivity (in vitro); USP <88>. Alternatives: ISO 10993-1, -5, -12; EN 30993-1, -5, -12	Qualification	Extracts are obtained by placing the test and control materials in separate cell culture media under standard conditions. Cells are observed for visible signs of toxicity (such as a change in the size or appearance of cellular components or a disruption in their configuration) in response to the test and control materials.
Biological Reactivity — In Vivo Evaluates the response in animals to exposure of polymeric materials.	USP <88>	Qualification	USP Biological Reactivity Test — In Vivo for Class VI Plastics, is a series of three tests: systemic toxicity, intracutaneous reactivity, and implantation. The first two are designed to determine the systemic and local, respectively, biological responses of animals to plastics and other polymers by the single dose injection of specific extracts prepared from a sample. The implantation test is designed to evaluate the reaction of living tissue to the plastic and other polymers by implantation of the sample itself into animal tissue.
Elastomeric Closures for Injections A battery of tests designed to determine pertinent physicochemical extraction characteristics of elastomeric closures.	USP <381>	Qualification	Three extraction solvents are indicated: purified water, drug product vehicle (where applicable), and isopropyl alcohol. Acceptance (pass–fail) criteria are not specified in the monograph, leaving interpretation of the significance of results to producers and/or end-users.
EP/Physicochemical A battery of tests specific to silicone (EP 3.2.9 applies to thermoplastic elastomers and tubing).	EP 3.1.9 EP 3.2.9	Qualification/ Audit Qualification	A series of *European Pharmacopoeia* monographs exists for a range of elastomeric materials. Each monograph specifies a battery of tests intended to characterize these materials. EP 3.1.9 is specific to silicone-based materials, and EP 3.2.9 applies to thermoplastic materials.
Medical Device — Hemolysis Test that measures the breakdown of red blood cells by chemical or physical means.	ISO 10993-4	Qualification	Alteration, dissolution, or destruction of red blood cells liberating hemoglobin into the medium in which the cells are suspended; usually determined using rabbit blood.
Physicochemical — Containers Evaluates the physical and chemical properties of plastics and their extracts.	USP <661>	Qualification	Material dependent: Measures the properties of impurities extracted from plastics when leached with extraction medium (such as purified water and isopropanol) over a specified period and temperature. Includes the following: heavy metals, buffer capacity, and nonvolatile residue.
21 CFR 177.2600 Rubber articles for repeated use (extractables)	21 CFR 177.2600	Qualification	An FDA-issued document that regulates rubber articles that are in repeated contact with food. The regulation describes four extractions that must be performed on rubber articles in repeated contact with aqueous and fatty foods, and the maximum amounts of extractables obtained from each of these extractions.
21 CFR 177.2400 (FFKM)	21 CFR 177.2400	Qualification	Perfluorocarbon cured elastomers; battery of tests used to qualify perfluorocarbon cured elastomer parts for repeated use in contact with nonacid food (pH greater than 5.0).
21 CFR 177.1550 (PFA) **21 CFR 177.1550 (PTFE)**	21 CFR 177.1550	21 CFR 177.1550	Perfluorocarbon resins used as articles intended to contact food.

Table 4 (continued): Tests common to tubing

Test Type and General Description	Test References	Test Frequency	Summary Description of Test Reference
Chemical/Biological (continued)			
21 CFR 177.2510 (PVDF)	21 CFR 177.2510	Qualification	Polyvinylidene fluoride resins used in articles intended to contact food.
21 CFR 177.1520 (PP)	21 CFR 177.1520	Qualification	Olefin polymers used in articles intended to contact food.
21 CFR 177.1550 (FEP)	21 CFR 177.1550	Qualification	Perfluorocarbon resins used in articles intended to contact food.
Functional			
Kink Resistance/Bend Radius The terms *bend radius* and *kink resistanc*e are used interchangeably to describe the change in the ability of a fluid to flow through the tubing when the tubing is bent.	Manufacturer defined method (supplier-specific)	Qualification	This measure can be used to quantitatively demonstrate pressure difference changes as tubing is wrapped around various radii. Determined by material stiffness, inside diameter, and the ratio of the wall thickness to diameter. Will vary with material and size.
Pressure/Burst Ratings Maximum pressure tubing will withstand at a given temperature.	Manufacturer defined method based on ASTM D1599-99 (2005)	Qualification	Burst resistance is the resistance of the tubing to intraluminal pressure. Results are reported as the pressure at which the tubing ruptures. Burst resistance can be modified by changing the tubing dimensions such as wall thickness, changing to a different material formulation or using a reinforcing material within the tubing. Burst resistance is typically reported in units of bar or psi.
Sterilization Validation			
Irradiation Validation Sterilization of healthcare products.	ANSI/AAMI/ ISO 11137 Method 1, Fluid Path	Qualification, followed by quarterly dose audits	Validates the minimum gamma irradiation dosage necessary to claim sterility at 10^{-6} sterility assurance level (SAL) based on the bioburden Level of the fluid path of the finished product.
	AAMI TIR27 VD_{max}, Fluid Path	Qualification, followed by quarterly dose audits	Validates a specific minimum gamma irradiation dosage necessary to claim sterility at 10^{-6} sterility assurance level (SAL) based on the bioburden Level of the fluid path of the finished product.
Sterilization Process Compatibility Confirmation of manufacturer's specified performance claims after sterilization process.	Manufacturer defined	Qualification	Manufacturer's supporting documents (poststerilization); outlines the claims of the product.