

An Update of the Bio-Process Systems Alliance's Latest Activities

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As introduced in the third installment of this supplement series one year ago (1), the Bio-Process Systems Alliance (BPSA) is an organization of suppliers and service providers involved in the manufacture and testing of single-use (disposable) systems for the bioprocess and pharmaceutical industries. Since its founding in 2006, the alliance has grown to represent more than 50 supplier members. BPSA is organized under The Society of the Plastics Industry, Inc. (SPI, www.plasticsindustry.org), a trade association based in Washington, DC, that supplies resources and support to its members. In addition to promoting and facilitating implementation of single-use biopharmaceutical manufacturing systems, an important role of BPSA is to develop technical guides for suppliers and users based on the expertise of those who supply disposable components, integrated systems, and related services. This is an update of recent work undertaken by BPSA members, specifically within its Guidelines and Standards Committee.

BPSA's objectives for promoting application of single-use biomanufacturing technologies extend to three areas: implementation, information, and quality. The association seeks to encourage and facilitate the adoption of single-use systems primarily by providing



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information about best practices to its members' customers, specifically biopharmaceutical manufacturers. Suppliers can derive consensus on best practices by sharing their knowledge among the group as well as with users and regulators who seek to understand the best ways to realize the benefits of single-use (disposable) manufacturing options.

Whereas BPSA's efforts to establish industry guides can encourage adoption of quality components and systems in processing, BPSA itself (as a supplier member organization) is not chartered to write standards. However, it is able to bring together the body of knowledge among suppliers to provide guides that can be used by standards-writing organizations, such as the ASME Bioprocessing Equipment (BPE) committee.

BPSA QUALITY TEST MATRIX

As its first activity, the BPSA Guidelines and Standards Committee decided to review current quality test methods applied by single-use component suppliers to qualify their materials and product designs from sourcing to release. One goal has been to identify existing guidelines and standards that can be used as references. Four subcommittees were formed to focus on the primary components that go into single-use bioprocess manufacturing systems: disposable films and containers, filter capsules, tubing and disposable connectors and fittings. With the oversight of SPI staff to ensure that discussions were kept on a technical, noncommercial level, this provided an opportunity for technical experts from product suppliers in each component

OTHER SOURCES OF INFORMATION

These organizations provide standards and guidelines with quality test methods that can be applied to single-use bioprocess systems. They are listed in alphabetical order, not intended to represent any kind of ranking.

Association for the Advancement of Medical Instrumentation (AAMI) www.aami.org

American National Standards Institute (ANSI) www.ansi.org

American Society of Mechanical Engineers, Bioprocessing Equipment Committee (ASME BPE) <http://cstools.asme.org/csconnect/CommitteePages.cfm?Committee=N10120000&CFID=324274&CFTOKEN=26293372>

American Society for Testing and Materials (ASTM) www.astm.org

British Pharmacopoeia (BP) www.pharmacopoeia.org.uk

European Pharmacopoeia (EP) www.edqm.eu/site/page_628.php

Federal Test Method Standard (FTMS) http://standards.gov/standards_gov/v/Standards/index.cfm

International Organization for Standardization (ISO) www.iso.org

International Safe Transit Association (ISTA) www.ista.org

Japanese Pharmacopoeia (JP) <http://jpdn.nihs.go.jp/jp14e>

US Code of Federal Regulations, Title 21 (21 CFR) www.access.gpo.gov/nara/cfr/cfr-table-search.html

US National Institutes of Health (NIH) www.nih.gov

United States Pharmacopoeia (USP) www.usp.org

class to discuss their practices and come to consensus on shared best practices.

The exercise enabled BPSA to compile a matrix of quality tests applied by leading suppliers, to identify the standard or guideline methods referenced, and to draft text explaining the bases for applying those reference methods. The matrices for films and containers, connectors, and fittings were first published last month in *BioProcess International* (2), and those for filters and tubing follow the current update in this special issue.

An initial challenge for the committee was that many applied test and performance references were not specific to bioprocess components. References were sourced from related fields. Also, some standards — including drug and biologic GMP regulations and guidelines, pharmacopoeial monographs, and informational chapters and medical device standards — often are not specific to large-scale bioprocess equipment. For this reason, many methods had to be reinterpreted and modified to make them more applicable.

For example, medical device standards published by the International Organization for

Standardization (ISO, www.iso.org) are closely applicable to the bioprocess industry because similar systems have been commonly used in therapeutic applications for many years, albeit at a smaller scale. Some systems use plastic bags, which can hold large-volume parenteral product formulations, blood, or blood plasma that pass through tubing and often have in-line filters. Quality standards have been developed for implantable plastic medical devices, and those also can be applied to the qualification of bioprocess system materials. Many process developers involved in sourcing large-scale bioprocess systems and components may be unfamiliar with the medical device standards. In such circumstances, BPSA's component supplier and service laboratory members who are familiar with those standards can help explain their applicability.

The "Other Sources" box lists organizations that provide standards and guidelines with quality test methods applicable to large-scale single-use bioprocess systems.

In developing a matrix of applicable quality test methods and references for each component class, we characterized tests as either physical, chemical/biological, or functional.

Some tests, such as those for extractables, bacterial endotoxins, or biological reactivity, are fairly common to all component classes. Other tests are unique to certain component types. For films and containers, significant physical tests included puncture resistance, tensile strength, and permeability. For filter capsules, cleanliness (fibers or particles shedding) is unique. For plastic tubing, unique testing parameters include strength and elongation, durometer (a measure of the hardness of the tube wall and modulus), and elasticity or stretching characteristics. And the connectors and fittings group had a difficult task because of the different varieties of connectors and fittings available for use with bioprocess systems. They range from simple double-hose barb fittings to aseptic connectors, which are much more sophisticated devices used to establish and maintain sterile pathways between two sterile systems or components.

BPSA recognizes the need to educate industry professionals, both experienced and novice, on how and why vendors test disposable components. So tests were characterized to help users better understand the types that are generally recognized as suitable quality tests. For each component group, the information to be provided includes classifying the type of test and providing a general description of it and its associated reference standards, guidelines, informational chapters, or industry guides, as well as where to source it.

The matrices also include minimum frequencies at which suppliers perform testing. Some tests (e.g. polymer identification) may be applied only at the material qualification stage and not repeated as long as the source material does not change (as certified by the polymer supplier). Other types of tests may be performed regularly, perhaps once a quarter or once a year, based on audits. Such auditing and scheduling varies by test type, component, and supplier. Thus, suppliers need to provide more specific recommendations on those

tests. Many other tests involve sampling from lots: Random units from every lot of the component or system are tested. Only sterilizing filters have an individual component test: Every sterilizing filter is integrity tested by a proprietary assay correlated to 100% bacterial retention before product release.

Finally, additional detail on each test is provided to further explain its applicability and how it is performed.

The Guidelines and Standards Committee completed its draft for the BPSA quality test matrix in December 2006. It was subsequently handed to the BPSA Education Committee for development of additional text and an introductory section. The draft was then circulated to selected prequalified peer reviewers outside of BPSA, a group that included end users and regulators who had expressed interest previously and had suitable expertise. The matrix debuted in the April issue of *BioProcess International* (Part One) and in this supplement (Part Two). Reprints were distributed by BPSA at the 2007 Interphex Conference and Exhibition, 24–26 April 2007 in New York, NY (www.interphex.com).

FUTURE ACTIVITIES

Targeted for fall 2007, BPSA's next industry guide will discuss sterilization and gamma irradiation standards and practices. In this guide, the group will explore how to apply medical device standards for gamma irradiation sterilization and validation to single-use bioprocess systems.

Large systems present particular challenges to practices such as sterility testing. For example, a standard method developed with small, implantable medical devices in mind might call for aseptic removal of the device from its sterile packaging and immersion into a container of sterile broth for incubation and determination of sterility. Such a practice is not directly applicable to large bioprocess systems that can include multiple 30-inch filter capsules, many feet of tubing, and large bags or rigid containers capable of holding hundreds (even thousands) of liters of fluid. One alternative is to focus on sterility of the fluid path only, which often is also applicable to medical devices. However, there is often a concomitant requirement that all equipment brought into a cleanroom (e.g. surgical suite or Class A biomanufacturing area) must be sterile externally as well. With single-use bioprocess systems, the sterile pathway may be sufficient by itself because such closed systems can be used in Class C or lower areas.

Another concern to be addressed in the sterilization and irradiation guide is the need for claiming a system to be sterile with appropriate validation and control — as opposed to a gamma-irradiation process established for high-efficiency bioburden control without sterility validation and testing. The latter can provide high assurance of very low or zero bioburden without the time and cost of validating and maintaining a sterile claim. BPSA's

goal is to provide recommendations for microbially controlled applications and determine when it would be necessary to validate and claim sterility and when users can rely on irradiation alone to control bioburden.

The BPSA guide to sterilization will present an overview of microbial control and sterilization of single-use systems for suppliers and end-users as well as providing key terms and definitions. It will summarize the medical device sterilization validation standards and reference their source documents (which are available for purchase). Additionally, it will discuss how such standards can be applied to bioprocess systems and suggest options and make recommendations for how to apply them. Some bioprocess applications need validated sterile systems, such as sterilizing filtration into a container for a sterile active ingredient and preparation of mammalian cell culture media or additives. But others, including buffer preparation and delivery to nonsterile chromatography or ultrafiltration/diafiltration processes, may require irradiation only for bioburden control.

Another project for the BPSA Guidelines and Standards Committee is to develop a guide to extractables, which has been targeted for spring of 2008. Suppliers could conduct studies to identify extractable materials from process contact surfaces under aggressive solvent conditions. That can provide much of the extractables information required by users and regulators. It is a standard practice for

Table 1a: Test types in the BPSA Quality Test Matrix (films and containers)

Physical	Chemical / Biological	Functional
Puncture	Physicochemical	Seal Integrity
Tear	Extractables	
Tensile	Endotoxin	Transport/shipping
Permeability	Biological reactivity	Shelf life

Table 1c: Test types in the BPSA Quality Test Matrix (tubing)

Physical	Chemical / Biological	Functional
Tensile, elongation	Physicochemical	Pressure/burst
Durometer, modulus		Kink resistance
Tear resistance	Endotoxin	Bend radius
Specific gravity	Biological reactivity	Shelf life

Table 1b: Test types in the BPSA Quality Test Matrix (filter capsules)

Physical	Chemical / Biological	Functional
Extract NVR	Extractables	Water flow and differential pressure
Fibers/particles	Flush TOC, pH, and conductivity	Bacterial retention
Pressure/burst	Endotoxin	Hydraulic and thermal stress
Irradiation	Biological reactivity	Shelf life

Table 1d: Test types in the BPSA Quality Test Matrix (fittings and connectors)

Physical	Chemical / Biological	Functional
Pressure/burst	Physicochemical	Leak testing
Thermal resistance		Water flow and differential pressure
Dimensions	Endotoxin	
	Biological reactivity	Shelf life

pharmaceutical filter manufacturers and has more recently been adopted by several biocontainer manufacturers as well. However, such information may not be available yet from tubing and connector suppliers or from integrators of single-use systems. BPSA is exploring common solvent extraction conditions and analytical methods that would help companies identify and quantify extractables in components and systems.

A challenging question is whether component or system suppliers can provide generic leachables data. Leachables have been defined as foreign materials in final drug formulations that come from fluid contact surfaces. The need to qualify them in specific user formulations will make it difficult for suppliers to provide such data generically. However, it may be possible to develop something similar to generic extractables data for common process fluids such as WFI or buffers within a defined range of formulations, ionic strengths, and pH values.


For those who are new to the industry, the BPSA guide will provide an overview of extractables. It will include key terms and definitions, reference the appropriate regulations and guidelines that are applicable to bioprocess systems, and provide some examples of typical extractable materials from commonly used process components. The guide will attempt to propose common solvents for extractable studies and minimum extraction conditions such as duration, temperature, and weight-to-volume, along with suggested analytical methods for confirming extractables identity. Variables such as pH, salt, and the presence of surfactants ultimately affect leachables and will need to be included in general models for leachables studies.

BPSA plans to propose roles and responsibilities for suppliers, who should be able to provide users of finished drug product with an extractable assessment of their systems using model solvent extracts to identify and quantify the source of what could be extracted out of the systems. Users will still be responsible

for providing regulators with their own full and complete extractables and leachables assessments, but having some extractables data available should make it easier to identify what may be leaching out of individual systems. Users and suppliers ultimately need to work together to correlate their leachables and extractables data so the users can present to regulators a complete understanding of system-derived materials that may be present in their process fluids. Furthermore, users will need to investigate the sources of those materials and conduct toxicology testing for safety evaluation.

Additional guides under consideration by BPSA include recommendations for qualification or integrity testing of integrated systems and connections, disposal of used systems, and process economics for decision-making. The organization encourages users to discuss these issues with its supplier members. BPSA can be contacted through www.bpsalliance.org and its executive director, Donna Dempsey (email ddempsey@socplas.org, 1-202-974-5218).

REFERENCES

- 1 Smith-McCollum B, Rosin LJ. The Bio-Process Systems Alliance. *BioProcess Int.* 4(6, supplement) 2006: 6–8.
- 2 BPSA Guidelines and Standards Committee. Part One: Bio-Process Systems Alliance Component Quality Test Matrices. *BioProcess Int.* 5(4) 2007: 52–67. 

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