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Best Practices for Quality Control and Implementation of Single-Use Systems

New publications from BPSA and PDA highlight best practices for particulate control, quality agreements, and implementation strategies.

JEROLD MARTIN

Three new industry white papers have recently been published that provide best practice recommendations for implementation of single-use technologies (SUT). Readers interested in single-use manufacturing should put these on their must-read list. Two are from the Bio-Process Systems Alliance (BPSA), the single-use trade association. The BPSA white papers cover management of particulate contamination risks from SUT and provide a template for establishing quality agreements between end users and suppliers. The third white paper is the highly anticipated technical report from the Parenteral Drug Association (PDA) on GMP implementation of single-use technologies.

THE BPSA PARTICULATES GUIDE

The BPSA particulates guide, titled *Recommendations for Testing, Evaluation, and Control of Particulates from Single-Use Processing Equipment*, was written by a BPSA member task group of suppliers, users, and engineering consultants (1). The group addresses the needs of the single-use industry and the risks of particulates from SUTs, how they may contaminate finished drug products and impact patients, and what manufacturers of SUT components and systems can do, along with drug and vaccine manufacturer users,

JEROLD MARTIN is senior vice-president, global scientific affairs at Pall Life Sciences.

to minimize this risk. Also covered are what steps can be taken to identify particles found in final dosages and uncover their source, which may be from SUT or other process equipment, from the container or closure materials, or even from the drug product itself. Recommendations are provided on how both SUT suppliers and users can control contamination or generation of particulates, and what steps can be taken when particulates are found and attributed to SUT.

The concern for particles in single-use equipment arises when the single-use equipment is not flushed prior to use, even if a supplier labels a system “ready to use.” This designation makes users highly dependent on the cleanliness of the SUT systems as delivered. While single-use systems are generally clean as manufactured, and incidence of particulate contamination is low, the risk of particulates being introduced into final dosages is always a possibility, especially downstream of particle-removal filtration steps or in systems for aseptic processing without particle removal filtration.

In the BPSA particulates guide, risks and characterization of particles are classified according to process application, location of particle, particle characteristics, along with size, appearance, chemical makeup, and number. Capabilities and limits of particle detection by visual means within dry single-use systems, in rinse liquids from system fluid path rinse samples, or in final dosage containers is discussed to enable readers to have a realistic understanding to help guide decision-making. These classifications are followed by a detailed discussion of the potential sources of parti-

cles in SUT and provide cautions and best practices for handling such incidents throughout the SUT product lifecycle.

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THE BPSA QUALITY AGREEMENT TEMPLATE

Among other factors, the quality of drug products manufactured using SUT is dependent on the quality of the SUT itself. Agreed definitions of SUT quality requirements for a given application and assured control are dependent on cooperation and partnership between system suppliers and users, as well as between system integrators and their component suppliers. Despite the importance of these requirements, BPSA surveys of SUT suppliers and users found there are often difficulties in establishing quality agreements between these parties.

Drafting a quality agreement between each supplier and user to anticipate and resolve potential problems can be challenging. The lack of standardization has led to a plethora of templates from individual suppliers and users, none of which have enabled rapid, easy establishment of quality agreements. The multitude of different suppliers and user templates is problematic because suppliers and customers/users cannot readily accommodate multiple different quality

agreements from each other. Through BPSA’s proposal, both users and suppliers agreed that a uniform template for organizing and identifying appropriate content for SUT quality agreements in a common structure would be beneficial to the entire industry, especially if published by an impartial, recognized trade association such as BPSA.

To craft a consensus template, a team of BPSA member supplier and user representatives familiar with establishing quality agreements worked to compile and review templates from multiple SUT suppliers and users. The representatives also drew from quality agreement templates from other organizations such as the Active Pharmaceutical Ingredients Committee (APIC), the International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS), and the Society of Chemical Manufacturers and Affiliates’ (SOCMA) Bulk Pharmaceuticals Task Group (BPTG). Rather than being entirely prescriptive, the BPSA Quality Agreement Template has been created to facilitate discussion and negotiation between SUT suppliers and users following a consensus outline of key topics. Sections include Terms and Amendments, Use of Third Parties, Product Specifications, Resolution of Quality Issues, Choice of Law (Jurisdiction, etc.), Compliance Requirements, Right to Audit, Product Quality, Change Notification, Complaints, Animal-Derived Materials, Qualification and Validation, Documentation and Records, Change Control, Deviations, Reprocess/Rework, Production and In-Process Controls, Packaging and Labeling, Storage

BPSA Releases Single-Use Testing Guide

The Bio-Process Systems Alliance (BPSA) released its 2014 technical guide to address the control, testing, and evaluation of particles in single-use process equipment. *Recommendations for Testing, Evaluation, and Control of Particulates from Single-Use Processing Equipment* (commonly known as the BPSA 2014 Particulates Guide) serves as a guide on mitigating particulates for the single-use technology (SUT) industry. The objective of the document is to “help to begin to define the requirements that SUT end users have and allow SUT suppliers to show how they can meet or strive to meet those requirements” (1).

The BPSA working group recognizes that achieving zero particles is not physically possible for process equipment used in the making and filling of injectable drug products. Instead, the goal of the group is to minimize particles in drug products while staying in line with realistic safety and quality expectations. Although the industry is still waiting for United States Pharmacopeial Convention (USP) guidance on subvisible particulates that are less than 10 microns, the BPSA report focuses on the higher risk posed by visible and larger subvisible particles approximately 100 microns in size. Continuous improvement in these areas will allow the group to address even smaller particles in the future, a BPSA spokesperson told *BioPharm International*. Until that time, BPSA’s report examines why particles are an issue with SUT, why particles associated with SUT could be a contamination risk for patients, how to limit particulates, and what steps to take when particles are found as a result of SUTs.

The Risk of Particulates

According to the report, risk awareness is one of the most important ways suppliers can minimize particulates. The risk increases as process steps get closer to the patient. While upstream particulates risks are often reduced with filtration, particulates downstream from filtration steps pose a greater risk, says BPSA. This is especially true with cell therapies that cannot be filtered.

Because SUTs do not typically undergo a final rinsing step, notes the report, particulates that may be generated during manufacture may remain on the SUT’s fluid contact surfaces. Particle risk is best assessed by looking at the process application that likely generated the particle, the location of the particle in or on the SUT, whether the particle is intrinsic or extrinsic to the process, the chemical make-up of the particle, and the count, or extent, of the particle contamination.

Particle Origin

Particulates are most commonly introduced in open operations, says the BPSA working group. Certain operations, such as peristaltic pumping, welding, mixing, and manipulations of assemblies can also generate particles. The manufacturing of connectors, tubing, samples, filters, and product bags can expose the biopharmaceutical product contact surfaces to particulates, however, says the BPSA working group, “Meticulous manufacturing operations and continuous control cleanroom management can minimize their number in the final SUT.” When analyzing the origin of particle generation, two phases of an SUT’s lifecycle must be considered, notes the report. Phase one includes the supplier’s sources, manufacturing and assembly, and packaging and shipping. Phase two includes end-user receiving, handling, and use of the SUT.

Although extrinsic particles are atypical in properly controlled SUT manufacturing processes, and are infrequently observed, according to BPSA working group, extrinsic particles of unknown source were cited by the report as an area of great alarm. The risk of particles of unknown origin cannot be adequately assessed, and may present more of a chemical risk than known particles. “This usually leads to discard of the SUT and, if already in use, the biopharmaceutical product,” notes the BPSA working group. The lower the particle load of incoming materials, the lower the chance that single-use assemblies with numerous particles will be manufactured and shipped.

Particle contaminant testing methods must be repeatable. Although some particles can be measured with the naked eye, others require additional methods, such as liquid measurement techniques. As the report notes, “Visual inspection may not be able to assess accurately the entire level of particulate contamination, especially through one or more layers of packaging.”

Quality Control

Suppliers and end users must work together to ensure a low particle load of incoming materials. “Control and improvement efforts should consider the full lifecycle of the SUT, from manufacturing supply chains to end-user deployment in biopharmaceutical production, rather than focusing on a supplier vs. end user perspective,” argues the BPSA report. BPSA advises an audit of the component supplier to ensure proper handling and packaging is used to reduce bioburden load. In addition, a visual inspection of bag manufacturing, film cutting, port bonding, leak testing, packaging, and assembly of tubing, fittings, bags, filters, and connectors should be conducted. BPSA recommends an ISO 8 or better environment (such as ISO 7 or ISO 5) for SUT assembly and component manufacturing. “Extra diligence, and steps such as pre-cleaning of parts by the component supplier, may be required to ensure parts meet the incoming needs of the SUT manufacturers.”

Reference

1. Bio-Process Systems Alliance Working Group, *Recommendations for Testing, Evaluation, and Control of Particulates from Single-Use Processing Equipment* (BPSA, Sept. 22, 2014).

—Randi Hernandez

and Distribution, Inspection and Test Equipment Control, Recalls and Corrections, and Field Actions. Appendices provide tables for product definitions and specifications, establishment of roles and responsibilities of suppliers and clients, and recording of key contacts.

BPSA recognizes that successful implementation of single-use technologies requires a unique partnership between suppliers and relies on users to share their application and process requirements. BPSA encourages all SUT suppliers and users to access this Quality Agreement Template document (2). Application of the template can facilitate cooperative agreements and help improve the quality of biopharmaceutical products manufactured using SUT.

PDA TECHNICAL REPORT ON SINGLE-USE MANUFACTURING

With the growing interest in single-use technology impacting approved drug products and vaccines, in 2008 PDA formed a task group of subject matter experts from users and suppliers to draft a detailed technical report on applying SUT to GMP. After extensive discussions and drafting sessions, PDA organized a series of public workshops in the US and Europe, where the co-authors presented the proposed content and encouraged participant feedback. Following incorporation of this feedback, and a thorough review by the PDA scientific advisory board, PDA has now published the long-awaited *Technical Report No. 66, Application of Single-Use Systems in Pharmaceutical Manufacturing* (3).

The extensive report is intended to provide a flexible, educational basis for applying the

strategies necessary to implement single-use processes successfully. With the help of the report and in partnership with qualified suppliers, each drug manufacturer can establish a single-use GMP strategy specific to its products and requirements and to be able to defend those decisions based on a thorough risk assessment.

The PDA task group recognized that each user organization and drug product may have its own circumstance regarding application of single use.

The technical report is designed to communicate the importance of eliminating cleaning and cross-contamination risks, process and product risks, economic and logistic risks, and process controls. The principles of quality risk management (QRM) and quality by design (QbD) are introduced to single-use manufacturing to enable risk mitigation and the process understanding necessary to ensure a robust, safe, and reliable process. Readers will develop a fuller understanding of how SUT may differ from reusable technologies, how the use of SUT may change operations, what factors should be considered in scale-up, and how to determine if SUT will be cost-effective.

Beyond its introduction on applying principles of QRM

and QbD, the report features an extensive glossary of terminology associated with single-use manufacturing to facilitate clear communication. Following that is a key section on developing a manufacturing strategy. The technical report provides a decision-making staircase where at each step, one considers specific aspects of risk in the single-use system and addresses each aspect before moving on to the next step. Steps include consideration of technical feasibility, economic feasibility, product and process risks, process-control strategy, implementation strategy (including qualification and process validation), and logistic strategy (supplier reliability and inventory management).

The PDA task group recognized that each user organization and drug product may have its own circumstance regarding application of single use. Consequently, the document guides the reader to define their unique situation requirements: new or existing facility, single or multiple products, development or production, synthetic or biological product, sponsor or CMO, grams, kilograms or tons per year, etc. Each of these puts different perspectives on the risks, suitability, and potential advantages or drawbacks of single-use manufacturing.

REFERENCES

1. BPSA, *Recommendations for Testing, Evaluation, and Control of Particulates from Single-Use Processing Equipment* (BPSA, 2014), www.bpsalliance.org.
2. BPSA, *Consensus Quality Agreement Template for Single-Use Biopharmaceutical Manufacturing Products* (BPSA, 2014), www.bpsalliance.org.
3. PDA, *Technical Report No. 66, Application of Single-Use Systems in Pharmaceutical Manufacturing* (PDA, September 2014), www.pda.org. **BP**