Sterile Filtration Process Control

Meeting Regulatory Expectations

Libby Russell

Sterile filtration is a pivotal process step in pharmaceutical manufacturing to ensure the sterility of injectable drug products. It eliminates microorganisms and particulates while safeguarding the integrity of a final product. Effectively managing and monitoring the sterile filtration process requires meticulous attention to manufacturing controls and encompasses key parameters such as flow rate, temperature, use time, and pressure. Pressure emerges as a critical factor, necessitating oversight to validate the efficacy of a filtration system and uphold the stringent standards of regulatory bodies such as the US Food and Drug Administration (FDA) and the European Commission.

Pressure monitoring of sterile filtration steps is a regulatory expectation for process design and is established during filter validation. According to the FDA's 2004 guidance on aseptic processing, pressure, flow rate, and other factors that can affect filter performance and validation should be conducted using worst-case conditions, such as maximum filter use time and pressure (**1**). The agency set further guidelines for single filtration of biotechnology-derived products (BDPs) in its *Biotechnology Inspection Guide Reference Materials and Training Aids* (**2**).

EU guidelines for filtration parameters and routine process controls state that "results of critical process parameters (CPPs) should be included in the batch record" (**3**). The Parenteral Drug Association's (PDA's) technical report on *Sterilization Filtration of Liquids* specifies that "process time and pressure drop can affect bacterial retention test results," and it advises that "pressure differential across the test filter during validation of the bacterial challenge test should meet or exceed the maximum pressure differential permitted during processing" (**4**).

Our organization has observed that companies initially exclude pressure monitoring of sterile filtration in their drug-product manufacturing processes, which leads to questions from regulators about their process controls. Although such companies had controls for staying within a validated flow, the FDA expressed concern about their lack of pressure-limit controls. Companies responded by implementing upstream pressure monitoring and setting pressure limits aligned with filter validation.

Those biomanufacturers implemented two process-control strategies, the first of which was continuous automatic pressure monitoring. Continuous monitoring using a pressure sensor is only possible for processes with high flow rates. The second strategy involved intermittent manual monitoring throughout filtration.

As part of implementation, one company categorized filtration pressure as a CPP and set the maximum value based on filter-validation studies. Management justified critical categorization based on the ability of parameters to affect sterility. The filter supplier conducted initial validation studies to monitor pressure and establish a validated flow rate, taking a conservative approach by setting the upper limit for process filtration at the lowest observed upstream pressure. Furthermore, a risk assessment was conducted to evaluate the compatibility of the pressure sensor with the product, considering construction material and the potential presence of leachables and extractables. No additional leachable studies were needed because of the low surface area and contact time.

Current trends in biologics manufacturing have highlighted the importance of pressure monitoring for sterile filtration of vaccines based on lipid nanoparticle (LNP)-encapsulated mRNA and glycoconjugates. Studies have shown the heightened risk of filter fouling with such products and the importance of monitoring pressure to minimize the impact to bacterial retention and product sterility (**5**).

As supported by current trends in biologics manufacturing, particularly in the context of advanced vaccines, the importance of pressure monitoring for sterile filtration cannot be overstated. Incorporating such controls into manufacturing practices will help ensure the integrity and sterility of pharmaceutical products.

References

1 *Guidance for Industry. Sterile Drug Products Produced by Aseptic Processing: Current Good Manufacturing Practice*. US Food and Drug Administration: Rockville, MD, 2004; https://www.fda.gov/media/71026/download.

2 *Biotechnology Inspection Guide (11/91)*. US Food and Drug Administration: Rockville, MD, 2014; https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-guides/biotechnology-inspection-guide-1191.

3 *Annex 1: Manufacture of Sterile Medicinal Products. The Rules Governing Medicinal Products in the European Union: Volume 4 — EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use*. European Commission: Brussels, Belgium, 2022; https://health.ec.europa.eu/system/files/2022-08/20220825_gmp-an1_en_0.pdf.

4 *TR 26. Sterilizing Filtration of Liquids*. Parenteral Drug Association: Bethesda, MD, 2008.

5 Messerian KO, et al. Pressure-Dependent Fouling Behavior During Sterile Filtration of mRNA-Containing Lipid Nanoparticles. *Biotechnol. Bioeng.* 119(11) 2022: 3221–3229; https://doi.org/10.1002bit.28200.

Libby Russell, *PhD, is vice president and senior consultant at Syner-G BioPharma Group, 100 Pennsylvania Avenue Suite 310, Framingham, MA 01701; info@synergbiopharma.com.*

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Featured Report SERIES

Jan/Feb: Quality Control

Essential to product safety and efficacy, quality control lies at the heart of regulatory compliance, process optimization, and drug-product consistency. It is patients' key line of defense against contaminated or otherwise compromised biotherapeutics and companies' most powerful means of ensuring a good reputation in the market. Quality control depends heavily on analytical technologies as well as environmental monitoring and other manufacturing-floor behaviors and protocols. Quality-assurance groups often work with both internal and external/outsourced laboratories, and related concerns should be part of everyone's job at a biopharmaceutical developer or contract-service provider. This featured report highlights technical aspects as well as training and other strategies related to the crucial goal of making biopharmaceuticals of the highest possible quality.

March: Vaccines

Recombinant vaccines include products based on proteins, virus-like particles, and nucleic acids delivered by lipid nanoparticles, viral vectors, and other means. To serve large markets and help protect millions of people from dangerous infections, these products must be offered at reasonable cost. Their formulations must be stable under a breadth of conditions. And technological and logistical solutions are needed to help vaccine developers succeed while complying with different regulatory requirements around the world. This featured report brings together perspectives on vaccine production, processing, and product development for a global market.

April: Antibody Engineering and Therapeutics

Despite much excitement around cell therapies and other modalities, monoclonal antibodies (MAbs) and their derivatives (fusions, fragments, multispecifics) continue to dominate the biopharmaceutical arena. MAb production and processing tend to follow a familiar platform based on Chinese hamster ovary (CHO) cell culture and protein A affinity capture — but companies working on biosimilars, pandemic therapies, and alternative expression systems are showing that the platform can change. So can the basic MAb structure as many companies and research groups seek to optimize antibody affinity, stability, and developability using the latest genetic-engineering techniques. As this featured report will show, MAb developers are still leading the way in the biopharmaceutical industry.

May: Cell Line Development

Every biologic product requires an extensively customized expression system obtained by cell line engineering and development, culture-mode evaluation and adaptation, and media/process optimization — all culminating in establishment of a master and working cell bank. Speeding biologic candidates into clinical trials — and thus toward early success or failure — requires development of cell lines that can produce target molecules in desired quantities at a requisite level of quality. Cell-line development groups must produce powerful, stable, high-expressing, and optimized cell banks as soon as possible. This report will feature advances in genetic engineering, clone screening and selection, analysis, and data management — and novel workflows that have brought about a revolution in cell-line development.

June: Raw and Starting Materials

The basis of every bioprocess must be high-quality raw materials: buffers, media, and feed supplements; purified water, analytical reagents, and dyes; chromatography resins and diatomaceous earth; cells; filters and tubing; and more. Quality-assurance groups use risk management, supplier qualification, and direct testing to ensure that these materials are fit for their purpose in process/product development and manufacturing. This featured report highlights strategies for characterizing and controlling variability, sourcing and storing, and preventing supply shortages related to raw and starting materials for biomanufacturing.

July/Aug: BPI Theater

For several years, the BPI Theater has brought technical discussions to the exhibit-hall floor at the Biotechnology Innovation Organization's annual convention. In case you miss the event, BPI summarizes key presentations and roundtable discussions in this midsummer featured report, which will come alongside our annual "Industry 360" issue. Topics reflect the most talked-about aspects of biomanufacturing, from single-use technologies to contract services to emerging therapies to "Bioprocessing 4.0."

September: Process Monitoring and Control

Knowledge is power in bioprocessing, and process control depends on rapid response to changing conditions. You can't have data analysis in the "Biomanufacturing 4.0" revolution without data — all of which has to come from somewhere. Sensor technology is vitally important to gathering the necessary process data and to maintaining closed systems and environmental controls. Thus, sensor accuracy has become crucial to quality by design (QbD). Bioprocesses must be well characterized, monitored, and controlled to keep results within design-space specifications. Especially in continuous operations, process control depends on rapid response to changing culture conditions. This featured report highlights means for optimization, monitoring, and real-time decision-making for upstream production, downstream processing, and drug-product manufacturing.

October: Gene Therapies

Many cell therapies are also gene therapies in that patient or donor cells are modified genetically to therapeutic effect before they are given to patients. Other biologics in development are intended to deliver genes directly to patients (in vivo). Either way, the genes must be manufactured and introduced somehow to the cellular machinery needed to express them. This featured report will examine both gene-therapy approaches, with an emphasis on process development, purification, and characterization of genetic therapies delivered by platforms such as viral vectors and liposomes. For instance, adenoassociated viruses (AAVs), lentiviruses, and other viral-vector systems present both production and purification difficulties that are different from those facing even the most complex protein therapeutics.

Nov/Dec: Formulation, Fill and Finish

Stability is key in formulation of biopharmaceutical products. Freezing, lyophilization, and specialized excipients help protect biologics long enough to confer a reasonable shelf life. Formulators use risk management and prior knowledge to find the best presentation for each new product. Filling and packaging — often highly automated processes — follow in transforming bulk drug substance to dosage-centered drug products for distribution. Because final biologic products cannot be sterilized, they must be processed under aseptic conditions in controlled environments, relying on single-use technologies and/or validated cleaning procedures, with integrity testing for container–closure systems and sterilizing filters. From buffers and excipients to containers and closures to specialized devices, this featured report focuses on biopharmaceutical drug products.

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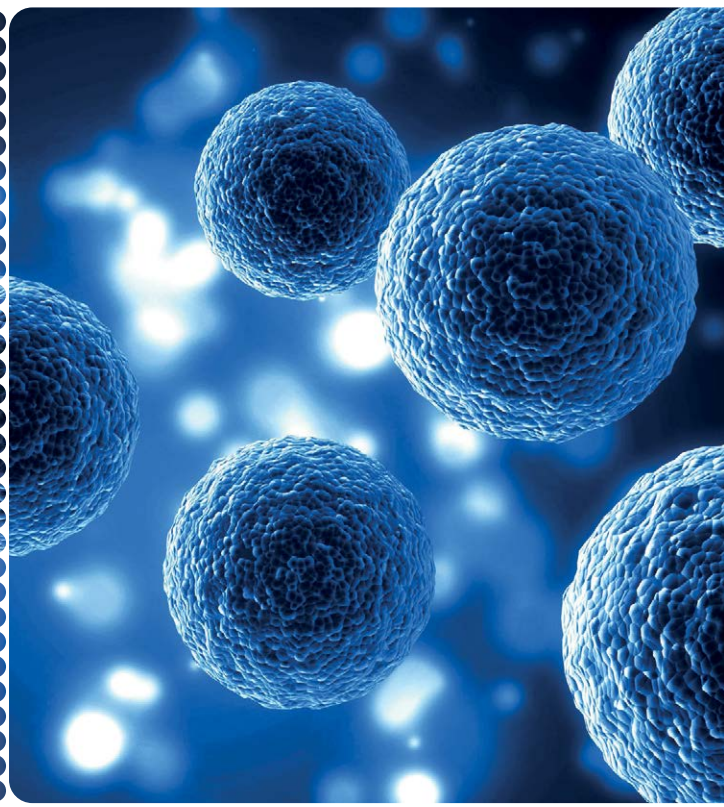

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