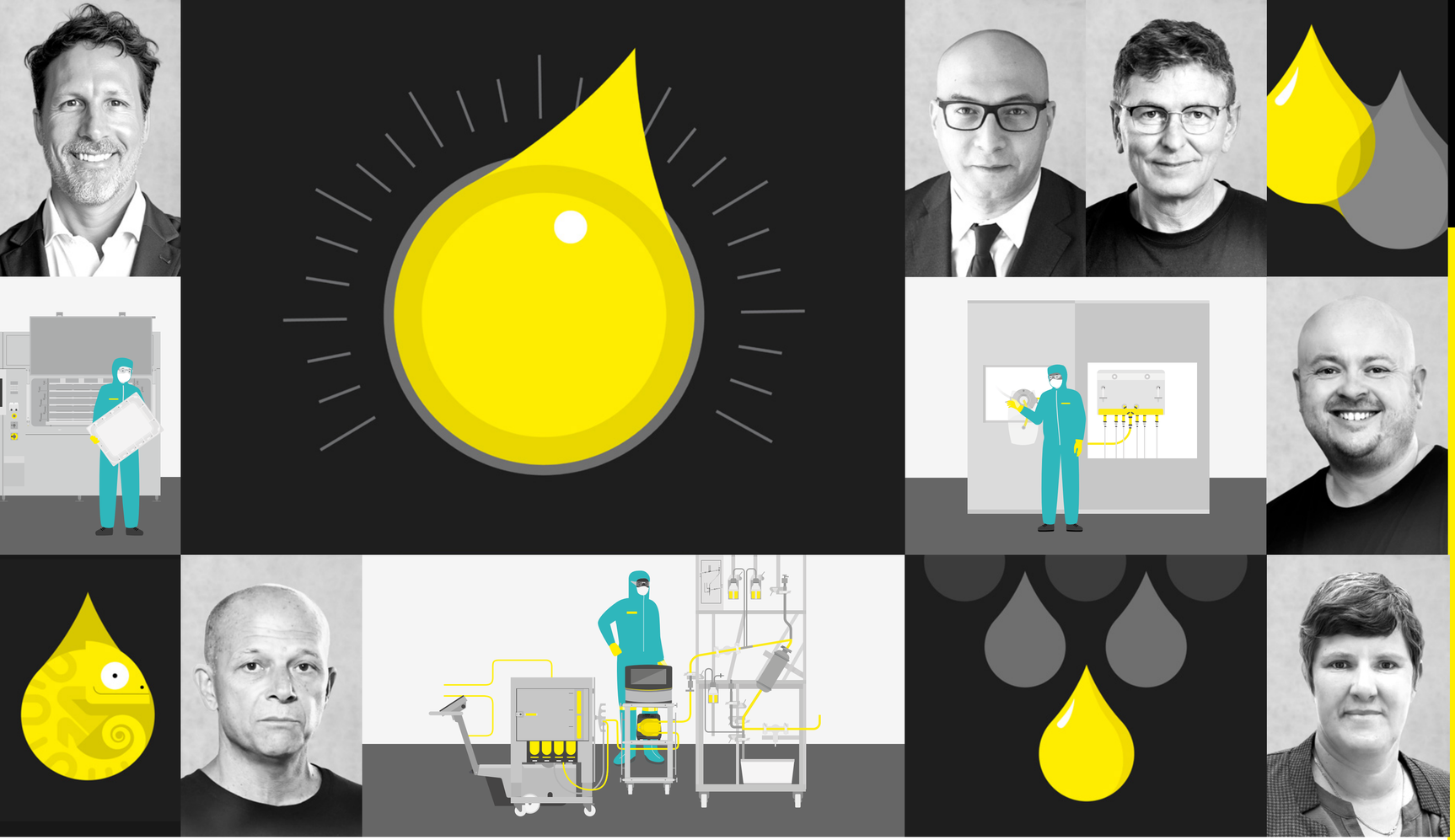

Simplifying Progress

Insights from fill and finish experts

Compliance in conversation: A fill and finish regulatory roundtable

Click here to start

SARTORIUS

Foreword

As the final step before a product reaches the patient, fill and finish is a high-value operation in the downstream process. Evolving expectations from regulatory authorities—particularly the updated EU GMP Annex 1 and proposed PFAS restrictions—have significant consequences for how these critical process steps are performed. Drug developers and manufacturers must navigate the changing regulatory environment while ensuring process complexity is minimized and product integrity is maintained.

Sartorius brought together five experts for a panel discussion on compliance topics affecting modern fill and finish operations. These specialists work daily at the intersection of sterility assurance, filtration, single-use processing, validation science, and material selection, making them ideally suited to help you strengthen sterility assurance.

Charles Meadows
Moderator

This eBook summarizes the key learnings from this discussion, examining three core dimensions of today's sterile manufacturing environment:

- How the updated Annex 1 regulations have reshaped contamination control
- How operational tools such as PUPSIT, single-use systems, and validation services impact sterility assurance
- How upcoming PFAS regulations require forward planning for material selection and supply chain resilience

Each chapter captures a single expert's viewpoint, forming a connected view of critical compliance topics facing fill and finish operations.

Watch the webinar on demand for more insights:
sartorius.com/en/pr/webinar-compliance-in-conversation

Meet the experts

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Validation Laboratory,
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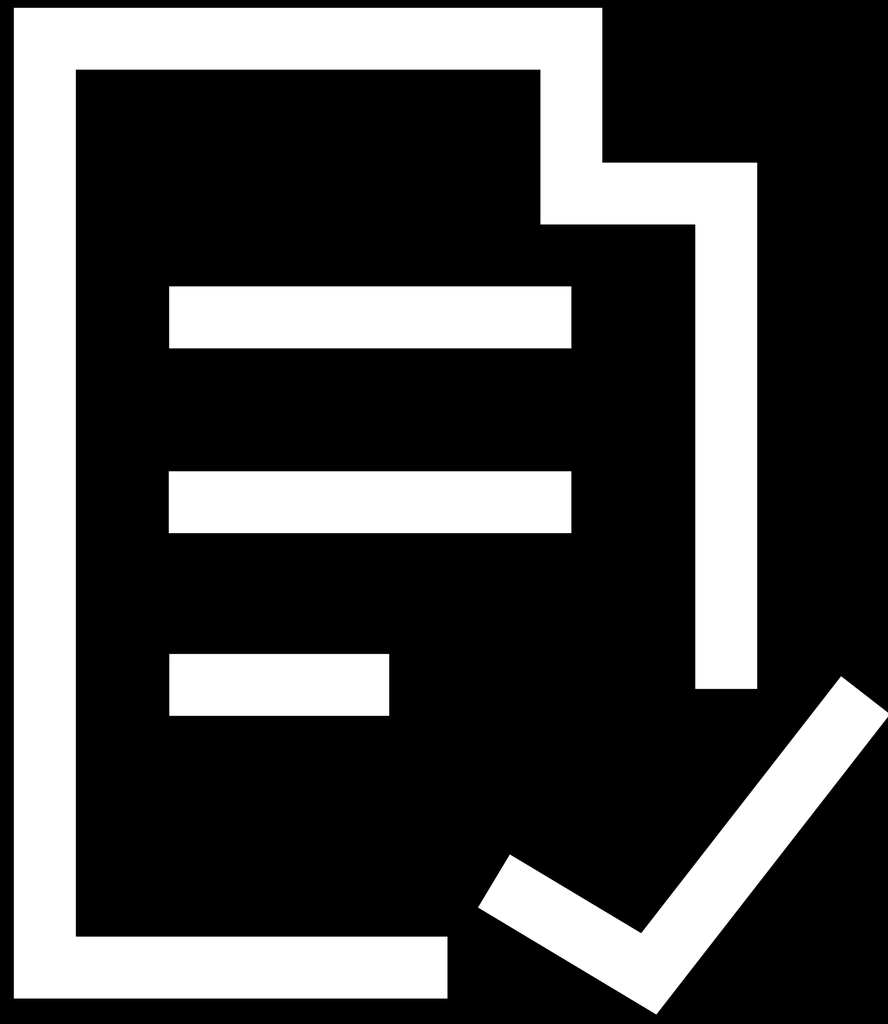
Annex 1 in practice: A shift toward proactive risk management



Annex 1 in practice: A shift toward proactive risk management

The revised EU GMP Annex 1 represents a fundamental transformation in sterile pharmaceutical manufacturing.[1] The new guidance emphasizes proactive risk management, continuous monitoring, and a robust Contamination Control Strategy (CCS), integrated within a Quality Risk Management (QRM) framework. There are now stricter requirements for pharmaceutical quality systems, personnel training, and container closure integrity testing, as well as a stronger focus on implementing pre-use post-sterilization integrity testing (PUPSIT), single-use solutions, and advanced barrier systems to prevent contamination and protect product integrity.

These elevated requirements have significant operational implications. Many companies have invested in barrier systems such as isolators and RABS, upgraded or redesigned facilities, expanded documentation requirements, and strengthened training programs. These changes often require considerable downtime and financial investment, as reflected in industry surveys showing that achieving compliance requires extended shutdowns and multimillion-dollar upgrades.[2,3]

Regulatory interpretation remains an area of complexity. Industry surveys show that interpretations of PUPSIT requirements vary across agencies, with some regulators accepting risk-based justifications (particularly in legacy systems or small-batch processes) while others push for stricter implementation.

Despite these challenges, the updated Annex 1 regulations have driven a culture of continuous improvement, advancing the industry toward a higher standard of quality, safety, and innovation.

Amine Djeffal
Process Expert,
Sartorius

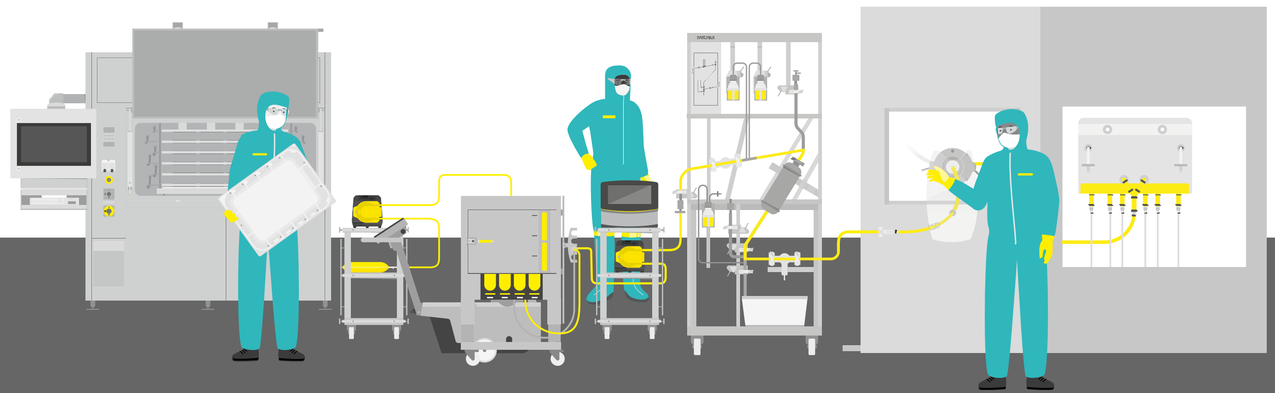
Q&A from the live discussion

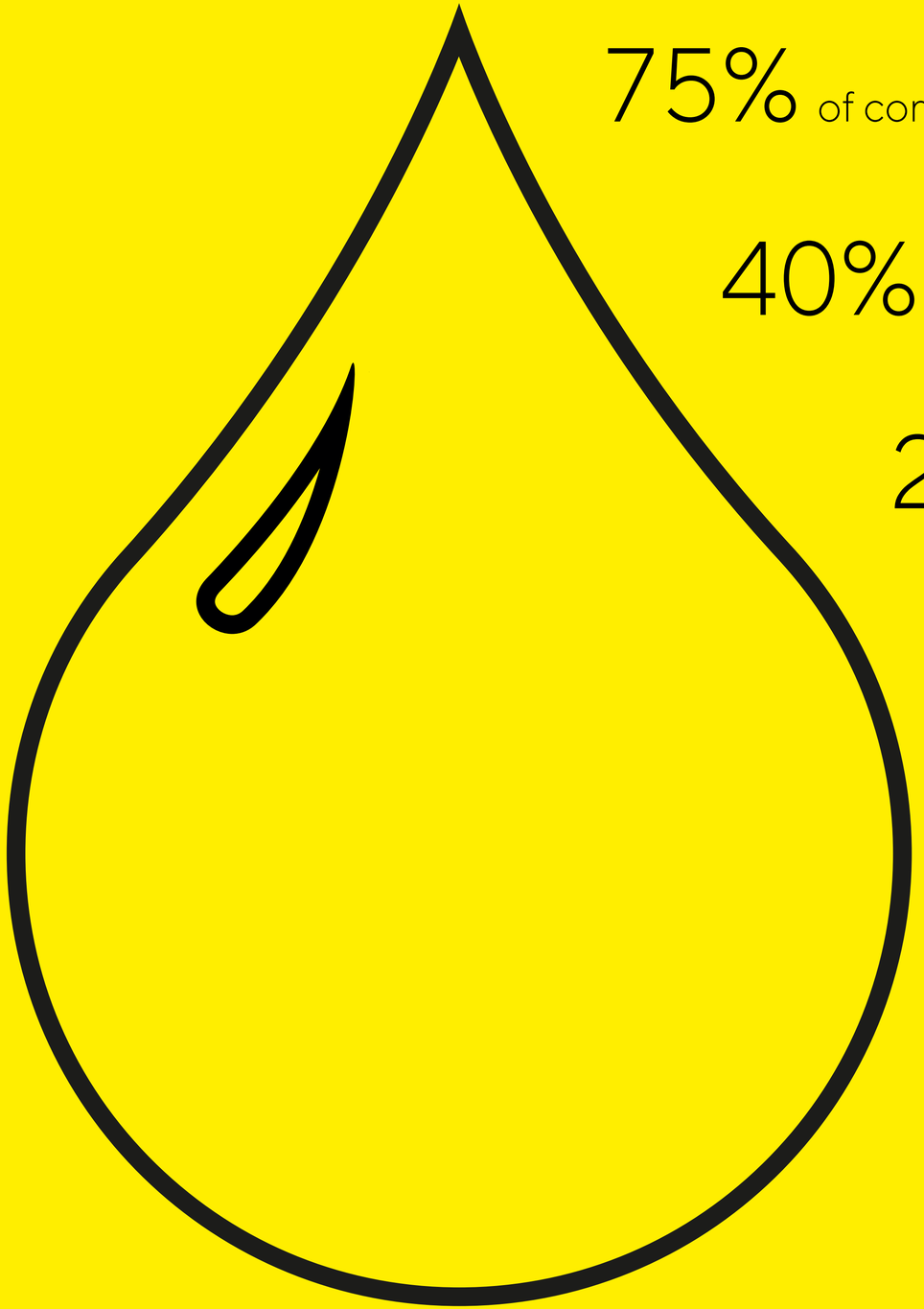
Q: How should companies operating across multiple global sites build a contamination control strategy, and what flexibility are regulators showing on timelines?

A: CCS should follow a global framework applied consistently across sites but adapted locally based on facility design, process maturity, and regional regulatory requirements. Frequent communication, i.e., sharing best practices, audit outcomes, and lessons learned, helps to maintain alignment. Industry surveys have shown this hybrid approach to be an effective strategy for compliance; however, strong documentation, training, and justification remain essential.

Key learnings

- Annex 1 establishes a shift from reactive to proactive, continuous risk management.
- CCS and QRM are now central to sterile manufacturing decision-making.
- Compliance requires extensive investment in infrastructure, documentation, and training.
- Regulatory expectations—especially around PUPSIT—vary across agencies.
- The revision has elevated quality culture and strengthened sterility assurance industry-wide.





75% of companies **report ≥ 75% compliance** with **Annex 1**

40% **requested extensions** beyond August 2023

23% **proactively informed** authorities

40% **required extended shutdowns**; 25% > 6 months

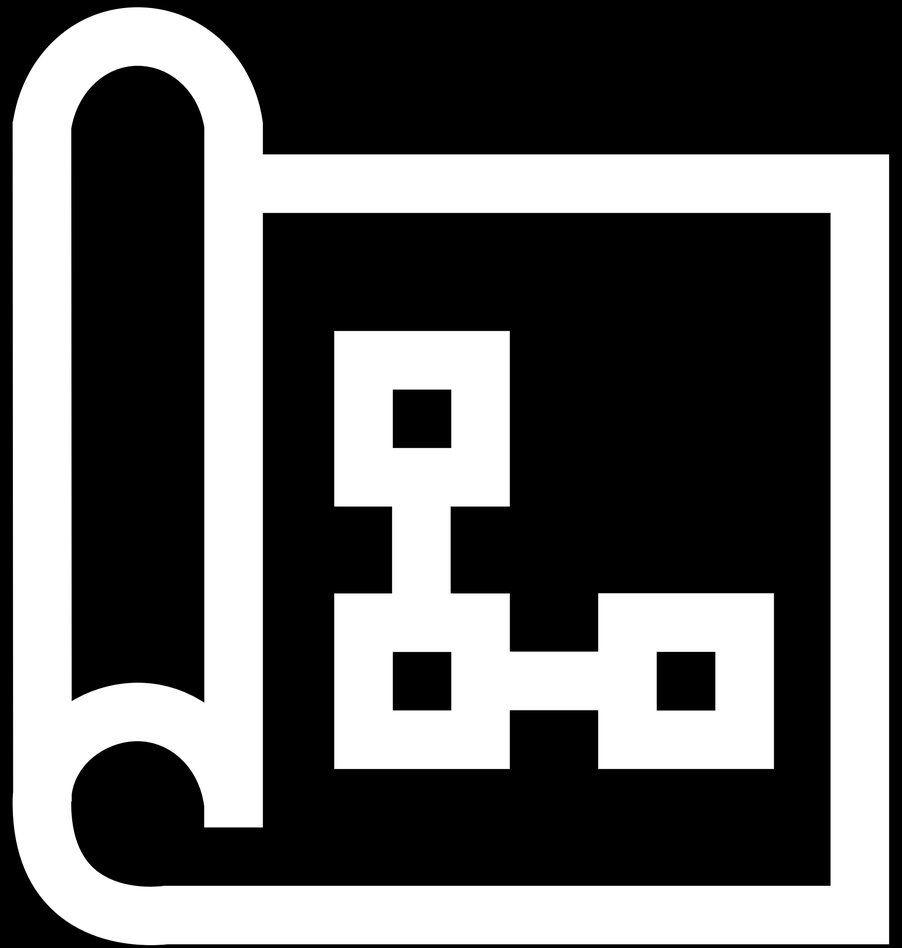
30% **spent > $2 million** (USD) **on compliance** upgrades

3 top challenges

- Contamination Control Strategy
- Barrier technologies
- Facility upgrades

Chapter 2

Engineering PUPSIT systems for modern aseptic operations



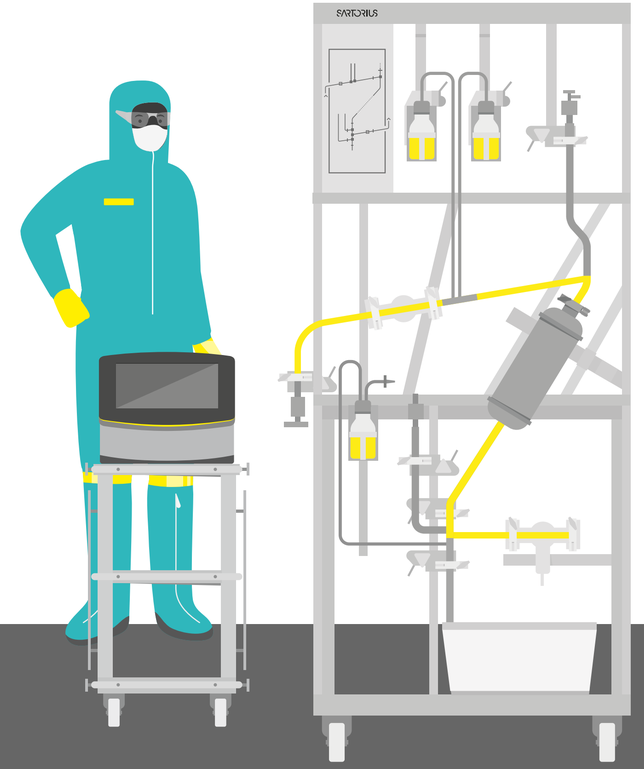
Engineering PUPSIT systems for modern aseptic operations

PUPSIT—a procedure used to verify the integrity of sterilizing filters before they are used in the final filling process — remains one of the most discussed elements of Annex 1 due to the engineering and operational complexity it introduces. The revised regulations position PUPSIT as the standard expectation wherever practical, with exceptions (e.g., for very small volumes) requiring a rigorous risk assessment and clearly defined controls.

PUPSIT implementation is highly dependent on facility layout, batch size, process pressures, and system architecture. Organizations must begin with a rigorous failure mode and effects analysis (FMEA), examining questions such as how much product loss a process can tolerate, whether filter blockage is plausible, and whether space constraints make implementation counterproductive. Legacy systems are particularly challenging, as adding vent filters and valve assemblies can introduce new risks.

Automated skid technologies now support controlled flow, integrated drying, automated integrity testing, and leak-testing of assemblies, significantly reducing product loss and manual manipulation risk. Point-of-fill placement remains essential but must be balanced with ergonomic and spatial realities: isolator-internal setups offer the strongest sterility, while RABS provide more accessible handling, and Grade C configurations require validated integrity assurance.

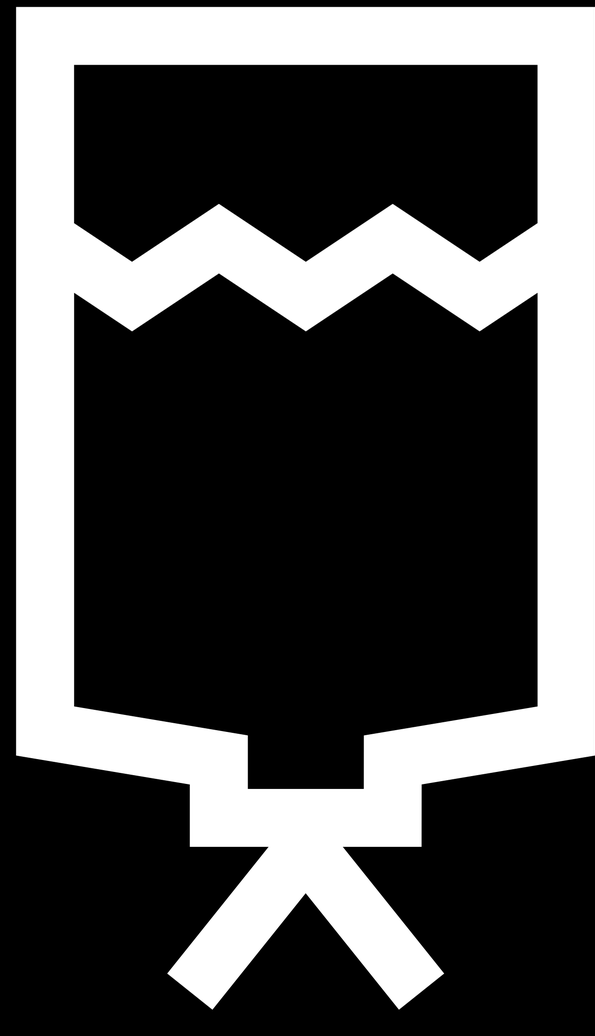
Dr. Mathias Siebner
Product Specialist,
ST Filtration | Product Excellence ST EMEA,
Sartorius



Key learnings

- Industry preference is shifting toward implementing PUPSIT wherever feasible.
- Effective PUPSIT implementation requires structured FMEA evaluation.
- Small-batch processes require careful consideration due to potential product losses.
- Modern PUPSIT skids reduce risk and improve operational efficiency.
- Point-of-fill placement must balance sterility with practicality.

Single-use systems: Managing design complexity and operator handling



Single-use systems: Managing design complexity and operator handling

Annex 1's new guidance on single-use systems (Chapter 8, Section 8.131–8.139)1 highlights the essential relationship between design and operator handling. Systems must be engineered to minimize manipulations, but handling, and therefore contamination risk, is shaped by the architecture of the filling system, how components are introduced into the isolator, and how well operators can maneuver the components.

Two primary installation strategies illustrate this balance. Fully pre-connected assemblies eliminate the need for aseptic connections within the isolator but increase handling complexity. In contrast, disconnected lines introduced into the isolator with protective caps require aseptic reconnection inside the isolator, but handling is simplified.

QRM determines which approach best suits a given process. Annex 1 supports both strategies. Ultimately, the system should be designed to reduce manipulation and minimize complexity. Robust validation is essential to identify and justify the best method for your process: FAT simulations, mock-ups, media transfer tests, and aseptic process simulations all generate evidence that handling practices support sterility.

Dr. Paolo Saccà
Field Account Project Manager | Sales Territory Italy, Sartorius

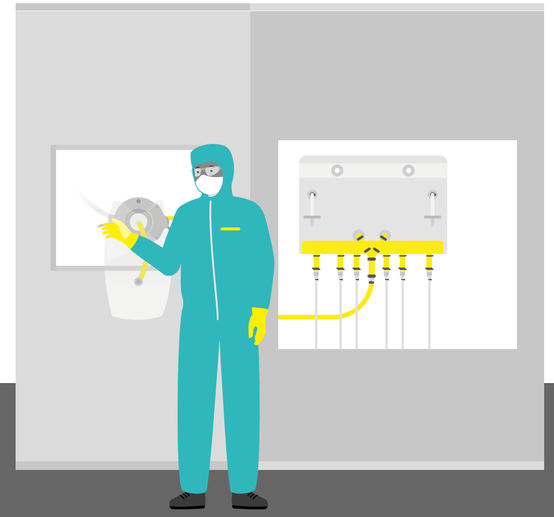
Q&A from the live discussion

Q: What handling practices have the biggest impact on reducing risk when using single-use systems?

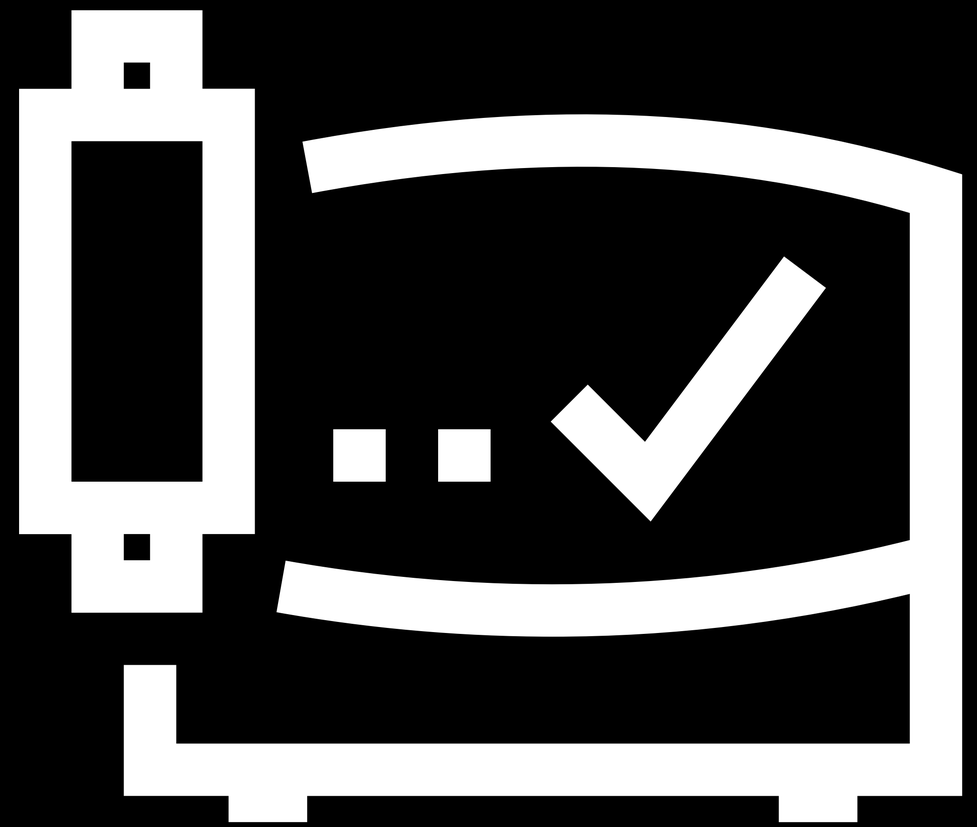
A: Proper handling begins long before system installation. Warehousing, storage, and transfer between controlled areas all influence contamination risk. Once inside the cleanroom, training becomes the most powerful risk-reduction tool. Because single-use system vulnerability increases once packaging is removed, operators must be trained extensively on correct handling, movement, and installation techniques. Moreover, early supplier involvement — ideally at the design stage — and consistent, hands-on training across all roles reduce risk.

Key learnings

- Single-use system design and operator handling must be evaluated together for effective contamination control.
- Pre-connected assemblies reduce aseptic steps but increase handling difficulty.
- Disconnected-and-capped assemblies simplify handling but require validated connection steps.
- QRM guides the choice of installation method for each facility and process.
- Aseptic process simulations, FAT exercises, and operator training are essential for validating handling approaches.



Process-specific bacterial retention testing and PUPSIT simulation



Process-specific bacterial retention testing and PUPSIT simulation

Annex 1 states that during filter validation, the product to be filtered should be used for bacterial retention testing of the sterilizing-grade filter.[1] The intent of a bacterial retention study or bacterial challenge test is to document reproducible evidence on the efficacy of a filtration process under process-specific worst-case conditions. These findings set the limit for the actual process.

The implementation of PUPSIT could impact the process-specific bacterial retention study indirectly. As such, PUPSIT simulations are sometimes performed as part of bacterial retention studies. It is important to consider that the role of PUPSIT during manufacturing is different than its inclusion during bacterial retention studies: During manufacturing, PUPSIT detects sterilization-induced filter flaws, during bacterial retention testing, PUPSIT simulation is intended to subject the filter to the worst-case process conditions, and to evaluate the impact on its ability to produce a sterile effluent.

The decision to include PUPSIT simulation in validation depends on a thorough risk assessment.[4] When it is deemed appropriate, it should be incorporated directly into the bacterial challenge study—not performed separately—to ensure cumulative stress effects are captured.

Yvonne Groß
Senior Scientist | Validation Laboratory, Sartorius

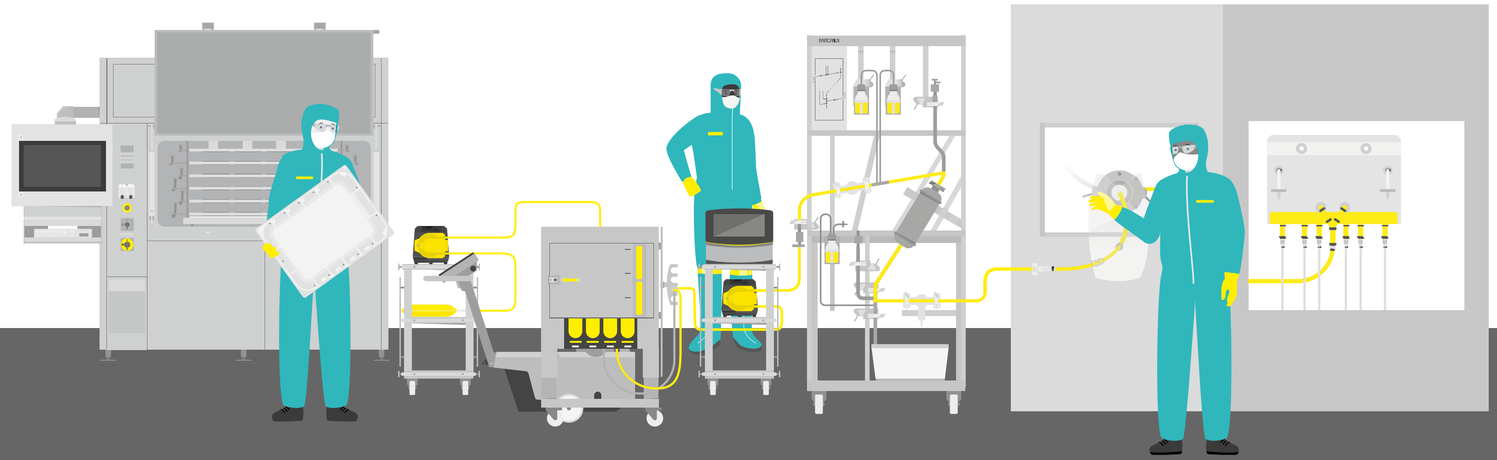
Q&A from the live discussion

Q: Do previously validated filtration processes need to be revalidated if PUPSIT will now be incorporated?

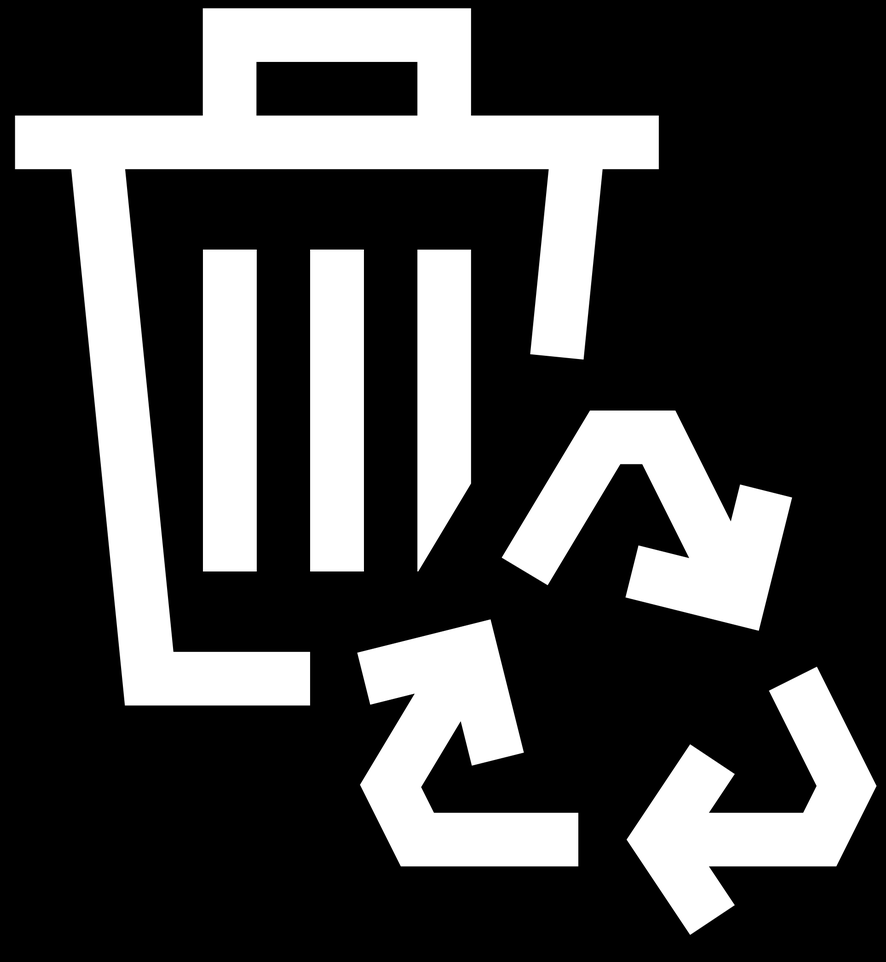
A: Not necessarily. The decision on whether revalidation is required should be based on a thorough risk assessment. For example, factors such as the wetting fluid and the type of filter can be considered when determining the need for revalidation.

Key learnings

- Bacterial retention testing defines the validated performance limits for sterile filtration.
- PUPSIT may or may not influence retention performance, depending on process risk factors.
- Only risk-driven scenarios require PUPSIT simulation within bacterial retention testing.
- Revalidation is not automatically required when adding PUPSIT.
- Simulation must reflect cumulative process stresses to be meaningful.



PFAS restrictions and the future of material selection



PFAS restrictions and the future of material selection

PFAS materials have long been integral to pharmaceutical filtration and single-use technologies due to their chemical stability and inertness. PFAS polymers do not naturally deteriorate, and therefore do not pose an immediate health risk. In contrast, PFAS surfactants, e.g., C8 (PFOA), exhibit ecotoxicity and are the main contributors to PFAS-associated pathologies.[5] These short-chained, water-soluble substances are already subject to regulation and restriction. However, growing evidence of environmental persistence and health risks has led to growing public attention and prompted regulators to reconsider their use.

Governments and industry groups are already actively tightening oversight of PFAS, driven by concerns about persistence, emissions, and exposure, and by significant societal pressure for reduction and substitution.

For example, within the European Union, the European Chemicals Agency has published a PFAS restriction proposal under the REACH restriction process, with a decision expected in 2027.[6] In the US, 3M is committing to cease all PFAS manufacturing, which includes fluoropolymers and PFAS-based additive products, by the end of 2025.[7]

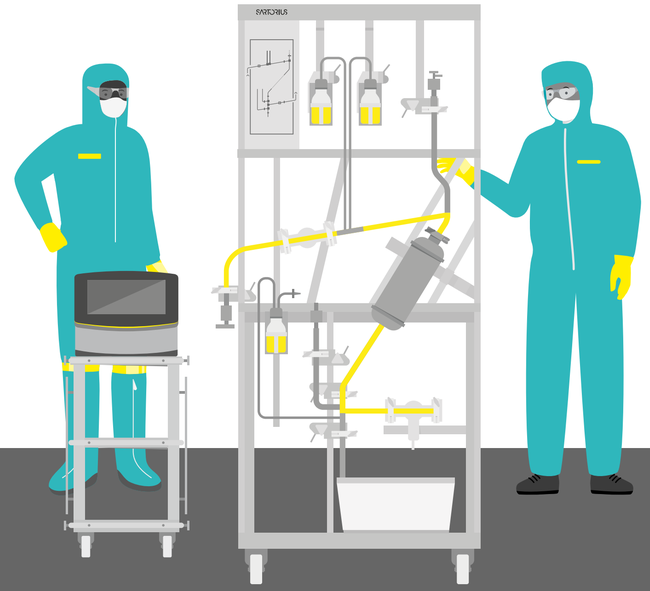
Biopharma manufacturers now face three principal challenges: preparing for regulatory inquiries and audits, mitigating supply-chain disruptions from diminishing availability of PFAS-based materials, and reducing environmental and health impacts associated with PFAS disposal and exposure. These shifts have driven innovation toward PFAS-"free" filtration materials.

Sartopore Evo® represents one such PFAS-"free" alternative, combining high throughput, low adsorption (especially of polysorbate 80), strong wetting behavior, and robust microbial retention. Its development reflects a broader trend toward sustainable material selection that reduces regulatory exposure while supporting long-term supply security.

Markus Maring
Product Manager | Filtration Consumables, Sartorius

Key learnings

- PFAS restrictions are accelerating globally and will likely affect materials used in filtration and other single-use technologies.
- Biopharma manufacturers should prepare for regulatory and supply-chain changes | shifts
- PFAS-"free"* technologies, like Sartopore Evo®, should be evaluated early to support long-term compliance and filter supply assurance.
- Future material strategies must prioritize alternatives that minimize regulatory and environmental burdens.

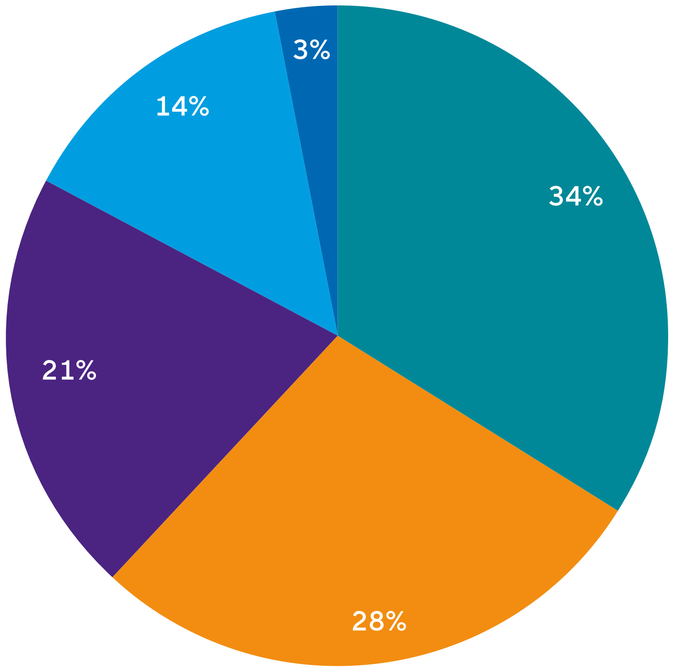


*Disclaimer: PFAS-"free" is used to describe products which are not using PFAS as a material of construction. NIA PFAS = non-intentionally added PFAS

Survey results

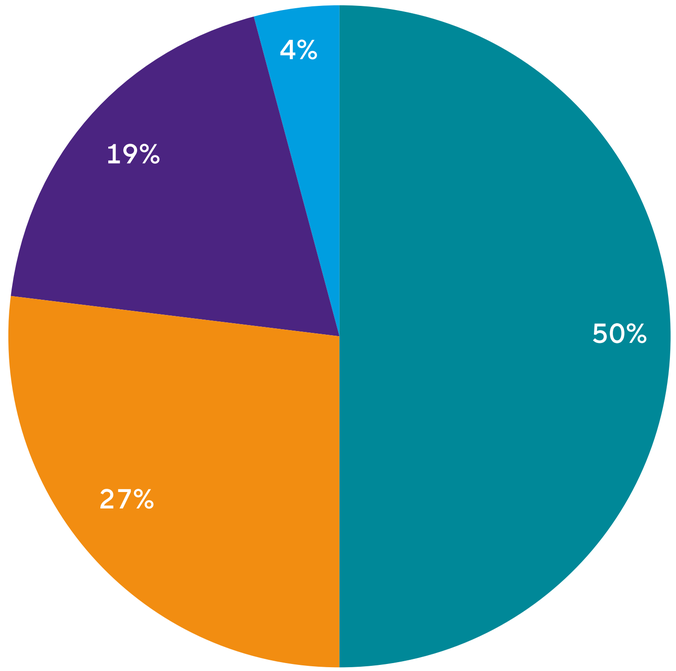
We conducted a short survey of participants during our roundtable. The results highlight the most significant challenges in achieving Annex 1 compliance and the key impacts observed across operations.

Which is, or was, the top challenge in your work toward Annex 1 compliance?



- Contamination control strategy
- PUPSIT
- Single-use systems design and validation
- Barrier technologies
- Other

What has been the principal impact of Annex 1?



- Enhanced product quality and patient safety
- Driven major new technology adoption
- Exposed gaps in existing contamination control strategies
- Increased burden of documentation and compliance

References

1. European Commission. (2022). *EudraLex: The rules governing medicinal products in the European Union, Volume 4, Good manufacturing practice (GMP) guidelines, Annex 1: Manufacture of sterile medicinal products.* European Medicines Agency. https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-4_en

2. Parenteral Drug Association. (2024). Annex 1: One year into implementation. https://www.pda.org/bookstore/product-detail/8160-2024-pda-annex-1-one-year-into-implementation

3. Parenteral Drug Association. (2023). Implementation of the new EU GMP Annex 1 and implementation of barrier systems: Survey results. https://www.pda.org/docs/default-source/website-document-library/pda-news/survey-report—implementation-of-new-eu-annex-1-and-implementation-of-barrier-systems-16-aug-2023.pdf

4. Salamatian, M., Groβ, Y., Stering, M., Le, T. V., & Bindels, A. (2025). A Risk-Based Approach for Pre-Use/Post-Sterilization Integrity Test Simulation During Bacterial Retention Testing as Part of the Process-Specific Filter Validation of Sterilizing Grade Filters. *PDA Journal of Pharmaceutical Science and Technology,* 79(4), 408–421. https://doi.org/10.5731/pdajpst.2024.012990

5. Panieri, E., Baralic, K., Djukic-Cosic, D., Buha Djordjevic, A., & Saso, L. (2022). PFAS Molecules: A Major Concern for the Human Health and the Environment. *Toxics, 10*(2), 44. https://doi.org/10.3390/toxics10020044

6. European Chemicals Agency. (2025). *ECHA publishes updated PFAS restriction proposal.* https://echa.europa.eu/-/echa-publishes-updated-pfas-restriction-proposal

7. 3M Company. (2022). *3M to exit PFAS manufacturing by the end of 2025.* https://news.3m.com/2022-12-20-3M-to-Exit-PFAS-Manufacturing-by-the-End-of-2025

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