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3 Key Takeaways of Annex 1: What It Means for Your Cold Chain Management

Why and How Are the Guidelines Changing for Manufacture of Sterile Medicinal Products?

The latest update to Annex 1 clarifies and expands EMA guidelines for the manufacture of sterile medicinal products.[1] Given that regulatory and manufacturing environments have changed dramatically since the last revision was issued in 2007, the new guidelines are much needed and largely welcomed within the pharmaceutical industry. In particular, the changes to Annex 1 take account of rapid innovation and adoption of technologies like SU assemblies, which have transformed conventional biopharmaceutical manufacturing over the past 15 years.

Notably, the new guidelines call for a more proactive, risk-based approach to quality management that extends beyond upstream and downstream processing to include product finishing, storage, and transport. To comply, manufacturers must apply QRM principles across manufacturing and cold chain activities to minimize the risk of microbial, particulate, and endotoxin | pyrogen contamination at every stage. This includes implementing a comprehensive contamination control strategy (CCS) to ensure consistent and high drug product quality, purity, and effectiveness.

The CCS is the cornerstone of Annex 1. As such, it plays a pivotal role in QRM across every aspect of drug product processing, storage, and transport. The introduction of new chapters on product finishing, closed systems, and SU systems (SUS) supports a more holistic approach to risk analysis and contamination control that extends across the cold chain.

What Does This Mean for Cold Chain Management and Single-Use Technologies?

Harmful contamination can occur at virtually any stage of drug product processing, storage, and transport. Consequently, the updated guidelines emphasize that manufacturers must integrate an effective risk management system into all aspects of the bulk drug product lifecycle. Recognizing the growing use of SU technologies as alternatives to reusable equipment, Annex 1 now highlights specific risks associated with SUS and cold chain processes that must be addressed by the pharmaceutical quality system (PQS) and CCS.

What are the practical implications of all this, specifically for cold chain management? We asked our in-house experts for their thoughts on the subject. Here are their top 3 takeaways:

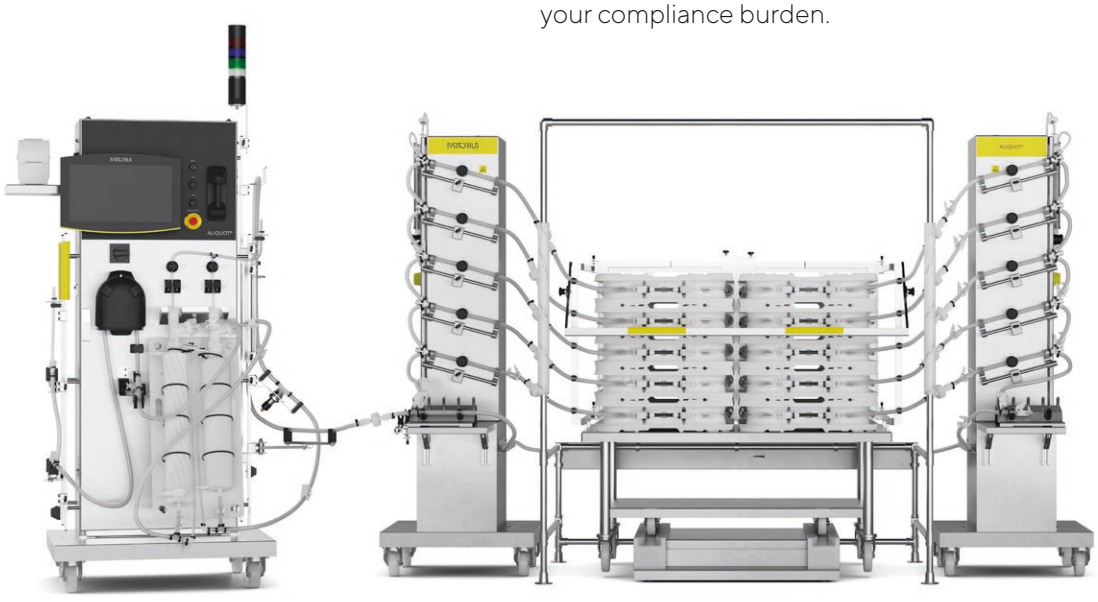
Takeaway 1. Single-Use Technologies Can Support Your Contamination Control Strategy

Contamination control is a top priority in the pharmaceutical industry, where the stakes are high in terms of patient health and the potential for financial loss. A comprehensive CCS is, therefore, a key element in QRM. SU systems offer significant advantages to support your CCS and help you comply with Annex 1.

These include:

- Sterility assurance—SU components and assemblies come pre-sterilized and ready-to-use
- Closed systems—reduce the risk of microbial, particle, and chemical contamination from the adjacent environment
- Purpose-built designs—fewer opportunities for contamination during routine operations
- Disposable devices—eliminate the risk of cross-contamination associated with re-use
- Reduced cleaning burden—no need for in-house SIP | CIP and cleaning protocol validation
- Pre-assembly—reduced risk of misassembly
- Pre-qualified and validated solutions—achieve GMP readiness and compliance sooner

It should come as no surprise that personnel are a common source of mishaps and drug product contamination at any point where there is human intervention. Automation systems go hand-in-hand with SU solutions to minimize manual handling steps and opportunities for human error. For example, a purpose-built automated filling station such as the AliquoT® can streamline the process of distributing bulk drug substances into SU containers by minimizing human intervention and reducing the duration of operations where the product could be exposed to contaminants. Ready-to-use closed SU assemblies and manifolded Celsius® containers also reduce the number of connections required. AliquoT® and the full platform are pre-qualified and validated, further alleviating your compliance burden.



The AliquoT® Automated Filling System

Takeaway 2. Ensuring Robustness and Integrity is Crucial
While SU technology offers significant advantages for contamination control, new guidance in Annex 1 (Section 8.132) raises awareness that SU solutions come with their own set of risks, which must be addressed as part of the CCS. A number of these risks relate to the relative fragility of SU containers compared with fixed reusable systems.

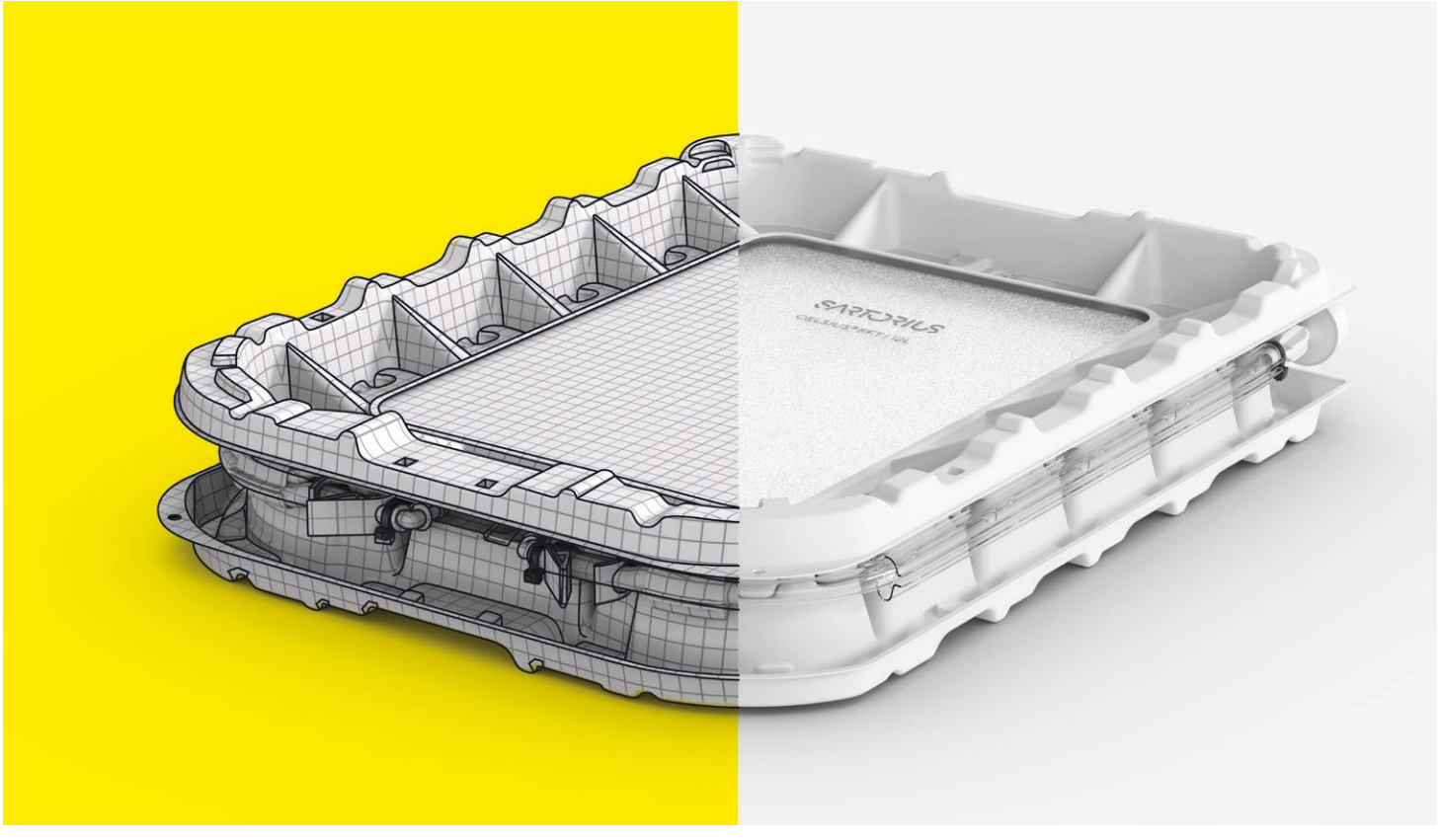
For example:

- Naked bags are vulnerable to micro-leaks and macro-defects that can compromise sterility
- Bottles or tubes are subject to breakage and breach of cap closure integrity
- Bags may be damaged during packaging or opening of the outer packaging, resulting in defects at the micro or macro level

At the end of every cold chain are clinicians and patients who rely on the integrity of temperature-sensitive drug products. Ensuring product integrity across the cold chain requires robust container systems that can withstand the harsh and variable conditions encountered during routine processing, storage, and transport of the bulk drug substance.

Of particular concern for cold chain operations is the structural integrity of SU components under extreme conditions, such as freezing and thawing procedures. Even if validation claims specify that an SU device is suitable for use at a low temperature, end-users still need to check whether the validation procedure is relevant to their specific application. If not, additional validation may be required to comply with Annex 1.

The design of SU containers is key to ensuring their robustness and integrity in the cold chain. In developing the Celsius® range of SU containers, Sartorius has taken a "robustness-by-design" approach, which involved comprehensive materials characterization, design simulations, and "real-life" application testing, including multiple freeze-thaw cycles and exposure to high-temperature environments for several days.[3,4]



The Celsius® FFT (Flexible Freeze and Thaw) platform offers a unique bag-in-shell system that replaces traditional freezing and thawing methods. The SU containers are sterile and pre-assembled for freezing and thawing biopharmaceutical solutions in commercially available equipment. This means you can incorporate them into the cold chain without disrupting the existing freeze-and-thaw infrastructure.

Large-scale frozen storage presents its own challenges relating to process efficiency, safety, product integrity, logistics, cost of ownership, and flexibility, all of which are addressed by the Celsius® FFT for Large Volumes.

Takeaway 3. Your Supplier Choice is Crucial to Compliance
In traditional fill-and-finish processes, compliance is managed directly on-site. When adopting SU components and ready-to-use containers, some of this responsibility shifts to suppliers. With greater reliance on SU suppliers for sterility assurance and a reliable supply chain, rigorous supplier selection and qualification are paramount.

"Assessment of suppliers of disposable systems including sterilisation is critical to the selection and use of these systems. For sterile SUS, verification of sterility assurance should be performed as part of the supplier qualification and evidence of sterilisation of each unit should be checked on receipt."

Annex 1, 8.134

In developing and maintaining the CCS, drug manufacturers need to be able to talk openly with suppliers about specific system needs or adaptations and have ready access to the critical information they need to assess and mitigate risks. For example, material characterization data is particularly important to support impact assessment and material interactions. It is crucial to put systems in place to ensure suppliers provide essential information and components on time and meet all the relevant qualification standards.

Another key consideration is the level of expertise SU suppliers have to offer and their capacity to provide guidance and training when needed. In fact, the words "knowledge" and "experience" are mentioned 19 times in Annex 1, underscoring the importance of these attributes.

Finally, selecting a supplier that provides solutions across the entire workflow supports end-to-end process validation, the importance of which is emphasized in the revised Annex 1.

Conclusion

Without a doubt, Annex 1 is a step forward for the industry, providing much-needed clarity and guidance around quality risk management, along with expanded scope to benefit from the latest SU platforms and technologies. Sartorius SU solutions are designed to deliver the consistent robustness and integrity you need across your cold chain processes and applications and at a range of volumes to suit varying production scales.

To find out more about the new Annex 1 guidelines and how SU technologies can support the challenges, watch our webinar.

Watch the On-Demand Webinar

References

1. Ec.europa.eu. 2023. EudraLex—Volume 4 Good manufacturing practice (GMP) Guidelines, Annex 1: Manufacture of Sterile Medicinal Products. European Commission. Available at: https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-4_en#annexes

Additional Resources

Addressing New Challenges in Bulk Drug Substance Management
www.sartorius.com/en/robust-by-design-white-paper-en-b-pdf-1345580

Explore Celsius® FFT (Flexible Freeze and Thaw)
www.sartorius.com/en/products/fluid-management/frozen-storage-shipping/commercial-scale-solutions/celsius-fft

Find Celsius® Solutions for Large Volumes
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Learn more about AliquoT® Automated Filling Solution
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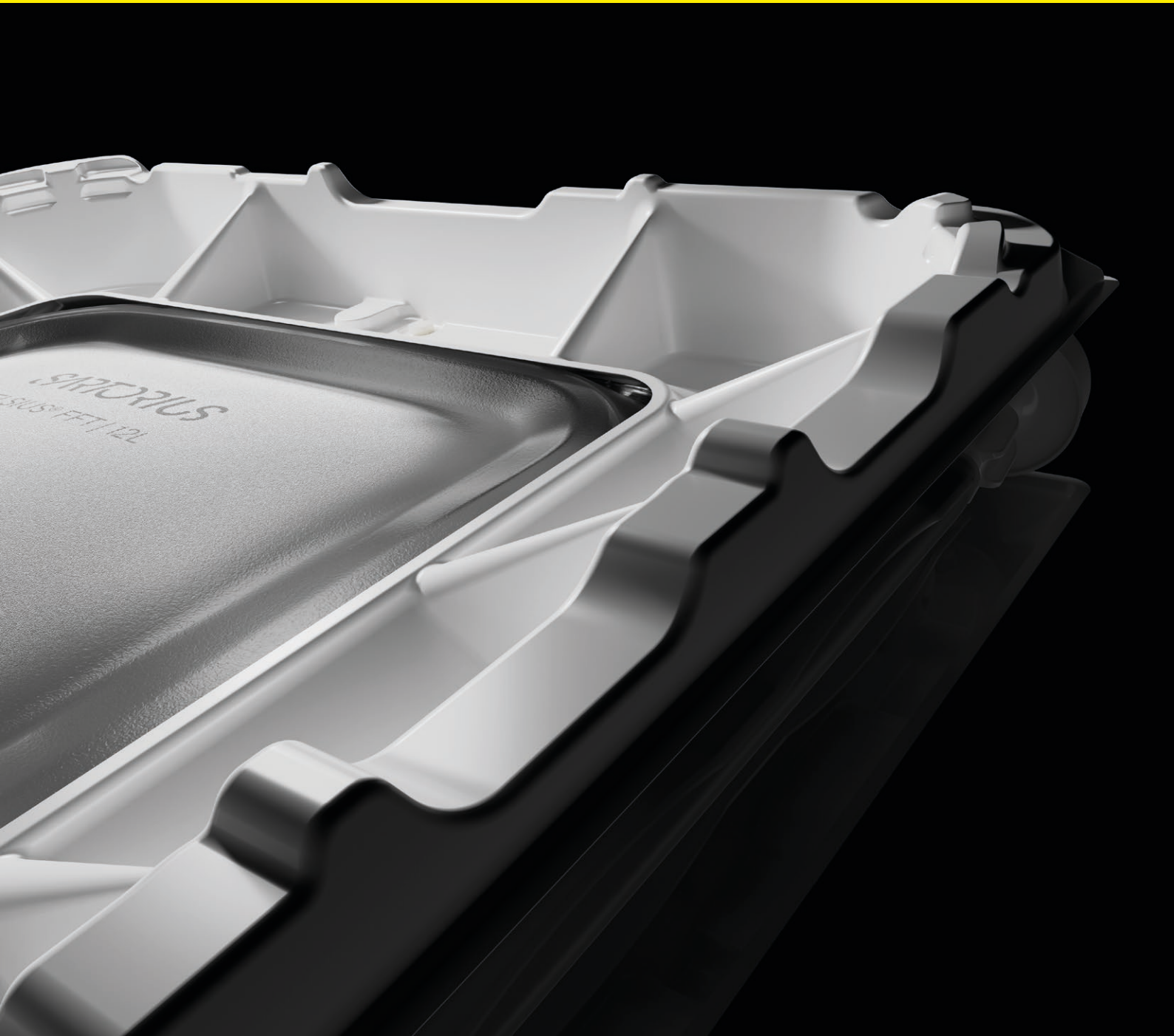

Germany
Sartorius Stedim Biotech GmbH
August-Spindler-Strasse 11
37079 Goettingen
Phone +49 551 308 0

USA
Sartorius Stedim North America Inc.
565 Johnson Avenue
Bohemia, NY 11716
Toll-Free +1 800 368 7178

For more information, visit
sartorius.com

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