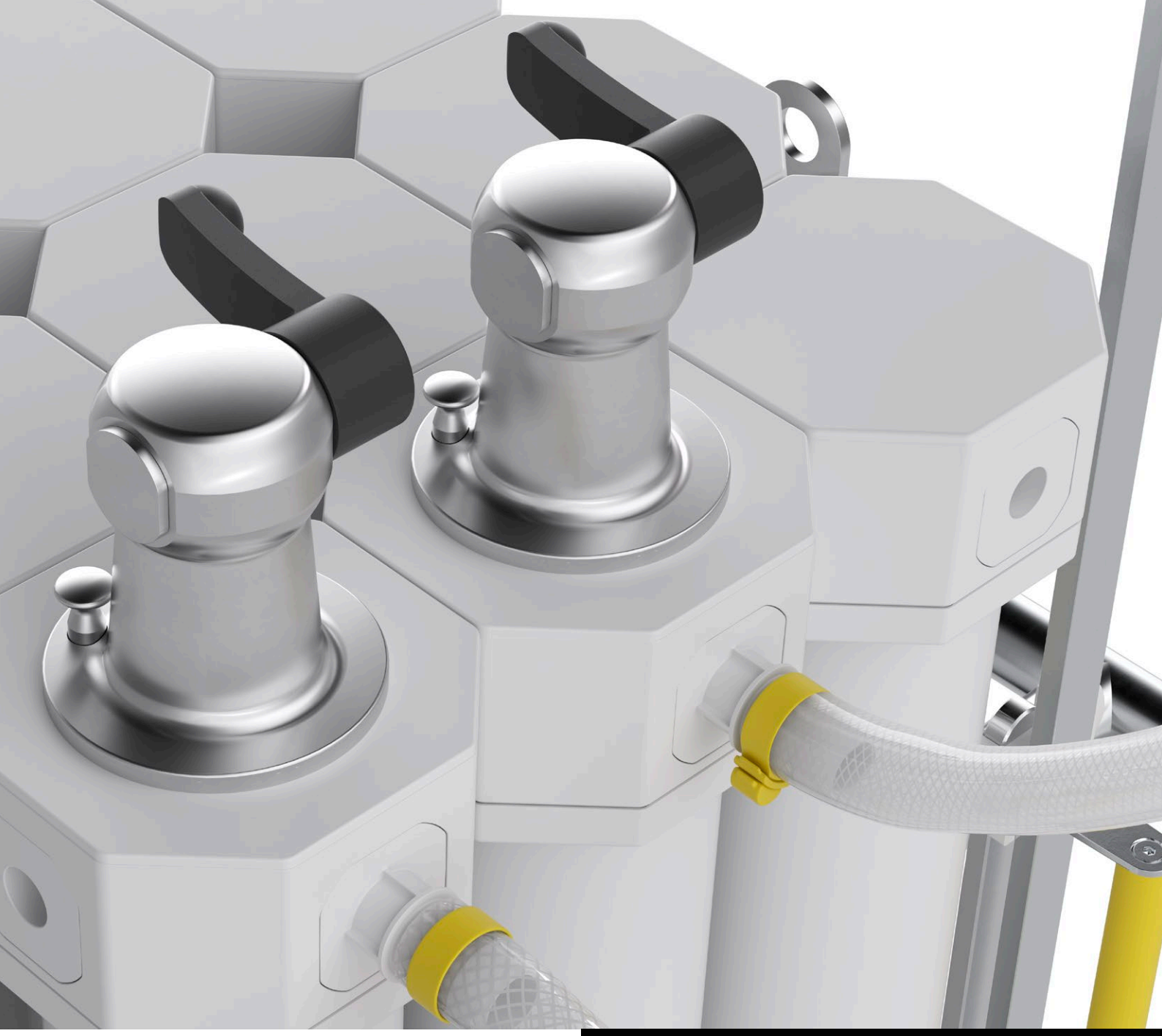

Simplifying Progress

# Risk Mitigation in Large-Scale Bioprocess Filtration

August, 2023 | Lucia Dinehart, Martine Barros, Andre Grebe, Katy McLaughlin

**Keywords or Phrases:**
Large volume filtration, single-use filtration system, Maxicaps® MR, bioprocess filtration, risk mitigation, stainless steel multi-round housing

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# Introduction

In bioprocessing, the filtration step plays a critical role in ensuring the safety, purity, and quality of biopharmaceutical products. However, this step also presents unique challenges and risks that must be carefully managed to avoid potential product quality issues, regulatory non-compliance, and costly setbacks.

The two most widely utilized methods in large-scale filtration, filter cartridges in multi-round stainless steel housings and single-use filter transfer sets requiring complex manifold assemblies, each present certain challenges that can impact process efficiency and productivity. These challenges arise due to issues each option has in terms of scalability, process integration, flexibility, and complex handling procedures.

Also, recent updates to EU GMP guidance Annex 1 emphasizes the significance of quality risk management (QRM) and the need for implementing a contamination control strategy (CCS). The guidance acknowledges the growing use of single-use systems in modern bioprocesses. To address these changes, it includes specific guidance on the implementation of single-use systems in the context of a CCS strategy, including complexity of the assembly , number and complexity of manual operations and connections made and system integrity.

This white paper first examines the limitations and obstacles presented by the conventional techniques, highlighting the challenges faced when using these systems, and then provides insights into how Sartorius, by combining innovation, efficiency, and cost-effectiveness, designed the Maxicaps® MR, as a state-of-the-art answer to single-use large-scale filtration for the biopharmaceutical industry.

## Large-Scale Filtration in Bioprocesses – What are the Existing Methods?

Stainless steel multiround housings are the established solution for conventional large-scale filtration processes. The single-use equivalent to stainless steel multiround housings consist of complex filter assemblies with multiple cable-tie connections, T-pieces, and manifolds (Figure 1).

Biopharmaceutical companies are increasingly transitioning from traditional stainless steel multi-round processes to single-use transfer sets with multiple filters. Ultimately, the choice of which to employ depends on the specific needs and circumstances of the process and facility.

**Figure 1:** *Conventional Large-Scale Filtration Systems*

Stainless Steel Multi-Round Housing

Single-Use Filter Assemblies

# Challenges Associated with Existing Methods

## Stainless Steel Multi-Round Housings

**Cost**
Stainless steel housing installations are expensive to acquire and maintain, including replacement parts, gaskets, seals, and regular maintenance. Moreover, there are significant costs associated with the supply of clean steam for sterilization and the related equipment and validation.

**Space and Footprint**
These filter housings require a larger physical footprint, which can be a limitation in facilities with limited space. This is particularly problematic if the facility needs to increase production size; space limitations and bulky equipment can block capacity expansion.

**Lacks Flexibility and Adaptability**
Switching between different filtration configurations or accommodating changing process requirements can be complex. Adjustments to handle different particle sizes, volumes, or fluids may require changing the filter elements or the entire housing, disrupting the manufacturing process.

**Limitations in Scalability**
Scalability may be limited compared to alternative filtration systems. As filtration demands increase, other options like modular or disposable systems offer greater flexibility and scalability.

**Cleaning and Cleaning Validation**
Thorough cleaning between batches or when changing filtration media are time-consuming and resource-intensive processes. Validation of cleaning procedures are required when using stainless steel multiround filter housings to comply with regulatory guidelines, and ensure product safety, process efficiency, and quality assurance.

**Cross Contamination**
Regulatory authorities have stringent requirements for product quality and safety. The burden of proof lies on the manufacturer to provide robust data and validations. The lack of standardized guidelines or specific acceptance criteria for proving no cross-contamination can make it challenging to meet regulatory expectations.

**Risk of Filter Damage During Cleaning-In-Place (CIP) or Sterilization-In-Place (SIP)**
These processes expose filter housings and elements to high temperatures, chemicals, or both and introduce risk of damage.

**Training and Expertise**
Maintaining, operating, and cleaning large, complex filtration systems requires specialist training to ensure high performance and safety.

**Risk of Operator Error**
Disassembly and reassembly increase the risk of human error. Improper installation, incorrect seating of filter elements, or inadequate cleaning can compromise the filtration system's integrity, leading to contamination and product quality issues.

## Single-Use Filter Assemblies

Single-use assemblies usually consist of individual single-use filter capsules connected via tubing and manifolds ; for example, filter transfer sets and manifolds can be ordered pre-sterilized and with aseptic connectors on the inlets and outlets. The components are then brought into the manufacturing suite and assembled via sterile connectors. This setup offers numerous advantages, including increased flexibility, reduced contamination risk, and saved time and resources because cleaning and validation procedures are not required.

However, while there are obvious advantages to single-use filter assemblies, challenges still exist when designing, implementing and operating complex, multi-component, filter assemblies for large volume filtration processes.

**Procurement Complexity**
Sourcing and procuring various components from different manufacturers or suppliers is time-consuming and complex.

**Supply Chain Challenges**
Using multiple single-use components, possibly from different manufacturers, can introduce challenges in managing the supply chain. Ensuring a consistent and reliable supply of compatible sets may require coordination with multiple vendors, potentially leading to logistical complexities and potential delays in procuring the necessary equipment.

**Inventory Management**
The logistics of intake, warehousing and management of multiple components with different shelf lives and storage requirements.

**Increased Waste Generation**
Conventional large volume single-use filtration systems comprised of multiple filter capsules, manifolds and components generate disposable waste in the consumable itself but also a large amount of waste from shipping boxes and packaging material.

**Training and Expertise**
Complex assemblies with many process connections require a high level of operator knowledge, specialized operator training, comprehensive operating instructions and process documentation.

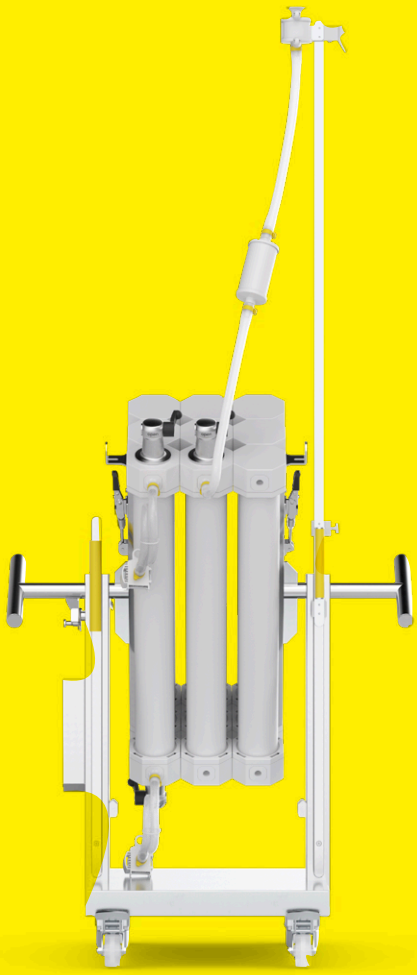
**Risk of Operator Error**
Assembling and configuring multiple components requires attention to detail and specific knowledge and poses an increase risk for operator error.

# Designing an Optimized Solution For Large-Volume Filtration

In response to industry's need for innovation and to address challenges in large scale filtration, Sartorius committed to the development of a ready-to-use single-use solution for large-volume filtration. The focus was on providing a standardized solution with a large effective filtration area (EFA) in a ready-to-use. single-use format with a high degree of design flexibility, while minimizing the complexity of installation and operation.

The result is the Maxicaps® MR — a novel technology for performing large-scale single-use filtration at clinical and commercial scales (Figure 2).

**Figure 2:** *The Maxicaps® MR is a Closed, Compact Solution for Large Scale Single-Use Filtration*



## Sartorius Developers' Key Focus Points

### Streamlined Assembly Process

Dealing with large (30-inch) filters, bulky manifolds, and multiple connections is challenging and introduces risk into the process. To solve this issue, the Maxicaps® MR was designed for fast and easy installation; it is pre-assembled via an innovative connection design that provides integrated fluid distribution. This advanced connection technology effectively replaces the manifold and reduces the amount of tubing by ~80%. The reduced connections are highlighted in Figure 3.

### Flexible Configuration

New developments in large-scale filtration systems must still offer the flexibility benefits associated with single-use technologies. Sartorius designed the Maxicaps® MR with configurability in mind: The system can accommodate a range of filtration areas, as between two and nine 30-inch filter capsules can be configured in a single filter module.

The system is also suitable for a broad range of modalities across different applications, including:

- Clarification
- Particle Reduction
- Bioburden Reduction
- Sterilizing Grade Filtration
- Mycoplasma Filtration
- Virus Pre-Filtration

### Reduced Environmental Impact

There is an ever-increasing focus on sustainability in the biopharmaceutical industry.[3] While single-use setups reduce water and energy consumption compared to stainless steel filter assemblies, the multiple individual components required create a significant amount of tubing and packaging. The single-unit design of the Maxicaps® MR significantly reduces plastic use within product design and limits overall waste production due to more efficient packaging methods. Consequently, the Maxicaps® MR uses up to 63% less material weight than a typical single-use filter assembly.

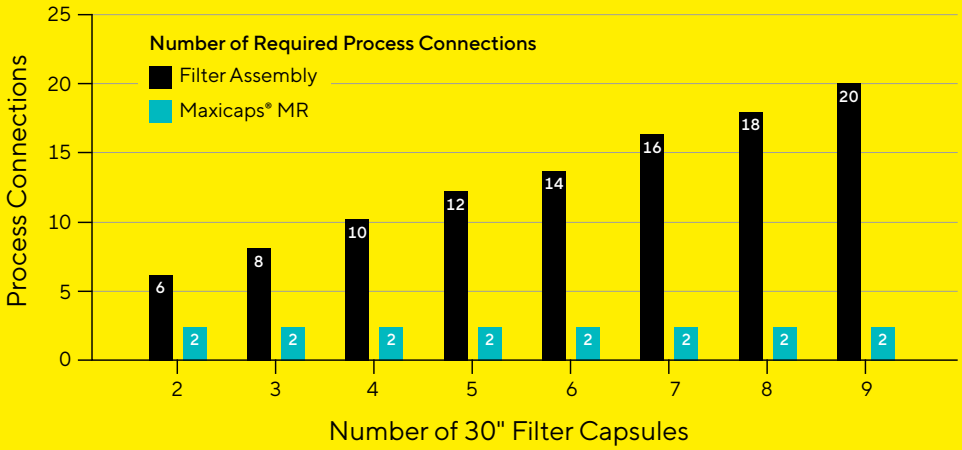
### Simplified Supply Chain

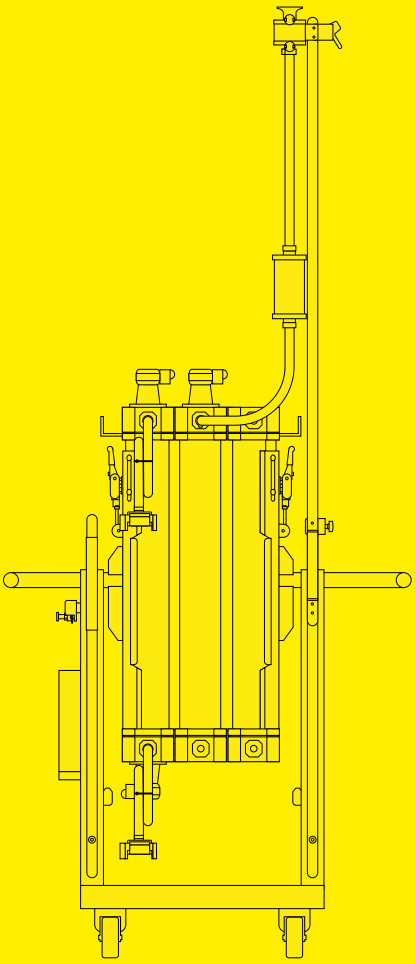
The pre-assembled nature of the Maxicaps® MR also offers the advantage of a single order code for the entire assembly. This eliminates the need to order and warehouse separate part numbers, simplifying the logistics of managing and handling all the components of the filter assembly.

### Reduced Risk

The fully closed system means contamination risk is reduced. Because it is pre-assembled, the operator only needs to perform two connections: inlet and outlet. This limits the opportunity for human error by reducing the number of connections and overall complexity of the assemblies (Figure 3).

**Figure 3:** *Comparison of Process Connections*



# Maxicaps® MR Supports Effective Quality Risk Management

Closed single-use filtration systems—such as the Maxicaps® MR—are delivered pre-sterile with pre-qualified components and connections to ensure they meet performance criteria and are compatible with the product being filtered.
This significantly reduces the time and resources required to perform in-house validation and qualification to comply with the latest guidance.

Documentation and technical support can also be provided to assist in risk assessment and implementation of the SU systems. This can include information on the materials of constructions, extractables & leachables, and comparability of process conditions. Finally, training can be provided to ensure the system is used in compliance with regulatory guidelines and avoid quality issues.

# Conclusion

Next-generation solutions are vital to keeping pace with the growing demands for efficiency across modern bioprocesses. These advances must be achieved while considering process sustainability, an increasingly important metric across the industry.

The updated Annex-1 guidelines emphasize the importance of quality risk management, including the design of facilities, equipment, and processes. It states single-use systems should be designed to minimize manual intervention.

Designed to reduce the need for manipulations and complexity of manual interventions, the Maxicaps® MR represents a paradigm shift in large-scale single-use filtration with its novel integrated connection and valve technology.

As such, the Maxicaps® MR represents a valuable alternative to traditional stainless steel and SU filtration systems, solving challenges associated with system complexity, footprint, and effective contamination control strategies. These advances create a more streamlined filtration process, effectively complying with sustainability goals and regulatory requirements.

# Author Bios

**Lucia Dinehart**
Product Specialist,
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Lucia is a Product Specialist with 20 years of experience supporting biotechnological manufacturing. In her current role, she is responsible for providing technical support and expertise in single-use solutions focusing on filter transfer sets.

Previously, Lucia worked for GE Healthcare and Amersham Biosciences, supporting large-scale chromatography applications. She was also a senior scientist at the Monoclonal Antibody/Hybridoma Core Facility at the University of Florida's Interdisciplinary Center for Biotechnology Research.

**Martine Barros**
Marketing Entry Strategy Manager,
Separation Technologies,
Sartorius

Since 2022, Martine has held the position of Marketing Entry Strategy Manager, in which she builds, develops, and executes go-to-market strategies for Sartorius solutions.

Martine joined Sartorius in 2018 as a filtration application specialist, providing technical knowledge across upstream and downstream filtration technologies. Previously, she worked at Oxford Biomedica as a biotechnologist and Lonza as a senior scientist in the Manufacturing Science and Technology (MSAT) department.

Martine holds an undergraduate degree in Biotechnology Engineering, a master's degree in forensic sciences, and post-graduate qualifications in mortuary science and marketing management.

**Andre Grebe**
Product Manager
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Since 2019, Andre has been a Product Manager for single-use filtration solutions at Sartorius, where he is committed to simplifying complex biopharmaceutical filtration processes and making them more sustainable.

Andre started his career as a junior process engineer in the world's largest Paclitaxel-producing plant cell fermentation facility before joining Sartorius in 1998. Throughout his time at Sartorius, Andre has been involved in product or platform management, focused on providing standardized and easy-to-use products to customers. He worked for 16 years as a Product Manager for bioreactors, followed by 5 years as Hardware Portfolio Manager for single-use systems.

He earned his biotechnology engineering degree at the University of Applied Science in Hamburg, Germany.

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**Katy McLaughlin**
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Katy is part of the Marketing Communications team at Sartorius, where she supports the creation of a variety of written pieces, from published articles to web content.

Before joining Sartorius in 2021, Katy was employed as a Post-Doctoral Research Associate at the University of Edinburgh, where she also completed her doctoral studies. Here, she carried out research in genetics and cellular biology and began taking on writing projects, eventually entering into a career as a freelance writer for various biotech companies and agencies.

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