3M™ HARVEST RC CENTRATE CHROMATOGRAPHIC CLARIFIER

Evolving the Role of Clarification in the Biopharmaceutical Manufacturing Process

FROST & SULLIVAN WHITEPAPER

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Introduction

The development and commercialization of novel modalities fuel growth in the biopharmaceutical production market. The need to move ever-expanding candidate pipelines from discovery to clinical use and to commercialization faster and more efficiently requires evolving and innovating manufacturing process strategy and technology. The next generation of manufacturing systems must be platformable across modalities, rapidly scalable up and out, and efficiently enable the commercialization of life-saving therapies beyond developed countries.

Qualitatively new bioprocessing strategies are the answer to this challenge, and these require novel process technologies designed from the ground-up rather than technologies carried over from other industries or incrementally improved legacy designs. The new solutions must effectively address specific bioprocessing challenges that are important now and in the future.

The biopharmaceutical manufacturing process involves engineered cells that express proteins of interest. While various cellular hosts continue to be used for biologic expression

systems, complex modalities—such as monoclonal antibodies (mAbs)—are produced in mammalian expression systems (typically Chinese hamster ovary [CHO] lineages). As a high titer of the biopharmaceutical is a critical parameter, the cell density and cell culture duration must be maximized. This creates increasing amounts of soluble and insoluble impurities that must be purified from the product during downstream processes. Impurity breakthrough greatly limits the ability to intensify and simplify future processes.

Legacy clarification strategies, typically centrifugation and depth filtration, rely on separation by density and size and suffer from inconsistent product recovery, lack of linear scalability along the product candidate development journey, and process complexity. Legacy processes are designed to remove insoluble impurities such as cell debris. However, these processes do not remove soluble impurities such as DNA and submicron particles that can impact the efficiency and effectiveness of subsequent downstream unit operations. Next-generation clarification solutions need to address these issues holistically and in a scalable fashion.

Challenges and Needs for Modern Clarification Solutions in the Biopharmaceutical Manufacturing Process

Challenges With Legacy Technologies

The clarification process for biopharmaceuticals has historically faced several challenges. While a centrifuge may be utilized to remove the bulk of cell mass and large cell debris, soluble impurities may remain post-centrifugation. Depth filtration, the use of multiple stages, and clarification at larger scales compound issues at hand due to different impurity profiles when centrifugation is included. As such, completely new clarification processes and modified downstream processes are needed. This will improve processing time, consistency, and robustness and will enhance predictable scalability. Once material needs (e.g., kg of mAb needed) or scale of the process (e.g., 1 L, 100 L, 10,000 L) become large enough, there is a need to move production or scale out the process, and transferring procedures involving a centrifuge often proves challenging.

Product Recovery

As the packed cell volume of the expression host increases, it becomes difficult to fully recover clarified fluid containing the biopharmaceutical without additional steps, such as excessive buffer chasing. This is inherent to the design of legacy clarification technology because wet-laid depth filtration media made of natural materials (e.g., cellulose) are inherently variable.[1,2] Additionally, recovering product from a clarification system with multiple stages is more difficult due to the increased system hold-up volume.

Scalability

Fluid quality post-clarification significantly impacts the design and execution of the downstream purification train and the resulting speed of candidate development, from discovery to clinical use and to commercial manufacturing. A scalable clarification system that can predictably address these processing needs is paramount. Existing clarification approaches cannot meet these needs because legacy clarification

1 Lutz, Herb & Chefer, Kate & Felo, Michael & Cacace, Benjamin & Piper, Rob & Zhao, Xiaoyang & Hove, Sarah & Wang, Bin & Blanchard, Mark & Oulundsen, George. (2015). Robust depth filter sizing for centrate clarification. Biotechnology progress. 31. 10.1002/btpr.2188.

2 Nejatishahidein, Negin & Kim, Minyoung & Jung, Seon Yeop & Espah, Ehsan & Fernandez-Cerezo, Lara & Roush, David & Borhan, Ali & Zydney, Andrew. (2022). Scale-up Issues for Commercial Depth Filters in Bioprocessing. Biotechnology and Bioengineering. 119. 10.1002/bit.28035.

technology cannot predictably scale from milliliters to tens of thousands of liters, as seen by today's processes. Manufacturers typically implement a complex patchwork of approaches and technologies, which can slow down process development, process scale-up, and technology transfer to manufacturing facilities.

Soluble Impurity Removal

As cell densities and the duration of cell culture increase, the concentration of soluble impurities increases. Ordinarily, removal of soluble impurities is relegated to downstream purification. However, excessive amounts of key impurities, such as DNA and the chromatin-DNA complex, can impact chromatography unit operation efficiency and effectiveness as well as make platforming of these technologies difficult.

Processing Time

Manufacturing productivity is a function of plant footprint and utilization. The processing time of each batch depends on the timely execution of unit operation in a manner that avoids process deviations and process interruptions. Additionally, avoiding inherently slow clarification strategies, such as centrifugation, can increase flexibility and facility utilization.

Facility Fit

The trend of increasing cell densities creates more cell mass and debris to remove, requiring a larger filtration bed volume to separate debris and other impurities. This places constraints on the ability to scale up, scale out, and rapidly transfer processes across internal manufacturing footprints and to external CMOs. Physical space to accommodate plumbing and utilities—such as buffers and water to flush filters—can become a limitation as processes become larger and more complex, lending credence to components that reduce water and electricity consumption.

Platform Processes

Clarification systems designed for a particular process may require replacement or retrofit when being repurposed for other pipeline candidates, especially those of different modalities. The preferred solution is to "platform" technologies or processes, meaning one system can handle multiple candidates in a pipeline. An alternate system or process will be investigated if the platformed technology doesn't work for a particular candidate. With a platform that works across multiple modalities and can address future challenges, the biopharmaceutical industry can rapidly push candidates through to commercialization.

Industry Needs

As cell densities and resulting production scales increase to meet patient demands, several harvest and clarification needs have emerged. For example, increasingly reliable, robust, and cost-effective solutions are required because current technologies have limitations in scalability, processing speed, and ease of use due to technology understanding. Tech transfer between manufacturing suites or sites should be seamless; clarifying a large 2,000 L batch, for example, needs to be comparable to the smaller research scale and larger commercial scale potentially done at a different site. Next-generation systems should be able to handle challenging feed streams, be fully integrated, and use regulatory-compliant technologies. Clarification processes should be designed with the following considerations in mind:[3]

- **Reduced operator exposure and bioburden control**—Fully enclosed primary harvest operations can help reduce room classification requirements. Current harvest operations are not fully closed, which requires the operation to be done in a classified space.
- **Low physical footprint**—Facility fit is increasingly important as scale increases and more filtration area is needed.

3 https://www.biophorum.com/download/process-technologies/

- **Minimal environmental impact**—Clarification systems with lower flush volumes lead to both lower water and energy requirements, helping from both sustainability and operational angles.
- **Rapid turnaround**—Decreased time at various steps ultimately leads to faster time to market. For example, the use of disc-stack centrifuges (which are critical in large facilities) comes with concerns about cleaning, and changeover can be extensive and time-consuming.
- **Increased step yields**—Each step in a clarification train can reduce overall yield. Product loss can occur during cell bleed, in the discharge stream of the centrifuge, or during filtration.
- **Impurity removal**—Host cell proteins, nucleic acids, lipids, and viral contamination must be removed, and while current filters remove some of these impurities, improved feed streams with reduced impurity loads for capture steps can improve performance.

Considering the existing challenges and needs of biopharmaceutical clarification, Solventum (formerly 3M Health Care) developed the 3M™ Harvest RC Chromatographic Clarifier and 3M™ Harvest RC Centrate Chromatographic Clarifier. Together, these are considered the 3M™ Harvest RC Chromatographic Clarifier platform. These novel clarification solutions are based on anion exchange (AEX) fiber chromatography and address variability in feed streams, resulting in a consistent effluent from both a particle size and key soluble impurity removal standpoint. Aside from improved fluid quality, other Solventum solution benefits include seamless scalability, process compression, and reduced preconditioning flush volumes when compared to legacy depth filtration technologies. When combined, these products constitute a platform solution, enable the use of the same technology from drug discovery to commercial manufacturing scale, and address many existing and emerging industry needs.

Evolution of Cell Culture Harvest Clarification Technology

As companies look to improve production productivity for mAbs and other biopharmaceutical products, cell productivity and cell density are on the rise due to increasing demand. These trends produce specific challenges for the downstream process, including more solids that need to be removed during clarification and a higher concentration of soluble impurities, which increases the burden on downstream unit operations.

Clarification utilizing AEX fiber chromatography enables high product recovery (greater than 95%), scalability from discovery to manufacturing, and high separation fidelity (less than 15 NTU with DNA reduction to less than 500 ppb), even at packed cell volumes higher than 5%.
The ability to remove whole cells and much smaller soluble impurities, like DNA and chromatin-DNA complexes, creates downstream benefits of simplified processes and longer unit operational life.

Additionally, downstream efficiencies can be improved by replacing multi-stage depth filtration with the single-stage 3M™ Harvest RC Chromatographic Clarifier. For example, in CHO cell culture clarification, benefits include a 17% to 30% overall cost reduction and 25% relative increase in cumulative yield.[4] Manufacturing cost of goods savings stem from reduced total filtration area, labor, time, and utilities. The use of chromatographic clarification, which is foundational to the 3M™ Harvest RC Chromatographic Clarifier product, also provides benefits to subsequent filtration and purification stages because it can increase Protein A resin lifetime and may reduce the number of later polishing chromatographic steps—this would remove host-cell proteins that often co-purify with mAbs.[5]

4 https://aiche.onlinelibrary.wiley.com/doi/10.1002/btpr.3323
5 https://www.sciencedirect.com/science/article/pii/S0021967319302110

While the 3M™ Harvest RC Chromatographic Clarifier provides consistent results at various scales, it is limited to the manufacturing facilities designed for direct clarification without the use of centrifugal cell mass separation. To enable seamless transfer, scale up, and scale out of manufacturing processes at clinical and commercial scales across manufacturing footprints, Solventum recently expanded its technology with the introduction of the 3M™ Harvest RC Centrate Chromatographic Clarifier. The new solution has similar benefits as Solventum's chromatographic clarification solution for direct clarification processes, but is designed for the clarification of centrate. 3M™ Harvest RC Centrate Chromatographic Clarifier can replace all depth filtration stages and guard membranes in centrifuge processes and provides protection for sterilizing filtration stage down to 0.1 µm. As the 3M™ Harvest RC Centrate Chromatographic Clarifier utilizes the same functional fiber technology as 3M™ Harvest RC Chromatographic Clarifier, there is seamless scale-up with little to no tech transfer burden. This means consistent performance can be achieved from the chromatographic clarification platform's innovative well plate devices through multiple process holders of production scale capsules capable of handling more than 10,000 L batches with high clarification fidelity. The high throughput and single-mode AEX clarification mechanism enables over 95% product recovery in a typical mAb harvest scenario, which enables rapid movement of pipeline molecules through the drug commercialization process due to scalability and consistency, ultimately impacting the overall time to market.

Evaluation of the Benefits of 3M™ Harvest RC Chromatographic Clarifier and 3M™ Harvest RC Centrate Chromatographic Clarifier

Developments in upstream cell culture processes have led to the realization that downstream technologies have not kept up, as seen through inconsistent product recovery, increased complexity, and increased purification train cost. The value that the 3M™ Harvest RC Chromatographic Clarifier platform provides to CHO cell culture harvest and clarification comes in many forms, including consistent results, ease of use, time savings, improved process economics, and sustainability. This legacy-free, all-synthetic, and all-encompassing platform can be used from the discovery phase to large-scale commercial production, derisking process development, facilitating seamless tech transfer, and decreasing overall process development time.

Consistent Results

Comparable effluent quality across development phases is achieved through the use of 3M™ Harvest RC Chromatographic Clarifier and 3M™ Harvest RC Centrate Chromatographic Clarifier. In the case of the former, the tailored AEX fiber chromatography matrix leads to excellent turbidity reduction (to less than 15 NTU) and efficient capture of DNA and DNA aggregates like chromatin (reduced to less than 500 ppb), which are removed just as efficiently as cells by the technology—a feat not possible with traditional depth filtration. The latter includes a combination of a tailored AEX fiber matrix and AEX functional 0.2 µm polyamide membrane to efficiently reduce the artifacts of disc stack centrifugation, such as particles less than 0.5 µm while providing the same DNA and turbidity reduction as the 3M™ Harvest RC Chromatographic Clarifier.

Ease of Use

Aside from eliminating multiple depth filtration steps, 3M™ Harvest RC Chromatographic Clarifier and 3M™ Harvest RC Centrate Chromatographic Clarifier are straightforward to use and do not need post-use cleaning. Utilizing the 3M™ Harvest RC Chromatographic Clarifier platform for both direct clarification and centrifuge clarification processes will provide comparable effluent quality so that downstream activities will not need modification. Additionally, the production scale devices of the 3M™ Harvest RC Chromatographic Clarifier platform are compatible with 3M™ Encapsulated System Holders, which allows capital equipment to be repurposed for an easy transition to this technology.

Time and Cost Savings

Switching from depth filtration to the 3M™ Harvest RC Chromatographic Clarifier platform would eliminate the need for clarification train optimization, a time-consuming and potentially frustrating process. Other downstream modifications may also be reduced, as robust impurity removal improves downstream unit operations and process economics. Compared to multi-stage depth filtration clarification processes, the single-stage 3M™ Harvest RC Chromatographic Clarifier platform can provide up to 30% cost savings.[4]

Sustainability

3M™ Harvest RC Chromatographic Clarifier and 3M™ Harvest RC Centrate Chromatographic Clarifier utilize separation media constructed of precision grafted synthetic fiber material followed by a synthetic membrane. This is in contrast to traditional depth filtration, which is constructed of wet-laid media containing natural materials like cellulose. The result is that the 3M Harvest RC Chromatographic Clarifier platform reduces preconditioning flush volumes by up to 50% when compared to depth filtration, leading to energy and water savings.

Solventum as a Partner for Harvest Clarification in Biopharmaceutical Manufacturing

The 3M™ Harvest RC Chromatographic Clarifier platform has revolutionized clarification unit operation for biologics manufacturing. As biologics processes increase in complexity, packed cell volumes rise, feed streams become challenging, and high product recoveries become increasingly important. An optimized and simplified clarification train can improve product quality, yield, and overall process economics. Simplified bioprocessing can be realized through process intensification and advanced technology innovations that are available for next-gen bioprocessing solutions.

When selecting a clarification technologies supplier, a true partner can make all the difference in realizing the full range of benefits. These include trial and evaluation support, ensuring the appropriate system is in place, optimized, and ready to handle even challenging feed streams.

Solventum strives to be this partner and deploys a global network of application engineers who are well-versed in understanding industry issues and goals. They provide on-site technical support and troubleshooting at no cost—before or after purchase—and help develop and optimize its solution's processes. Solventum's application engineers can help determine process parameters such as optimal flow rate and filter sizing, as well as characterize impurity profiles, provide product training, and support technology transfer to internal and external entities.

Additionally, the predictable linear scalability across the 3M™ Harvest RC Chromatographic Clarifier platform can enable the streamlining of clarification process development, de-risking technology transfers, and provides seamless integration into existing infrastructures.

Solventum is ready to be a reliable partner in improving biopharmaceutical clarification and purification. For more details about Solventum, visit go.solventum.com/harvestrccentrate to learn more.

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