Powering clients to a future shaped by growth

A Frost & Sullivan White Paper

3M™ Harvest RC
Powering Single Stage Clarification

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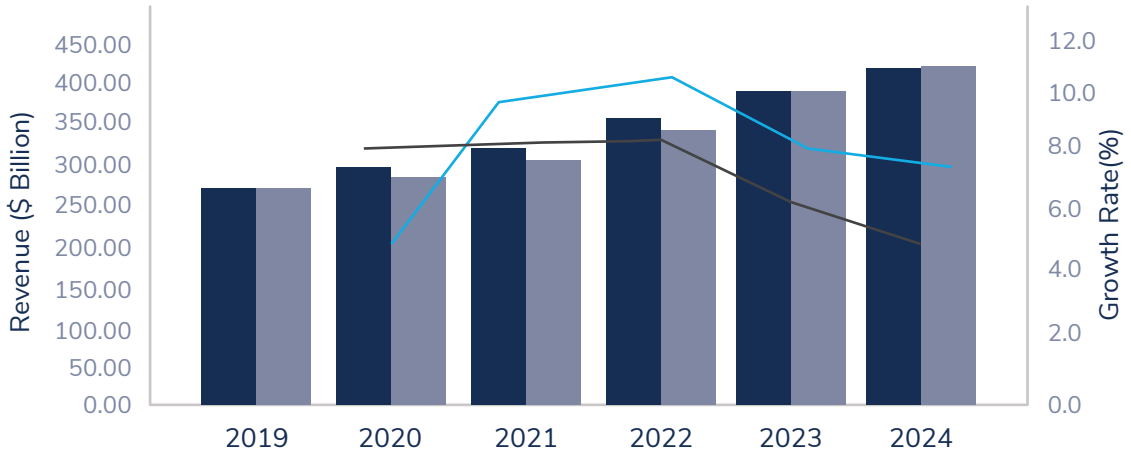
Monoclonal Antibody Therapies Transforming the Global Biologics Market

Advances in recombinant deoxyribonucleic acid (DNA) technologies have facilitated large-scale manufacturing of biologics products such as human growth factors, monoclonal antibody therapies (mAbs), and fusion proteins. In addition, improvements in analytical technologies have enabled improved characterization of macromolecules, including proteins and nucleic acids. This allows for the screening and identification of novel biologics with complex structures and various therapeutic functions. As a result, a number of biologics, including Humira®, Keytruda®, Opdivo®, Enbrel®, Eylea®, Avastin®, Stelara® and Rituxan®, accounted for the largest sales revenues in 2019 (Source: Evaluate Pharma and Frost & Sullivan Analyses).

The global biologics market is expected to grow from $284.08 billion in 2019 to $419.66 billion in 2024, registering a CAGR of 8.1% (Figure 1). Coronavirus 2019 (Covid-19) is expected to drive down market revenues in the short term due to delays in product launches and a decline in sales revenue of drugs. However, the development of Covid-19 vaccines and therapeutic drugs targeting the virus will have a positive impact on the recovery of the global biologics market over next five years.

Figure 1: Global Biologics Market: Revenue Forecast 2019–2024



	2019	2020	2021	2022	2023	2024
Pre-Covid-19	284.08	308.70	334.66	364.03	389.42	413.08
Post-Covid-19	284.08	298.43	328.14	361.76	391.68	419.66
Pre-Covid-19 Growth Rate	-	8.7	8.4	8.8	7.0	6.1
Post-Covid-19 Growth Rate	-	5.1	10.0	10.2	8.3	7.1

Source: Frost & Sullivan

The clinical stage pipeline of more than 1,000 candidates and remarkable success in the oncology, central nervous system, and metabolic segments has fueled the revenue dominance of mAbs. These therapies will continue to generate the highest revenue among all sub-segments of biologics during 2020-2024.

Producing mAbs consistently at commercial scale is both a complex and expensive process with sales per gram ranging from $1,000 to $50,000 depending on the dosage. Such high costs and variability has put biopharmaceutical companies under pressure to improve manufacturing plant productivity (5–10 gram/liter).

Biopharmaceutical companies have rapidly adopted single use technologies to increase flexibility on batch volumes (2000–6000 L, depending on the application), decrease capital cost, and reduce footprint because of their improved designs. Limitations around scaling capacity and articulate purification requirements pose risk factors as the latter is critical in the final protein manufacturing steps where no further filtration is present.

This paper outlines the value proposition of 3M™ Harvest RC technology, a platform that allows the clarification and polishing train from discovery to commercial manufacturing to be simplified in a more intuitive way.

Rising demand for new monoclonal antibody therapies, stringent requirements to achieve consistent quality, and most importantly, focus on higher productivity is driving biopharmaceutical companies to optimize their downstream processing operations. The typical mAb manufacturing process has several steps, including multiple clarification stages which are the first steps of the purification process. The clarification train, if not properly designed, negatively impacts yield, purity, and cost.

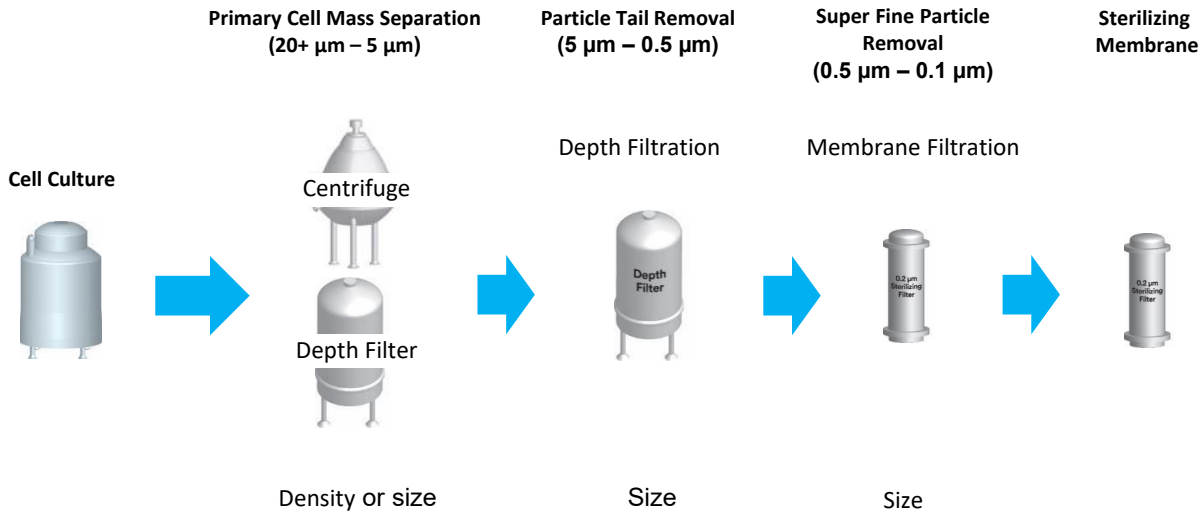
1 3M™ Harvest RC: The Need to Re-imagine Clarification

Briefly, the primary goals for harvest and clarification operations are to remove cells and cell debris from mammalian cell culture, and further clarify the resulting product in order to capture the mAbs via chromatography downstream.

In cell cultures, it is essentially a slurry of contaminants varying in different sizes and shapes. They can range from the host cells to cell debris to much smaller particulates such as DNA, viruses and proteins. As the stream becomes cleaner and purer, the level of separation gets harder as operators/scientists start dealing with soluble contaminants and particle sizes that cannot be removed by simple filtration.

Traditionally, various technologies are used for clarification processes such as centrifugation, tangential flow filtration (TFF), depth filtration, and microfiltration. These methods exploit the differences in “size” to remove large particles such as cells and cell debris.

Figure 2: Legacy Clarification Strategy



Source: 3M

However, the need to achieve higher concentration, compress operations timelines, and increase mAb purity and safety has prompted operators/scientists to carefully evaluate the limitations of these technologies.

The fact that centrifugation may damage sensitive mammalian cells and release undesirable intracellular proteins and DNA is a common challenge. Although operators/scientists have found that TFF and depth filters can reduce this risk, they struggle with large set up times and are beset with large flush volumes to eliminate extractables. Operators/scientists also worry about the versatility of these technologies for single use bioreactors.

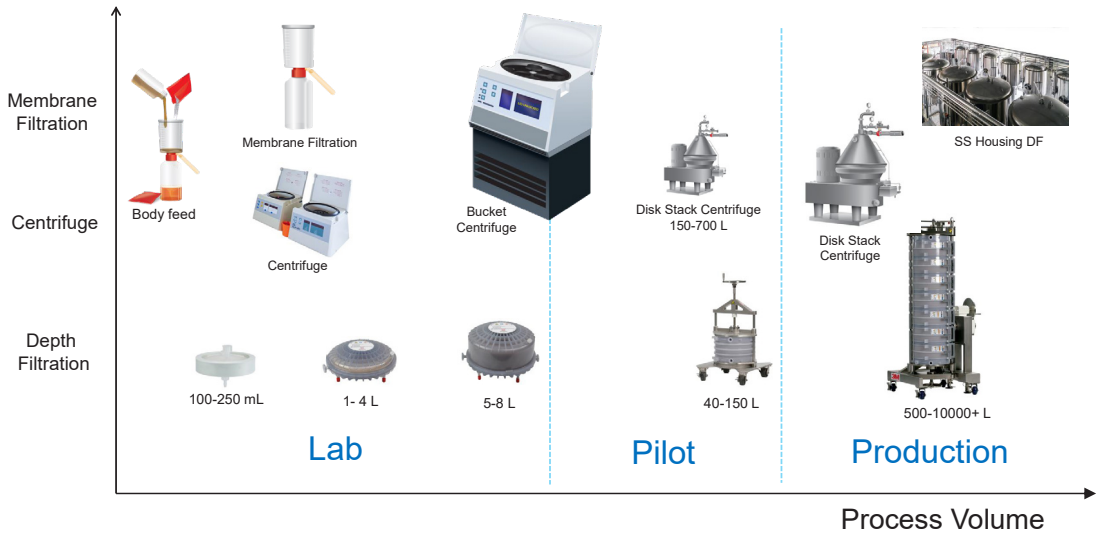
Finally, a major drawback with the current clarification strategies is that there is no single approach that can span across discovery to manufacturing scale. As a result, it is imperative that operators/scientists examine porous chromatography platforms to get further separation during the capture and polishing steps to truly achieve the resolution and purification levels needed.

Current bioreactor processes producing mAbs with higher drug titers and yields increase cell debris and raise concentrations of organic constituents. The colloidal characteristics of such components severely impede the separation process.

There are different scales of clarification technologies: depth filters, centrifuges, and membrane filters that exist for clarification. The onus is on operators/scientists to work with a combination of these different technologies in order to arrive at the downstream purification steps (Figure 2). The choice of these technologies must also take the requirements for integration with downstream processes, such as ultrafiltration, into account.

As the scrutiny on purification levels rises, operators/scientists will have to be more careful and vigilant in managing variable and unpredictable filtration outcomes from discovery to manufacturing stages. Therefore, operators/scientists will have to consider other approaches that span the entire process scale space.

Figure 3: Current Clarification strategy from Discovery to Manufacturing



Source: 3M

It is now much-discussed that the traditional approach of looking at purification and separation in terms of "size" can be reimagined based on "charge." This means that operators/scientists can visualize mAbs as positively charged while most of the contaminants, viruses, and cell/cell debris (due to the lipid bilayer and their phosphate groups) can be viewed as negatively charged.

Until recently, this approach was exploited on a limited basis. For example, improved consistency and predictability across different cell culture streams has been very well demonstrated by using a traditional approach (centrifugation or depth filter) combined with a chromatography platform such as 3M™ Emphaze™ AEX Hybrid Purifier.

In the long run, chromatography's ability to advance single stage clarification platforms capable of removing all contaminants by "charge" will support biopharmaceutical industry's move into compact flow through single use clarification and polishing trains.

As cell line development and cell culture engineering continues to accelerate, so do the opportunities to enrich discovery, clinical and manufacturing programs with innovative clarification technologies. To capitalize on this potential, there are certain key steps biopharmaceutical companies can take to evaluate the relevance of fiber chromatography technologies such as 3M™ Harvest RC and build the competencies required to leverage them to best effect.

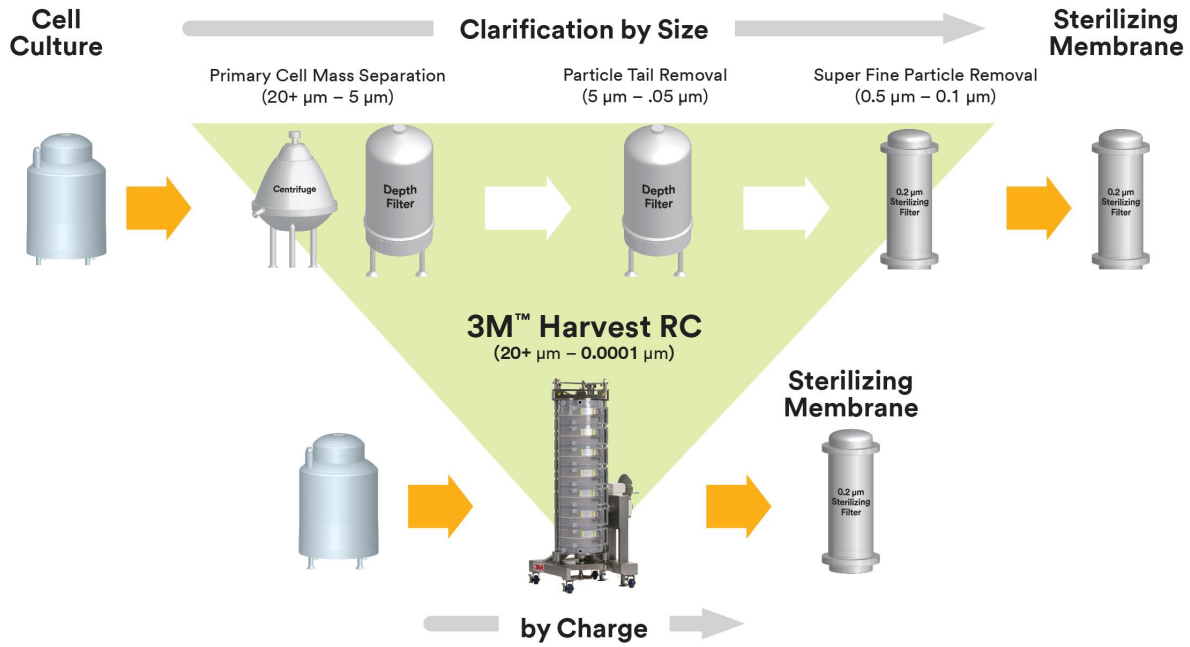
Producing mAbs consistently at commercial scale is both a complex and expensive process with sales per gram ranging from $1,000 to $50,000 depending on the dosage. High costs and variability has put biopharmaceutical companies under pressure to improve manufacturing plant productivity by increasing titer (5–10 g/L) and cell densities >20 × 10 6 cells/mL. Limitations around scaling capacity and higher densities necessitate more sophisticated purification steps using advanced materials.

2 3M™ Harvest RC: Establishing Value of Single Stage Harvesting

3M™ Harvest RC is a chromatography-based clarification technology using 3M's proprietary fibrous (synthetic) material that is truly scalable ranging from discovery phase all the way to manufacturing.

This technology will have separation capabilities that have never been seen before; not only for small particles but also larger particles from several microns to ten and twenty microns for capture of whole cells and cell debris.

Figure 4: 3M™ Harvest RC – Simple Single Stage Harvesting



Source: 3M

3M™ Harvest RC will not have to operate as an island, but as a component of a much larger connected bioprocessing system. On a day-to-day basis, the most immediate effects of 3M™ Harvest RC will be noticed in its ability to achieve chromatographic separation of large particles.

With the capacity to support single stage clarification spanning across a wide range of cultures with different cell densities, packed cell volumes and cell culture characteristics, this technology will be able to achieve predictable performance, without operators/ scientists having to program every step.

3M™ Harvest RC offers a sand box approach; providing the ability to purify both large and small contaminants and soluble and insoluble particulates, which are both imperative to improve yield in biopharmaceutical manufacturing.

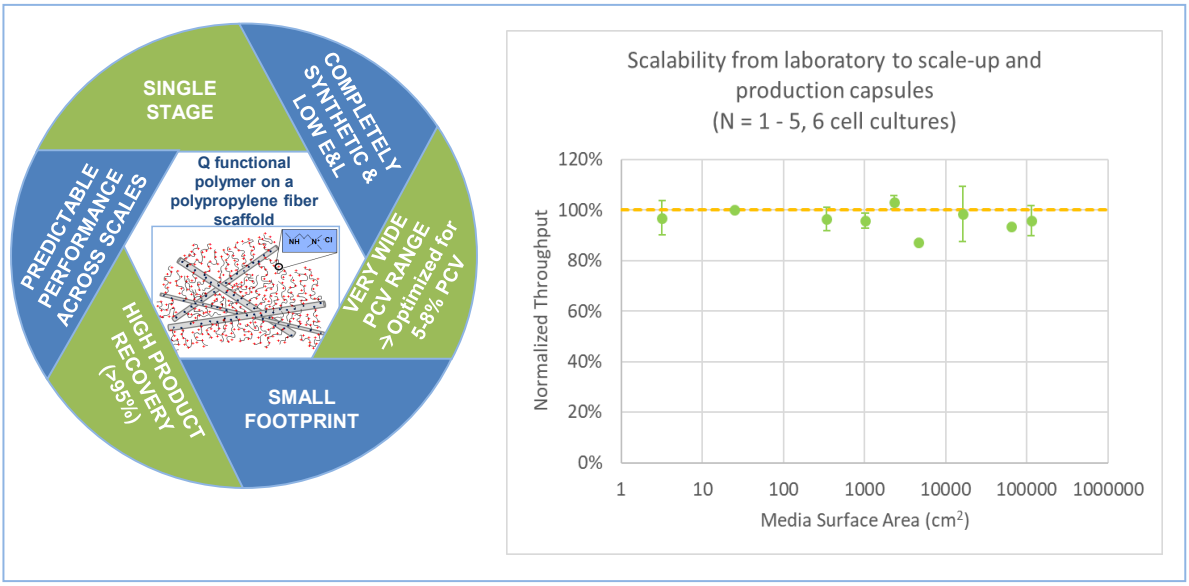
Based on several advantages listed in Figure 5, 3M™ Harvest RC was able to get a very high yield and product recovery with almost greater than 95% product yield across the board with several different mAb cell cultures at high packed cell volume (PCV) of 5 – 8 %. This is an impressive result as it is almost unimaginable to attain recovery close to 85 to 95% with other traditional clarification technologies such as centrifugation and depth filtration.

Figure 5: Why this technology will be a game changer?

3M™ Harvest RC
BC16000 Capsule
Media surface area : 1.6 m^2
Clarification capacity : ~ 8 L of solid

3M™ Encapsulated System Holder
Capacity : 7 BC16000 capsules
Media surface area : 11.2 m^2
Clarification capacity : ~1000 L @ 5-6% PCV
Clarification time : <1 hour

Source: 3M



Source: 3M

It may sound like 3M™ Harvest RC is just another iteration of improved traditional clarification technologies such as single use centrifugation systems or synthetic depth filters. However, past improvements from traditional clarification technologies have not moved the needle enough to compress purification timelines or increase product recovery rates compared to what 3M™ Harvest RC has demonstrated.

3M™ Harvest RC's potential goes beyond increasing yield limits and product recovery rates. The other consideration and probably more significant benefit is the technology's ability to be seamlessly deployed in a predictable manner at any scale (small and large).

As shown in Figure 5, 3M™ Harvest RC technology's one large scale capsule would have 1.6 square meter of filter area which corresponds to about 8-9 L of solid capacity. This basic unit architecture will then allow 7 capsules to be put together, allowing operators/scientists enough solid capacity to clarify 1000 L with around 6% PCV.

3M™ Harvest RC solution scales linearly across lab, pilot, and manufacturing scales. Fibrous chromatographic clarification assures scalable performance from discovery to manufacturing. Performance is consistent from lab capsules (BC4 and BC25), to pilot capsules (BC340 and BC1020), to manufacturing capsules (BC2300 and BC16000) within ±20% of BC25 throughput. This significant leap to extract the same performance and throughput whether it is at bench scale, one capsule scale or multiple capsules for one fully loaded holder, is nothing short of revolutionary.

Based on differential test results (factors listed in Figure 5) it is clear that 3M™ Harvest RC technology will eventually replace DFs by 2030 due to its ability to support single stage clarification spanning across a wide range of cultures with different cell densities, packed cell volumes, and cell culture characteristics. These results will have profound implications for operators/scientists, who can now take advantage of 3M™ Harvest RC technology and set ambitious goals in terms of scalability, fidelity, and predictability.

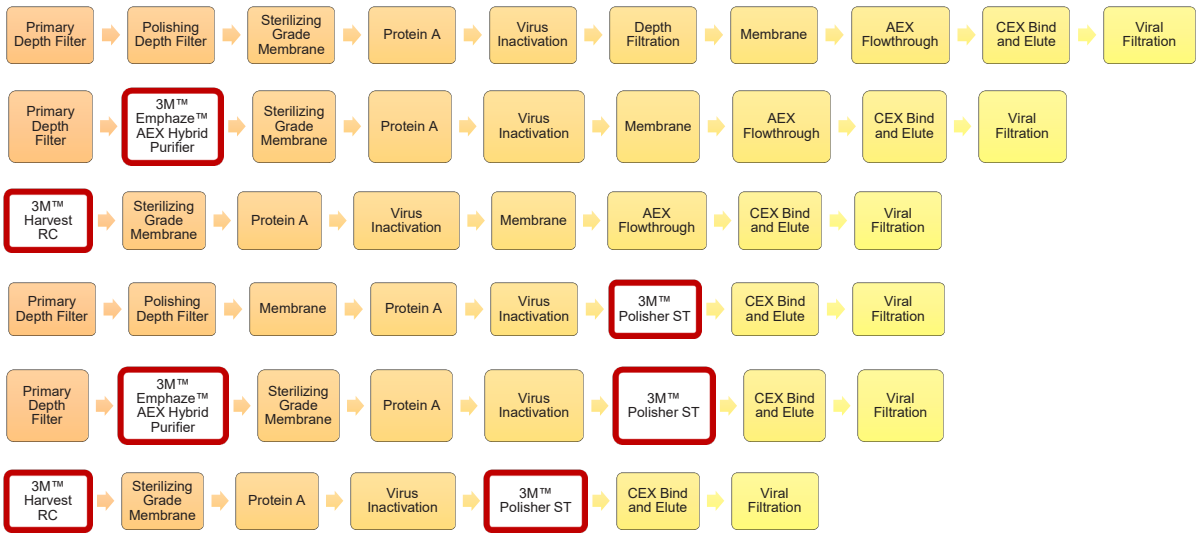
The biopharmaceutical industry is faced with challenges to meet demand for intensified bioprocessing of mAbs and must embrace operational excellence strategies. First and foremost is a pivot that embraces "single-product or multi-product" capacity management as a catalyst for better utilization on manufacturing footprint, which requires facility flexibility. In order to achieve this, biopharmaceutical industry's priorities must lie in shortening product changeovers or downstream processing times and looking at every step in the process to reduce manufacturing costs.

3 3M™ Harvest RC: Process Economic Analysis

Biopharmaceutical companies looking to future-proof their clarification strategies from discovery to manufacturing stages, must recognize the potential of 3M™ Harvest RC. Its scalable, high yield quality, and ease of deployment across discovery to manufacturing are set to revolutionize the bioprocessing world. Let's examine the cost benefits of 3M™ Harvest RC and how this promising technology will supercharge single use clarification and polishing trains.

Direct experience using an industry standard platform (BioSolve™) enabled 3M to model the impact of inclusion of 3M™ Harvest RC technology on bioprocessing costs of goods sold (COGS). 3M investigated a total of six processes (Figure 6).

Figure 6: Impact of 3M™ Harvest RC & 3M™ Polisher ST on Bioprocessing



Source: 3M

The first process is a typical mAb purification process. The sixth process is the next generation process that includes 3M™ Harvest RC technology & 3M™ Polisher ST technology. It is evident that the practical impact of the changes from first to sixth process by introduction of these two technologies has made the process simpler. In these model scenarios that show gradual reduction in steps by intensifying the anion-exchange chromatography (AEX) polishing step and then the harvest step, there was an increase in the yield accompanied by an overall cost of good reduction of about 30%.

3M further analyzed impact on mAb COGS and capacity across the six processes (Figure 7a & 7b).

Figure 7 (a): Impact on mAb COGS

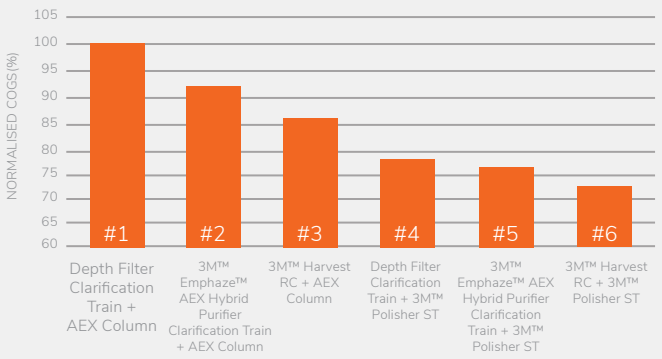
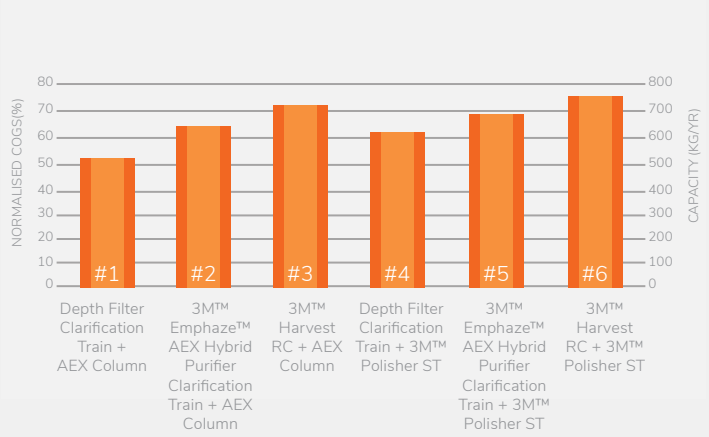


Figure 7 (b): Impact on mAb Capacity



Source: 3M

Figure 7 (a) shows the (normalized) cost per gram of manufacturing for mAb product and measures relative changes between the different process iterations. It is clear that as unit operations get smaller, the process becomes more efficient. There is reduction in COGS through the different process iterations and overall the difference in COGS between process one and process six is approximately 30%.

Figure 7 (b) shows the capacity to manufacture mAb product (kilograms per year) and which is plotted for each of six processes. The results show that there is an upward trend in mAb manufacturing capacity. This indicates that with each iteration, it is feasible to produce more mAb in the process, driven by increased yield in downstream processing.

In conclusion, it is important to note that the overall cost of the process is decreased when high performance single use technologies are implemented. Yield is also important in terms of reduced cost of goods resulting from implementing the high performance solution and combining multiple steps, and also in terms of increasing facility flexibility.

3M brings a world class approach and a suite of technologies to fulfill these growth opportunities. 3M™ Harvest RC is being tested in different mAb clarification trains and will be on target to eventually replace centrifugation, tangential flow filtration (TFF), depth filtration, and microfiltration in many mAb process trains. This is an excellent opportunity for biopharmaceutical companies to clear the bar on investments in new clarification technologies and demonstrate a significant increase in return on assets/investment (RoA/RoI) and plant productivity.

Single Stage Harvesting: Breaking ground for New Growth Opportunities

Biopharmaceutical companies face numerous challenges to meet demand for intensified bioprocessing of mAbs. As the development of single use bioreactors continues to accelerate, so do the opportunities to enrich discovery, clinical and manufacturing programs with single stage clarification technologies. To capitalize on this potential, there are certain key steps biopharmaceutical companies can take to evaluate the relevance of fiber chromatography technologies such as 3M™ Harvest RC and build the competencies required to leverage them to best effect.

First and foremost is a pivot that embraces “single-product or multi-product” capacity managment as a catalyst for better utilization on manufacturing footprint. Secondly, the biopharmaceutical company’s priorities must lie in shortening product changeovers or downstream processing times and looking at every step in the process to reduce cost of goods sold.

3M brings a world class approach and a suite of technologies to fulfill these growth opportunities. The approach relies on well-tested strategies to achieve very high purity early in the process train and then simplify by reducing the number of required steps. The technology portfolio enables replacing multi-use unit operations by robust single use solutions that drive efficiency and reduce the total cost of ownership.

The 3M™ Harvest RC is being tested in different polishing mAb process train layouts and will be on target to eventually replace centrifugation, tangential flow filtration (TFF), depth filtration, and microfiltration in any mAb process train, no matter the conditions. This is an excellent opportunity for biopharmaceutical companies to clear the bar on investments in new clarification technologies and demonstrate a clear increase in return on assets/investment (RoA/RoI) and plant productivity.

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WPD-2021

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