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Application Note

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Intensifying a mAb Polishing Platform – Targeting Time, Cost, and Space Efficiency

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Abstract

The growing utilization of highly efficient cell lines and optimized upstream processes continue to raise upstream monoclonal antibody (mAb) titers, amplifying inefficiencies in chromatography operations. There is widespread acknowledgment that process intensification presents the best solution to solve challenges related to low productivity, high resin costs, long process timelines, and large facility footprint. It is assumed by traditional process owners, innovators, and CDMOs that implementation of process intensification approaches means incurring risk due to significant process changes, reconfigured manufacturing setups, and huge investments. This concern is unsurprising, as large biopharmaceutical companies have their processes set in stone and are limited by regulatory approvals; small biopharma companies and start-ups have investment limitations and need a cost-oriented process development approach.

At Sartorius, we encourage the industry to re-imagine chromatography by demonstrating that small and easy-to-implement changes could significantly improve process output, speed, and facility footprint. We welcome collaborations with our customers for more hands-on and customer-oriented research and industrial developments. This application note presents a platform that was established in partnership with Enzene Biosciences Ltd. and is a simple process development study showing how a mAb purification batch process can be converted into a stepwise intensified batch process using Sartobind® Q and CMM HyperCel™, achieving elimination of intermediate steps and more than13% cost reductions at the polishing | secondary purification steps.

ENZENE Biosciences Ltd.

Introduction

mAbs are key therapeutic molecules and serve a range of critical medical applications. The technology for mAb purification has been well established in the last decade and typically relies on Protein A-based affinity chromatography for capture followed by two ion-exchange or hydrophobic resin-based polishing steps, which help remove the undesired product- and process-related impurities further to improve the quality of the drug substance for therapeutic formulation. However, continuous improvement is essential to meet the rising demand for mAbs.

In a fast-growing biopharmaceutical world, accelerated, flexible, and cost-effective manufacturing has become essential to address challenges in therapeutic manufacturing. Process intensification (PI) — a holistic framework to maximize the overall productivity of the unit operation(s), the manufacturing process and | or the facility output — is one of the key approaches for targeting high efficiencies. However, there is a misconception that process intensification is an all-or-nothing strategy, requiring significant changes to the existing process to realize its benefits.

For mAbs, chromatography steps have been the area of focus for downstream productivity improvements.[1] Resin-based chromatography matrices have been well established for affinity and flow through polishing steps due to their higher yield and effectivity in clearing impurities such as DNA, host cell proteins (HCP), and viruses. However, resins pose limitations due to their lower binding capacities, diffusion limitations, the requirement of intermediary buffer adjustment steps, risk of column packing failures and quality, and process risk associated with re-use over multiple batches or campaigns. Higher capacity single-use stationary phases like membranes have the potential to address these issues.

Another area for improvement is to reduce intermediate holds in the process. Intermediate holds can increase facility footprint and cause delays due to mixing times and pretreatment (adjusting pH or conductivity) required before loading the next polishing step. The implementation of these solutions comes under the umbrella of PI,[2] as they enhance the effectiveness of the existing process steps.

Process Intensification Levels

To help with the real-life implementation of process intensification as part of continuous process improvement, we have defined four different levels of PI strategies, from a basic batch process (Level 0) to a continuous process (Level 3), (Figure 1). A basic batch process is a conventional resin-based procedure in which the operations are scheduled to run consecutively. It is currently employed in most facilities and has significant scope for intensification.

In level 1 intensification, an individual operation or number of operations in the process train are targeted to increase cost efficiency and productivity. For a level 2 intensification process, two or more operations are connected to each other to run in parallel with overarching automation. This reduces processing time substantially as shown the Figure 1. Level 3 intensification is achieved if and when a continuous process with a steady state operation for all the process operations can be adopted. Applying level 2 and 3 intensification strategies can reduce the downstream process time significantly, for example, from 75 hours for a batch process to less than 30 hours.

Sartorius has developed a range of technical solutions and support services to help our partners build intensified processes with our equipment and consumables.

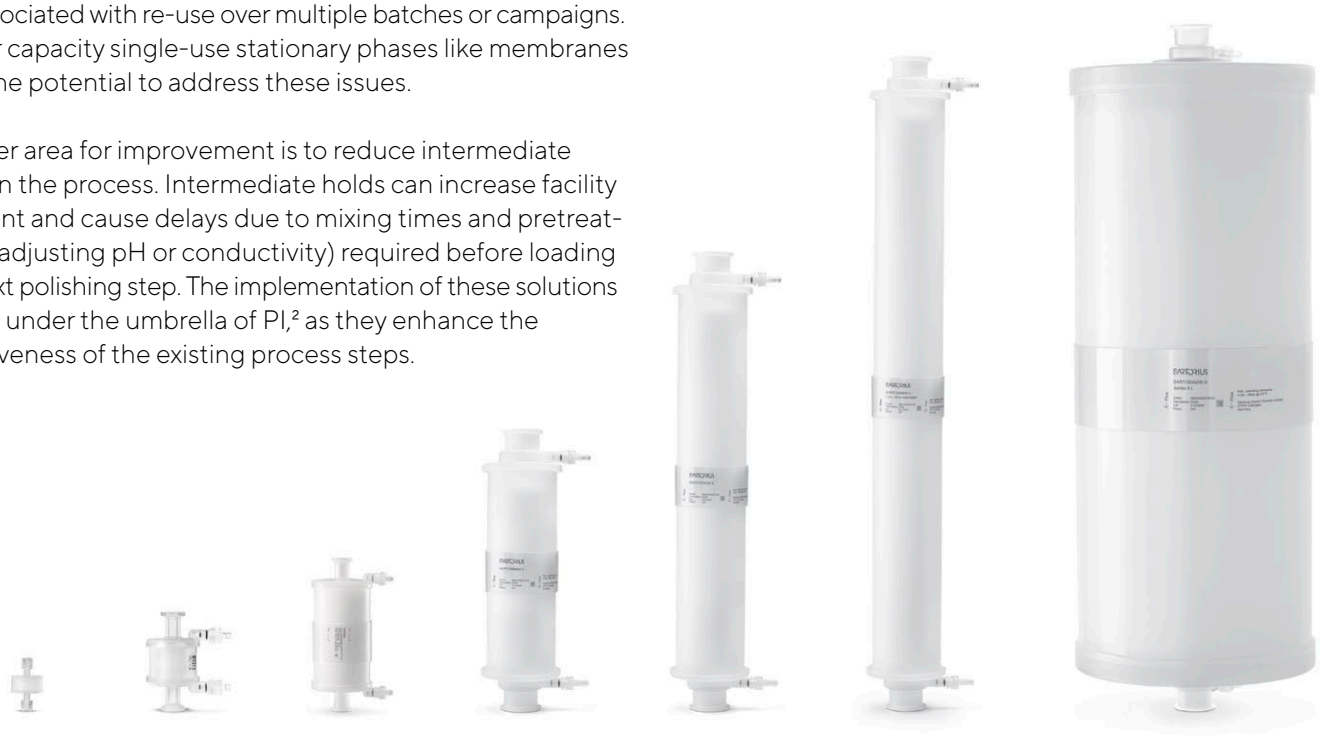
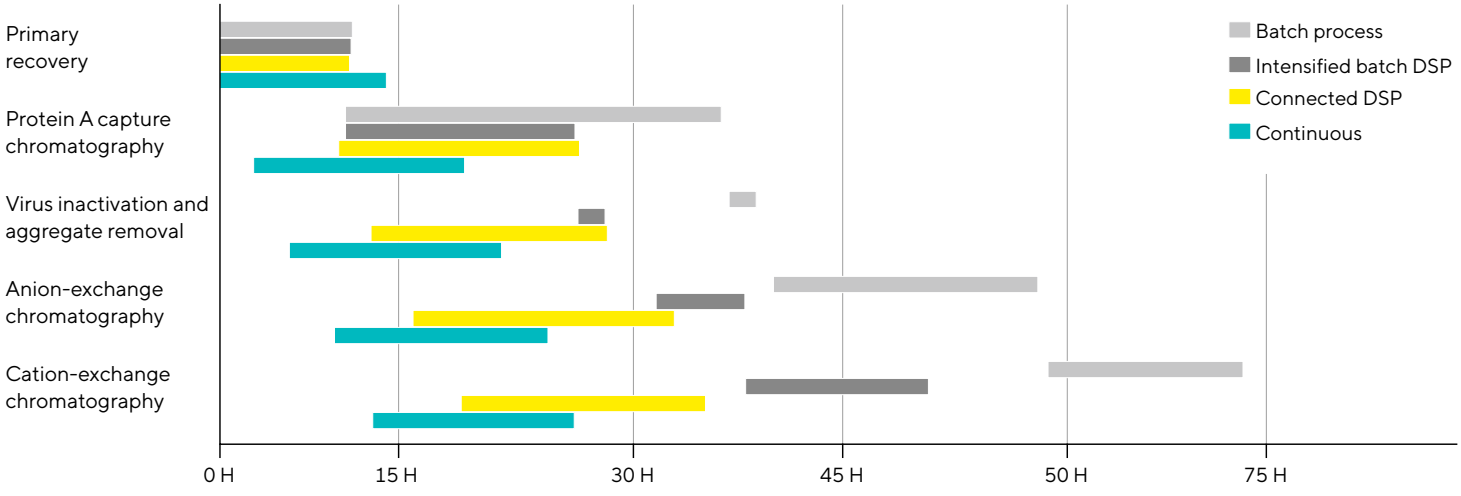


Figure 1: *Timeline for Downstream Process (DSP) Intensification Approaches Targeting Chromatography*



Note. Level 0 – Batch Process, Level 1 – Intensified Batch Process, Level 2- Connected Process, Level 3 – Continuous Process

Building an Intensified Chromatography Platform

Moving from resins to membrane chromatography for anion-exchange (AEX) polishing chromatography is one of the simplest approaches to intensification. Mass transfer in resins is diffusion controlled; in membrane adsorbers, it is convective with a partially diffusive layer. This is due to large pore sizes in membrane adsorbers. Such a mechanism offers excellent scalability and low back pressure (even at high flow rates) without compromising purification, encouraging lower residence times in membranes compared to resins. This is especially true in a flowthrough mode, where the target molecules do not bind to the stationary phase; membranes have a better loading capacity than resins[3] before impurity reaches its breakthrough.

Accordingly, Sartobind® Q membranes offer much higher loading capacities than traditional resins in AEX flowthrough mode.[4] With reduced residence times and higher loading capacity, Sartobind® membranes increase the productivity of the first polishing chromatography step. Additionally, buffer consumption is expected to decrease due to the reduced stationary phase volume requirements of membranes.

For the second polishing step, using a mixed-mode technology such as CMM HyperCel™ as an alternative to traditional cation exchange (CEX) | hydrophobic interaction chromatography (HIC) is particularly suitable owing to its ability to bind at a wider pH range. Mixed-mode chromatography also eliminates an intermediate buffer adjustment step between two polishing steps.[5]

In this application note, we present a step-wise intensification (Figure 3 A – C) approach to solve the productivity and cost bottlenecks associated with traditional resin-based polishing with CEX and AEX steps. This is achieved by replacing these unit operations with a membrane-based AEX flowthrough process and a mixed-mode bind and elute (B/E) resin process to increase productivity, lower buffer consumption, and eliminate intermediate buffer adjustment steps. The data presented here provide a proof of concept for how this new approach would reduce the overall cost of goods and improve facility utilization.

Materials

The model mAb (Adalimumab biosimilar) harvest was generated from a Cellca cell line (Sartorius). The harvest was clarified using Sartoclear® depth filters to remove cell debris, and the filtrate was processed through the chromatography steps.

Automated chromatography systems were used for execution of all the chromatography experiments. Cytiva XK series glass columns were used for packing the resins used in the lab scale process. Post-Protein A and virus inactivation, intermediate filtration was carried out through a dual layer Sartopore® 2 XLG filters of pore size from 0.8 to 0.2 µm.

Column configurations for three chromatography steps were as follows:

Protein A Capture Chromatography

Parameter	Details
Stationary phase	MabSelect SuRe™ resin (Cytiva)
Dimensions	83 mL, 2 columns, 32 mm diameter, 103 mm height
Matrix	Highly cross linked agarose
Ligand	Alkali-stabilized Protein A derived (*E.coli*)

Polishing 1 (AEX)[6]

Parameter	Details
Stationary phase	Sartobind® Q
Dimensions	1 mL capsule, 4 mm bed height
Matrix	Stabilized reinforced cellulose
Ligand	Quarternary ammonium
Ligand density	2 - 5 µeq/cm²

Polishing 2 (Mixed Mode)[7]

Parameter	Details
Stationary phase	CMM HyperCel™
Dimensions	140 mL, 44 mm diameter, 92 mm bed height
Matrix	Stabilized reinforced cellulose
Ligand	Aminobenzoic acid
Ligand density	Av. 70 µeq/mL

Buffer details for the three chromatography steps are as follows:

Protein A

Parameter	Details
Equilibration	50 mM sodium phosphate, pH 7.0
Wash 2	50 mM sodium phosphate, 1 M sodium chloride, pH 7.0
Wash 3	50 mM sodium acetate, pH 5.5
Elution buffer	200 mM acetic acid, pH 2.7
Regeneration	100 mM sodium hydroxide
Storage	20% v/v ethanol in WFI

Sartobind® Q

Parameter	Details
Equilibration and wash 2	20 mM sodium phosphate, pH 8
High salt buffer	20 mM sodium phosphate, 1 M Sodium chloride, pH 8.0
Regeneration	1 M Sodium hydroxide
Storage	20% v/v ethanol in equilibration buffer

CMM HyperCel™

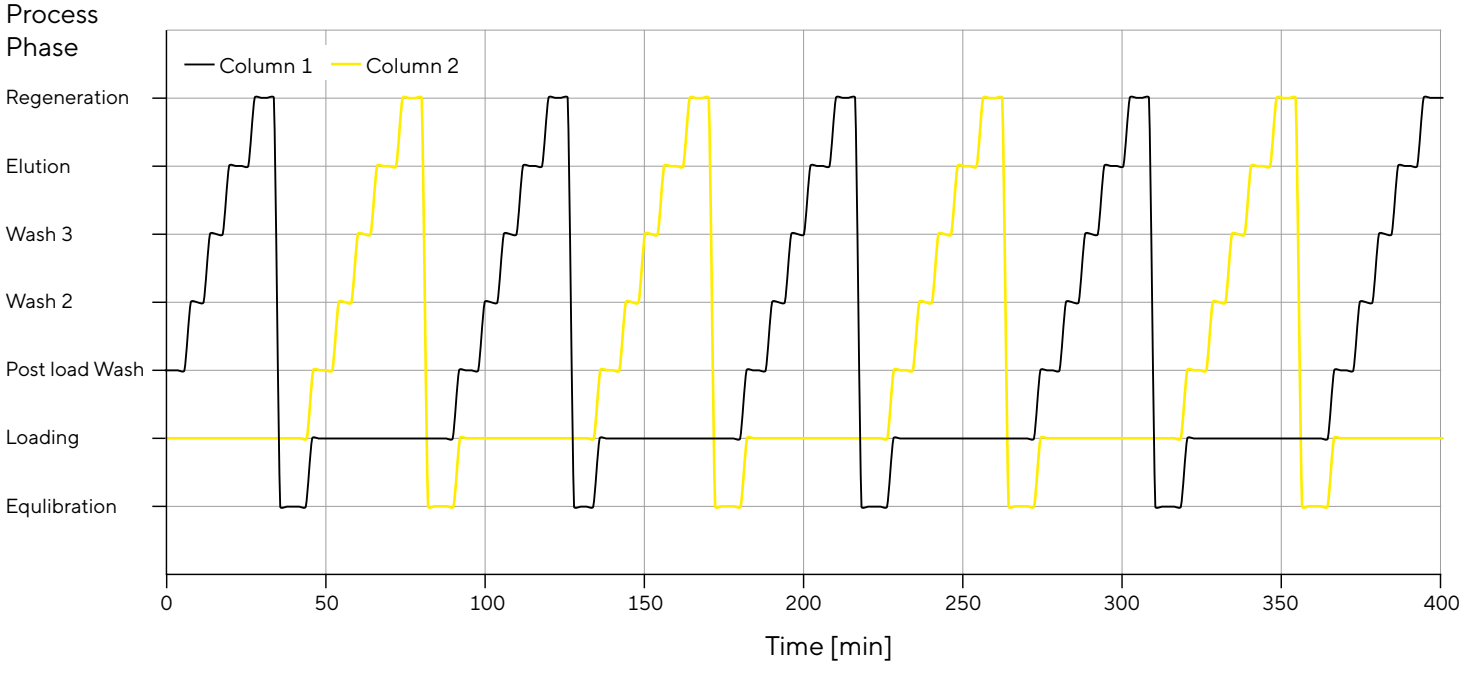
Parameter	Details
Equilibration	25 mM Tris-HCl, pH 8.0, Cond. 1.4 mS/cm
Wash	25 mM Tris-HCl, pH 7.6, Cond. 1.88 mS/cm
Elution	Tris-HCl, 300 mM NaCl pH 7.4, Cond. 30mS/cm
Regeneration	1 M Sodium hydroxide

Methods

Each bioreactor batch was run for 14 days to generate sufficient material and collect 4 g/L mAb titers. Following clarification using Sartorius Sartoclear® DL90 and DL20 filters, capture chromatography was performed with Protein A resin (MabSelect SuRe™) in a twin-column chromatography setup (Figure 2). This achieves intensification by reducing processing time through continuous loading on alternating columns. Post-capture, virus inactivation was performed by holding the elute for 60 minutes (mins) at acidic pH, followed by neutralization to pH 8. The virus inactivation process led to the increase in turbidity of the neutralized eluate to pH 8, which was clarified by intermediate filtration. The filtered and neutralized protein eluate was used to further assess polishing platforms.

Sartobind® Q membranes were considered as a replacement for anion exchange resins. As polishing platforms can either be CEX followed by AEX, or AEX followed by CEX, Sartobind® Q was tested during the first and second polishing step to find the most effective approach to optimize efficiency and connectivity. This led to two different platforms, described below.

Figure 2: *The Capture Step was Carried Out in a Semi-Continuous, Twin Column Chromatography Mode*



Note. Source - Enzene: H. Londhe & A. Bhori. Sartorius: B. Raut, B. Chauhan, G. Kumar, S. Lahir, & S. Jadhav.

Chromatography Methods for Polishing

Sartobind® Q

CMM HyperCel™

Parameters	Details
Membrane	Sartobind® Q
Bed height [mm]	4
Membrane volume [mL]	1 (1 × 1 nos)
Non-loading phase residence time [min]	0.1
Non-loading phase flow rate [mL/min]	20
Loading residence time [min]	0.2
Loading flow rate [mL/min]	10
Load pH	8.0
Load conductivity [mS/cm]	<4
Load material	Neutralized protein eluate post intermediate filtration
Loading density [g/mL]	>5 (at 1st polishing step) >8 (at 2nd polishing step)

Parameters	Details
Resin	CMM HyperCel™
Bed height [mm]	92
Membrane volume [mL]	140
Loading residence time [min]	4
Load pH	8.0
Load conductivity [mS/cm]	4
Load material	Sartobind® Q output
Loading density [mg/mL]	34

Buffer	No of MV
Pre-equilibration	30
Equilibration	75
Load [mAU]	Load based on DBC and MV Collection*: ↑ 10 to ↓ 20
Post-load Wash	50
Strip	15
Regeneration	30
Wash 2	30
Storage	30

Buffer	CV
Regeneration	2
WFI	2
High salt wash	2
Equilibration	5
Post-load wash	3
Wash 2	2
Elution [mAU]	Collection**: ↑ 50 to ↓ 50
Regeneration	2
WFI	3

* 20 mAu, 2 mm path length
** 2 mm path length

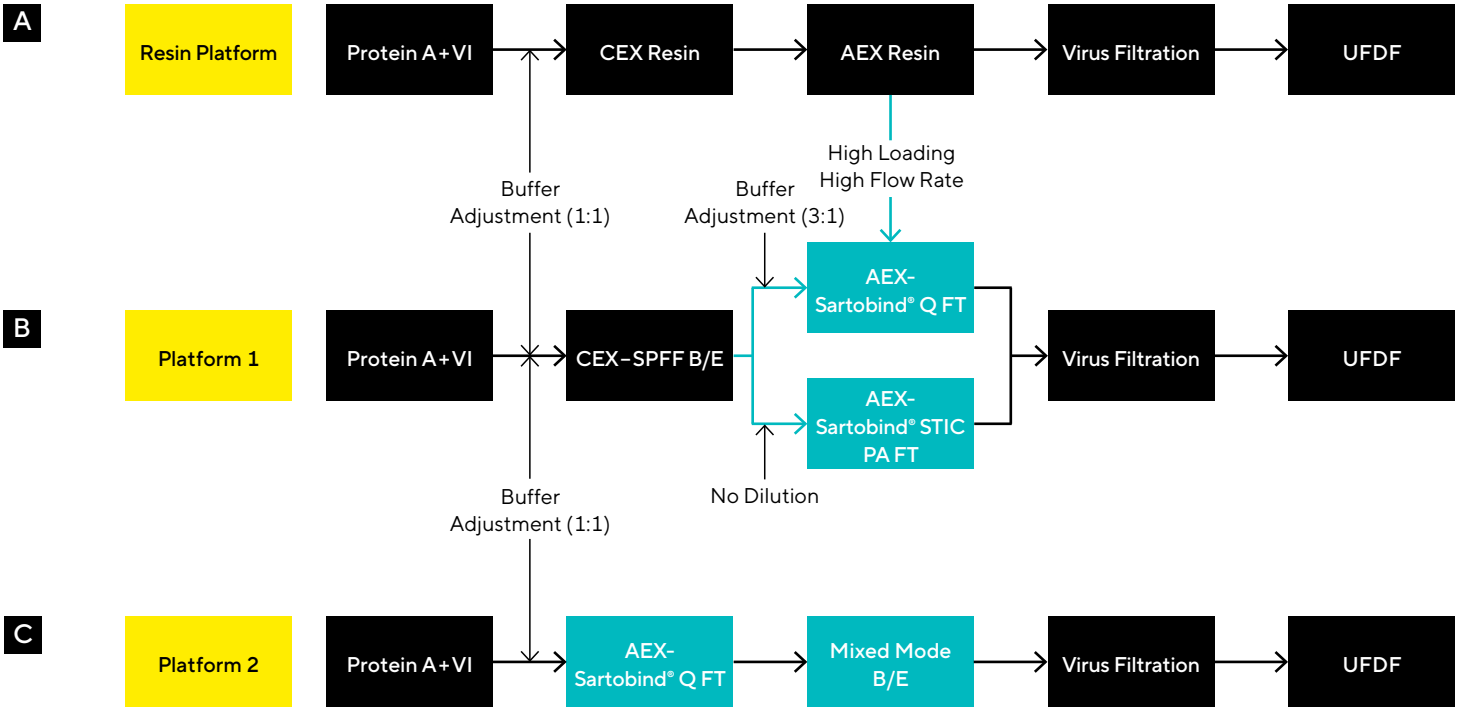
Polishing Platform 1

For the polishing in platform 1 (Figure 3B), the second polishing step with AEX resin B/E operation was replaced with a Sartobind® Q membrane in flowthrough mode, as shown in Figure 3A. This approach gave a single-step intensification. The load preparation for Sartobind® Q requires an additional 3:1 dilution to bring the conductivity below 4 mS/cm. Therefore, Sartobind® STIC — a salt tolerant membrane adsorber that does not require < 4 mS/cm conductivity for its operation — was also used as an alternative to anion exchange resin.

Polishing Platform 2

For the first polishing step in platform 2 (Figure 3C), we transitioned from traditional ion-exchange resins to Sartobind® Q membrane to achieve 10 – 30x higher productivity and enable up to 25 – 50x higher loading capacity for mAbs. CMM HyperCel™ was chosen as the resin for the second polishing step as it gives a considerably higher binding capacity at a basic pH (distinct from normal cation exchange resins). This enabled the loading of flowthrough from the Sartobind® Q directly onto the CMM HyperCel™, eliminating the need for an intermediate buffer adjustment for pH and conductivity. This saved corresponding time, equipment, floor space, and buffer consumption. Platform 2 is discussed in detail in this application note. Furthermore, design of experiments (DoE) was performed for CMM HyperCel using MODDE® (a Sartorius tool) to optimize buffer volume (BV) and elution volume (EV) using the pH window of 7 – 8 and conductivity window of 25 – 35 mS/cm.

Figure 3: *Strategy of Platform Intensification Showing Elimination of Intermediate Steps*



Note. (A) Resin-based platform (PI level 0)
(B) Incorporation of Sartobind® Q in place of resin polishing step for increasing productivity (PI Level 1)
(C) Final intensified platform – Sartobind® Q in 1st polishing and CMM HyperCel™ in 2nd polishing steps (PI Level 1)

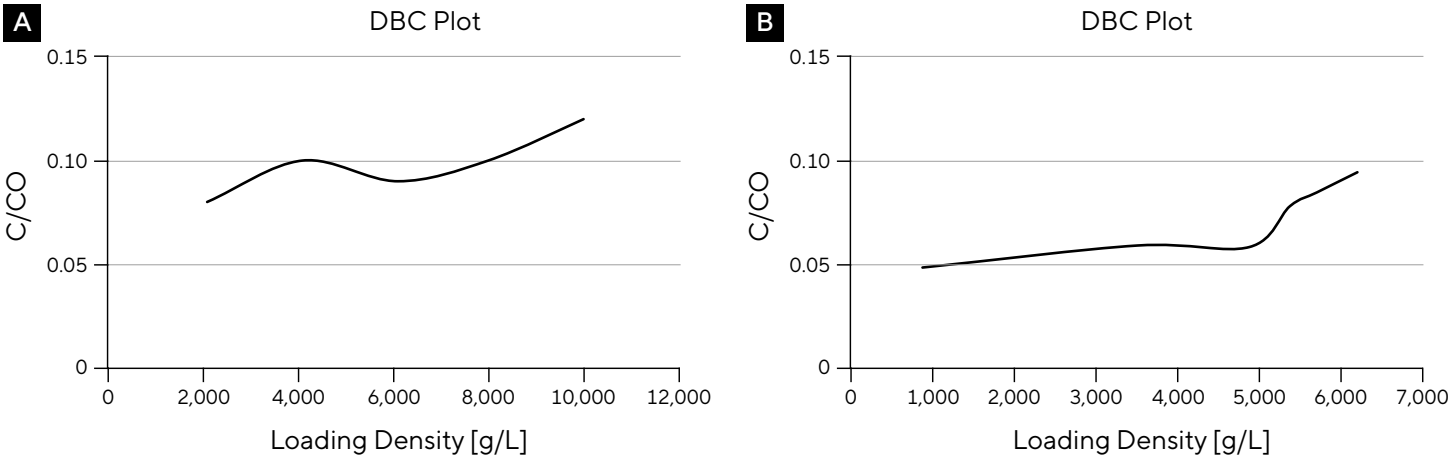
Results

Protein A chromatography in twin-column mode gave a recovery with an average of >94%. Virus inactivation and intermediate filtration did not lead to product loss and had no impact on the purity.

Platform 1

Platform 1 was carried out with a cation exchange SP Sepharose Fast Flow™ resin in the first polishing step (data not shown), followed by Sartobind® Q in the second polishing step. The loading capacity for the Sartobind® Q was high >8 kg/L (as shown in the dynamic binding capacity (DBC) curve in Figure 4A). This amounts to >10x increase in loading capacity compared to resin-based flowthrough processes (~300–800 g/L loading). However, this required a 3x dilution to bring the conductivity back below 4 mS/cm (criteria for Sartobind® Q operation), which required extra water for injection (WFI), an intermediate buffer adjustment step (and associated additional footprint) for the buffer adjustment. Another salt tolerant membrane, Sartobind® STIC PA, was tested to determine whether the dilution step can be removed. However, the loading capacity was not high enough to realize the benefits of the Sartobind® Q. This called for an alternative approach, so platform 1 is not a focus of this application note and the data for is not shown here.

Figure 4: *Breakthrough Experiments for Host Cell Protein (HCP) Binding During the (A) First and (B) Second Polishing Step with Sartobind® Q*



Loading density [g/L]	C/C_o
0	1.00
2,100	0.08
4,100	0.10
6,100	0.09
8,000	0.10
10,000	0.12

Loading density [g/L]	C/C_o
900	0.05
3,500	0.06
4,900	0.06
5,400	0.08
5,700	0,08
6,200	0.09

Parameters	Values
Flow rate	10 MV/min
Loading	>8 kg/L IgG
HCP	70 ppm (Load) → 6 ppm (FT Pool)
Monomer	98%

Parameters	Values
Flow rate	10 MV/min
Loading	> 5 kg/L IgG
HCP	120 ppm (Load) → BQL (FT Pool)*
Monomer	97.4%

Platform 2

To address the drawbacks from platform 1 (like the 3x dilution required for loading Sartobind® Q, requiring an additional tank for operation and increased water | buffer consumption for dilution), platform 2 was designed. Sartobind® Q was placed in the first polishing step in a flowthrough mode for platform 2. Following viral inactivation, the neutralized Protein A eluate was diluted with WFI at a ratio of 1:1 to achieve the target pH of 8 and conductivity of <4 mS/cm. This achieved a loading capacity of >5 g/L (Figure 4B), considerably higher (>10x) than other resin flowthrough processes on the market, reducing the number of cycles for the first polishing step. A 1 log reduction of HCP was also achieved with Sartobind® Q,[8] and DNA values were below quantitation limits (results not shown here).[9]

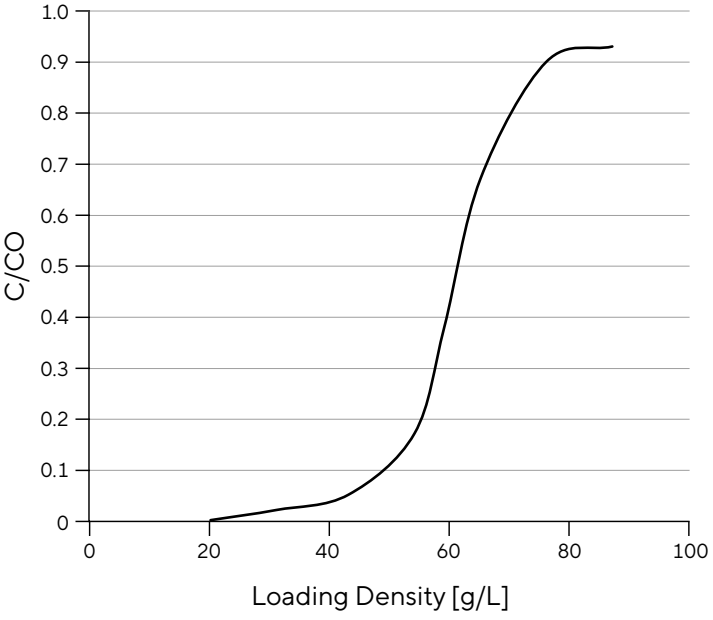
CMM HyperCel™ was chosen as a second polishing step post-Sartobind® Q because it can be directly loaded at pH 8.0. Due to a steep DBC curve (Figure 5), the binding capacity for CMM HyperCel™ was marked at 5% of the breakthrough (43 g/L), and 80% of that was considered for the actual experiments (34 g/L). Direct loading on CMM HypeCel™ helped eliminate the need for an intermediate buffer adjustment step and reduced the corresponding time, equipment, floor space, and buffer consumption. The optimization using Umetrics® MODDE® was successful as shown in Figure 6 and is summarized below:

1. Buffer volume passed and elution volume collected are minimal at higher pH. However, they are not affected by the conductivity values.
2. Recovery is a function of both the pH and conductivity of the elution buffer. Higher recovery is obtained at higher conductivity.
3. Aggregate removal is better at lower pH.

The findings show that buffer consumption (BV) and elution volumes (EV) were a function of pH (higher pH results in lower elution volume) and that recovery is a function of both pH and conductivity.

Post-DoE exercise, sweet spot analysis was performed to find the most optimized window of operation for the best results. The optimized parameters were elution buffer pH (7.4 ±0.1) and conductivity (30 ±1 mS/cm). The optimization helped to reduce the BV by 33% and EV by 35%. Validation experiments and further runs showed consistent results as predicted by the model (purity: >98.5%, recovery: >95%, and HMW: <1%).

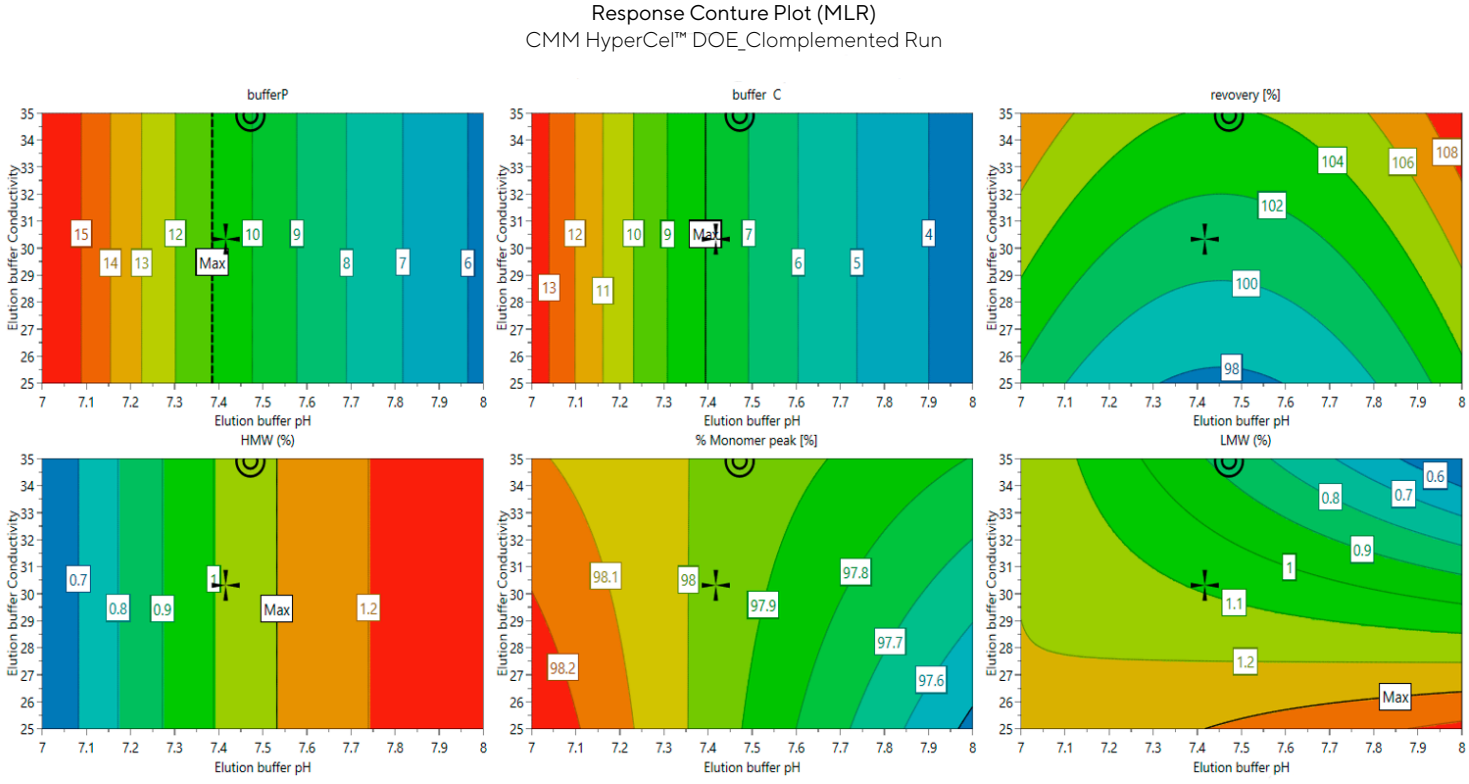
Figure 5: *Dynamic Binding Capacity Experiments for CMM HyperCel™ Applied During the Second Polishing Step*

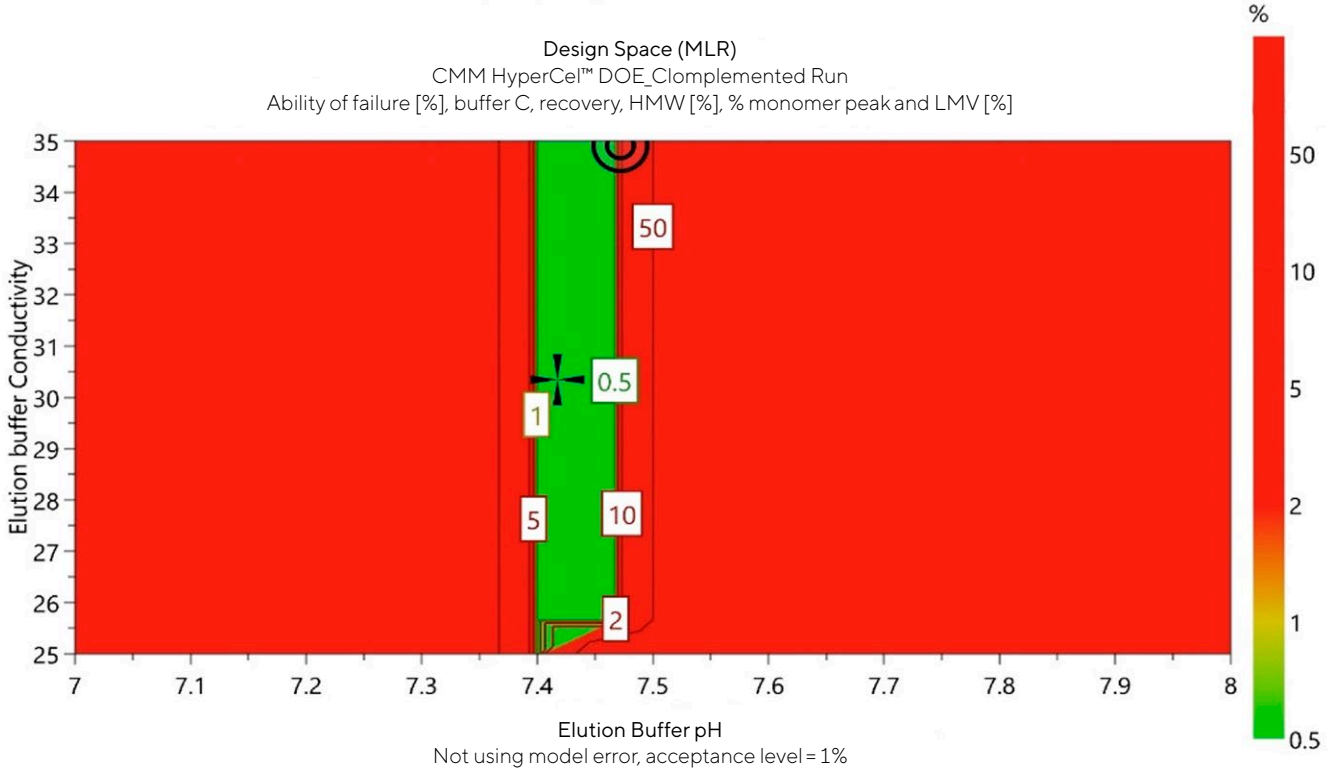


Loading density [g/L]	C/C_o
20	0.00
31	0.02
43	0.05
54	0.17
59	0.38
65	0.67
76	0.90
87	0.93

Parameters	Values
Linear flow rate	240 cm/hr
Residence time	4 min
Loading	85 g/L resin IgG
HCP	6 ppm (Load) → BQL
Monomer	>97% (optimization carried out using DoE subsequently, results discussed)

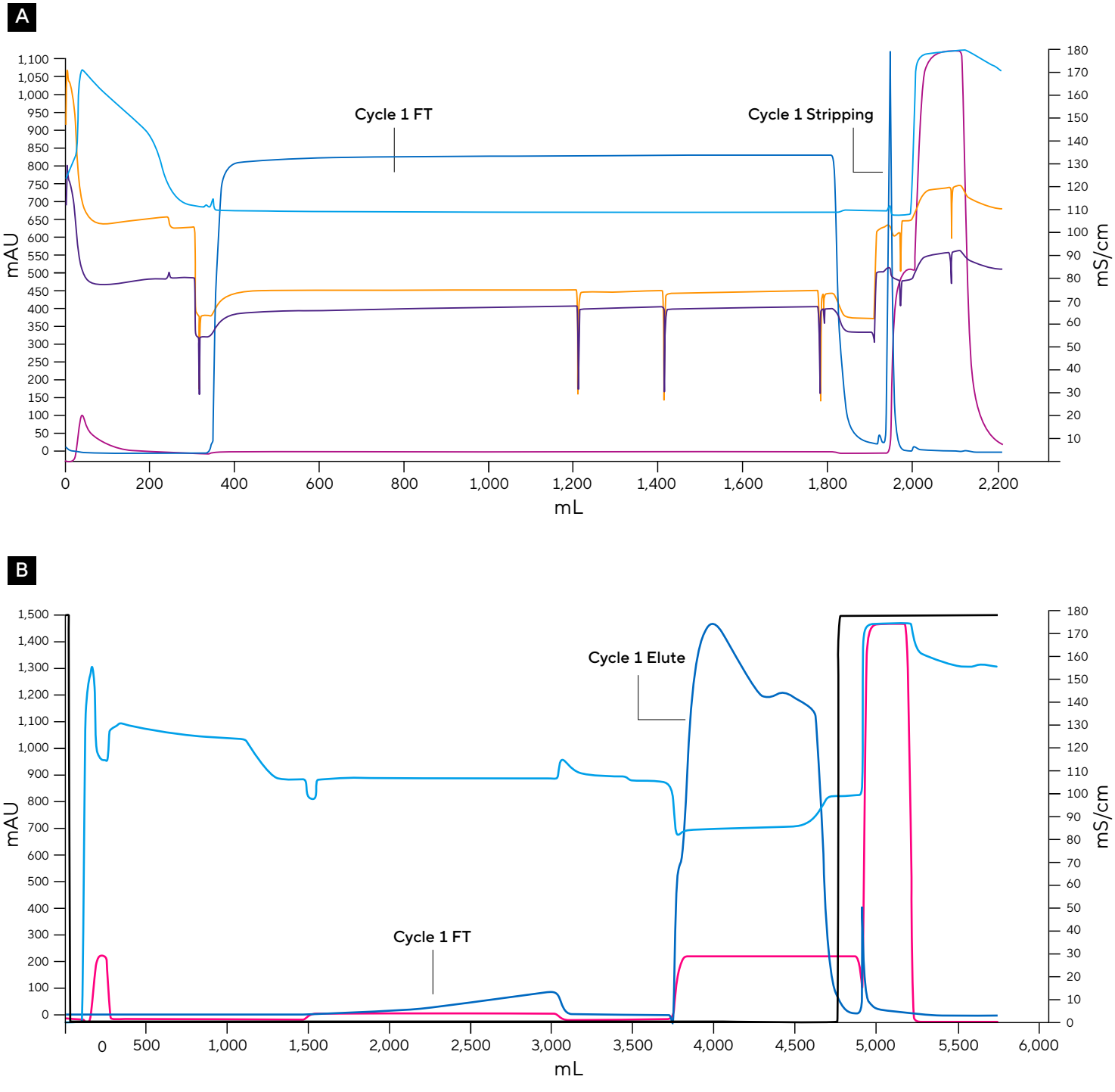
Figure 6: *CMM HyperCel™ Full Factorial DoE on Umetrics® MODDE® Outputs*





Note. (A) Optimization contour plots showing the effect of elution buffer, pH, and conductivity on different parameters
(B) Sweet spot analysis indicating the best conditions to maximize benefits

Figure 7: *Chromatograms for (A) Sartobind® Q and (B) CMM HyperCel™*



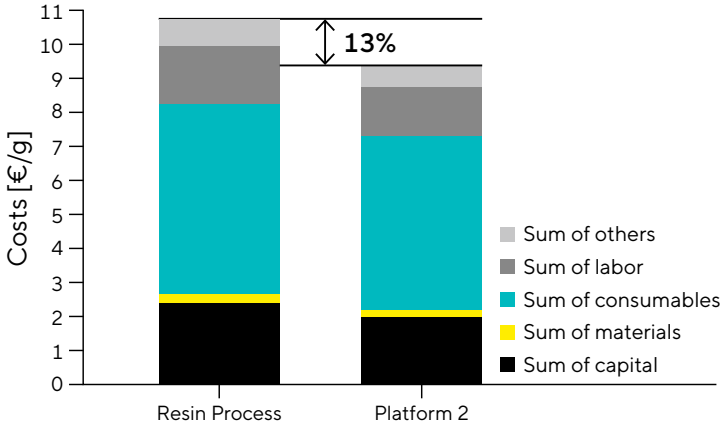
Discussion

The intensified chromatography platform 2 offered a number of benefits versus a standard batch process. High loading and low residence time on Sartobind® Q improved the throughput and productivity of the first polishing step. Loading was done at high flow rates with 0.2 min residence time, showing almost >20 times higher productivity against resin-based flowthrough processes.[9] The achieved loading capacity of >5 kg/L of stationary phase volume is considerably higher than the other technologies available on the market.[10] This reduces the column | membrane footprint in the facility, as a high volume of feed can be loaded onto smaller membranes. The implementation of prepacked and ready-to-use membranes reduced the risk associated with resin packing procedures and saved time and resources.

As the flowthrough from Sartobind® Q was directly loaded onto CMM HyperCel™ (due to its binding capacity for mAbs at pH 8),[11] the intermediate buffer adjustment and pretreatment steps were avoided, reducing buffer adjustment time and footprint while enabling efficient integration of the two polishing steps. CMM HyperCel™ also achieved the desired product purity.

Once platform 2 was optimized and validated cost modeling was performed in BioSolve® Process to compare a conventional batch process (full resin platform level 0) to the intensified platform 2 (PI level 1). Assumptions set for both processes were the same (4 × 2,000 L fed-batch bioreactor process with 6 g/L mAb titer, 70% facility utilization, 500 kg/year plant capacity, 71 batches per year). Cost modeling showed that the intensified platform reduced the cost of goods by 13% due to the implementation of Sartobind® Q and the elimination of the intermediate buffer adjustment step before the second polishing step (Figure 8).

Figure 8: *BioSolve Cost Modeling a Conventional Batch Process to the Intensified Platform (€/g at Polishing Step for 2,000 L, 6 g/L with Throughput of 500 kg/yr)*



Conclusion

Despite the progressive history and well-established process for the purification of mAbs, there is still plenty of scope for further intensification. Continuous improvement requires time, but a mindset shift is necessary to transition from conventional processes to next-generation consumable-based processes where benefits can be realized by changing the steps one at a time or in a series of unit operations. Strategic choice of consumables; implementation of cost, data-modeling, and process optimization; and efficient decision-making based on process insights are required to make these changes.

The process intensification strategy applied here showcases the advantages of implementing a stepwise approach to intensify mAb production processes. The benefits delivered by Sartobind® Q and CMM HyperCel™ are summarized as follows:

Sartobind®Q

- Offered a high loading capacity of >5 kg/L of membrane material with a residence time of 0.2 mins at the second polishing step, making it a fast operation
- Ready to use nature of Sartobind® Q made it easy to install and reduced variability, which could be induced by resin column packing
- Eliminating column packing saved time and resources
- Buffer consumption was lowered due to the reduced size of the stationary phase

CMM HyperCel™

- DoE helped optimize the conditions for the implementation of CMM HyperCel™, maximizing process robustness
- Directly feeding the flowthrough from Sartobind® Q to CMM HyperCel™ eliminated the intermediate buffer adjustment step, driving lower costs and reducing operation time

By implementing an intensified platform, mAb biomanufacturers can significantly improve operational efficiency, leading to substantial cost savings (up to 13% reduced cost of goods.

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