

January, 2026

Keywords or phrases:

Process intensification, scale-up, membrane chromatography, affinity chromatography, design of experiments, rapid cycling chromatography

Design of Experiments-Guided Optimization of Sartobind® Rapid A mAb Capture Achieves Resin-Like Buffer Efficiency

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Abstract

Membrane chromatography outperforms resin chromatography in productivity due to extremely short residence times that significantly accelerate purification. However, higher buffer consumption remains a key drawback compared with resin-based chromatography.

To address this challenge, we collaborated with LFB Biomanufacturing and applied a design of experiments (DoE) approach based on experimental data from monoclonal antibody capture using a small-scale Sartobind® Rapid A Nano device (1.2 mL membrane volume; MV).

Optimal wash conditions achieving buffer consumption comparable to resin-based capture were identified, while critical quality attributes (host cell DNA and host cell proteins) were maintained at levels comparable to the non-optimized Sartobind® Rapid A process. Direct transfer of DoE-optimized wash conditions to two Sartobind® Rapid A cassettes (0.8 L MV each) demonstrated linear scalability by a factor of >1,000, with host cell impurity clearance fully preserved across scales. A theoretical cost of goods analysis further confirmed lower production costs when downstream purification incorporated Sartobind® Rapid A membrane-based mAb capture compared to the traditional resin approach.

Introduction

Monoclonal antibodies (mAbs) represent a substantial and rapidly expanding market, with annual sales of ~250 billion USD in 2024, and a projected compound annual growth rate (CAGR) of 14.5% until 2029.¹ Since mAb capture using Protein A affinity chromatography represents an essential step in downstream processing, even incremental improvements in this unit operation can significantly enhance productivity and reduce overall manufacturing costs.

Membrane-based Protein A capture has emerged as an efficient alternative to traditional resin-based capture, combining diffusive mass transport within its agarose gel layer with convective flow through the membrane structure. This dual mechanism enhances binding capacity while enabling substantially lower residence times compared to resins. Additional advantages include the elimination of column packing, reduced fouling propensity, and a smaller footprint.² However, membranes also exhibit specific hydrodynamic effects such as dispersion, back-mixing, and a relatively high ratio of system hold-up volume to membrane volume.^{3,4} These factors can lead to increased buffer consumption, which remains a key limitation of membrane adsorbers compared with resin-based affinity columns.

In collaboration with LFB Biomanufacturing (a contract development and manufacturing organization in Alès, France), we applied a design of experiments (DoE) approach to address the challenge of higher buffer consumption in Protein A membrane-based mAb capture. The objective was to reduce the wash buffer volume to levels comparable with resin-based processes while maintaining critical quality attributes (CQAs), specifically host cell DNA (hcDNA) and host cell proteins (HCP). Experimental data from Sartobind® Rapid A Nano runs (1.2 mL membrane volume; MV) served as the basis for the DoE. The statistically derived parameters from the DoE were directly scaled up to process scale using two Sartobind® Rapid A cassettes (0.8 L MV each).

In addition, a cost of goods (CoGs) evaluation was conducted comparing two typical downstream purification processes: one employing membrane-based and the other resin-based mAb capture, as part of the overall process assessment.

Materials

Optimization of wash conditions using a DoE approach

A chromatographic protocol established for small-scale mAb capture using Sartobind® Rapid A Nano (1.2 mL MV) was employed to optimize buffer consumption. This setup was also used to assess whether wash conditions could be improved without compromising hcDNA and HCP clearance.

The initial Sartobind® Rapid A capture protocol included three wash steps (W1–W3), with W1 and W2 performed using 5 membrane volumes (MV) of wash buffer and W3 using 10 MV:

- W1: equilibration buffer to remove residual media and loosely bound impurities
- W2: high-salt buffer to eliminate antibody-associated or non-specifically bound impurities
- W3: equilibration buffer to rinse out residual salt and prevent precipitation during elution

A DoE strategy using MODDE® 13 Pro software was employed to minimize wash buffer volumes while maintaining consistent CQAs. Wash buffer volumes from a resin-based Protein A mAb capture protocol (4.7 mL CV) served as benchmarks for optimizing buffer consumption.

Analytics

Total mAb titer and monomer content were analyzed by high-performance liquid chromatography size-exclusion chromatography (SEC-HPLC). Quantification of HCP and hcDNA was performed using a commercial HCP ELISA kit and a dPCR kit, respectively. The log reduction value (LRV) of host cell-derived impurities was calculated as the common logarithm of the ratio of impurity concentrations (ppm) in the load (harvest cell culture fluid; HCCF) and in the elution fraction:
$$\text{LRV} = \log_{10}(\text{ppm}_{\text{HCCF}}/\text{ppm}_{\text{Elution}})$$

CoGs evaluation

The economic impact of reduced wash buffer volumes on CoGs was evaluated by comparing the optimized Sartobind® Protein A capture process with a traditional resin-based process. The analysis considered the entire downstream purification process, assuming identical materials and procedures for all unit operations except the capture step. Calculations were performed in BioSolve Process v8.3 (Biopharm Services) using the standard mAb single-use BioPhorum Technology Roadmap (TRM) cost model for biomanufacturing facilities included in the software. The model was applied and modified as described by Saballus et al. (2023).⁷

Results

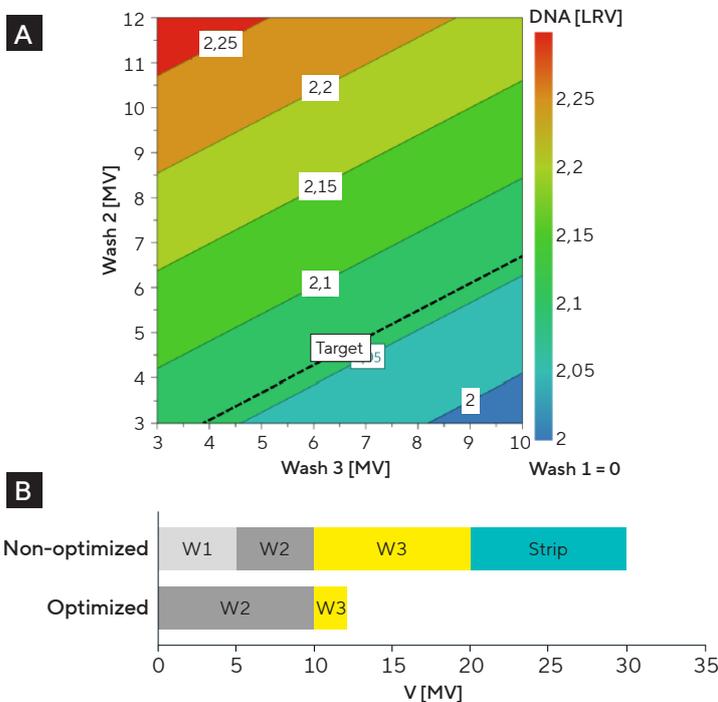
DoE optimization enables a 35% reduction in wash buffer consumption

The initial DoE experiments indicated that wash buffer volume had no impact on HCP clearance (data on file); therefore, subsequent optimization focused on hcDNA removal.

The DoE prediction (Figure 1A) indicated that low-salt wash 1 could be omitted, high-salt wash 2 should be maximized, and low-salt wash 3 minimized, serving only to reduce salt concentration prior to elution.

The optimized protocol reduced wash buffer consumption from 20 to 13 MV across all three wash steps by omitting W1, increasing W2 from 5 to 10 MV, and reducing W3 from 10 to 3 MV, corresponding to a wash buffer reduction of 35%. In addition, membrane stripping, which required 10 MV in the initial protocol, was omitted. Although not part of the DoE, previous experiments have shown that stripping provides no added benefit in Sartobind® affinity chromatography. Overall, these modifications resulted in a total buffer reduction of 39%, with W1-W3 reduced from 20 to 13 MV, elution maintained at 10 MV, stripping omitted (10 to 0 MV), and clean-in-place kept constant at 3.8 MV.

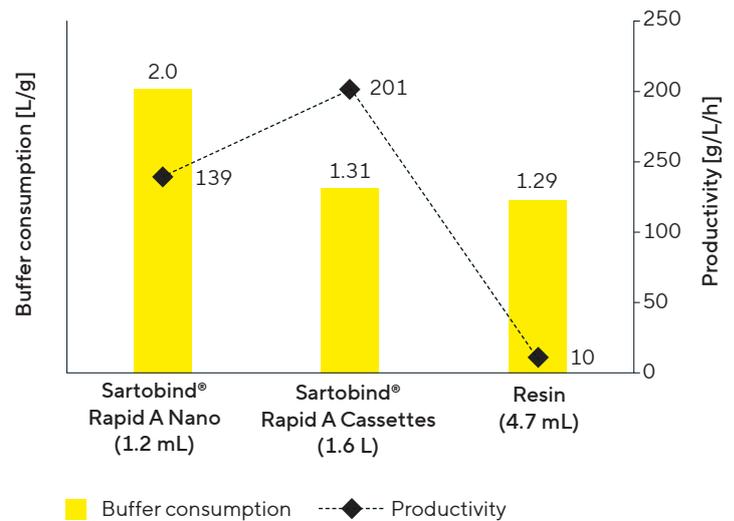
Figure 1: MODDE® Pro 13 contour plot showing the effects of Wash 2 and Wash 3 MV on model-predicted hcDNA removal (LRV), with Wash 1 set to 0 MV (A). Comparison of buffer volumes in the three wash steps for Sartobind® Rapid A-mediated mAb capture between the non-optimized protocol and DoE-optimized protocol (B).



Wash buffer consumption comparable to resin processes, with a 45% productivity increase

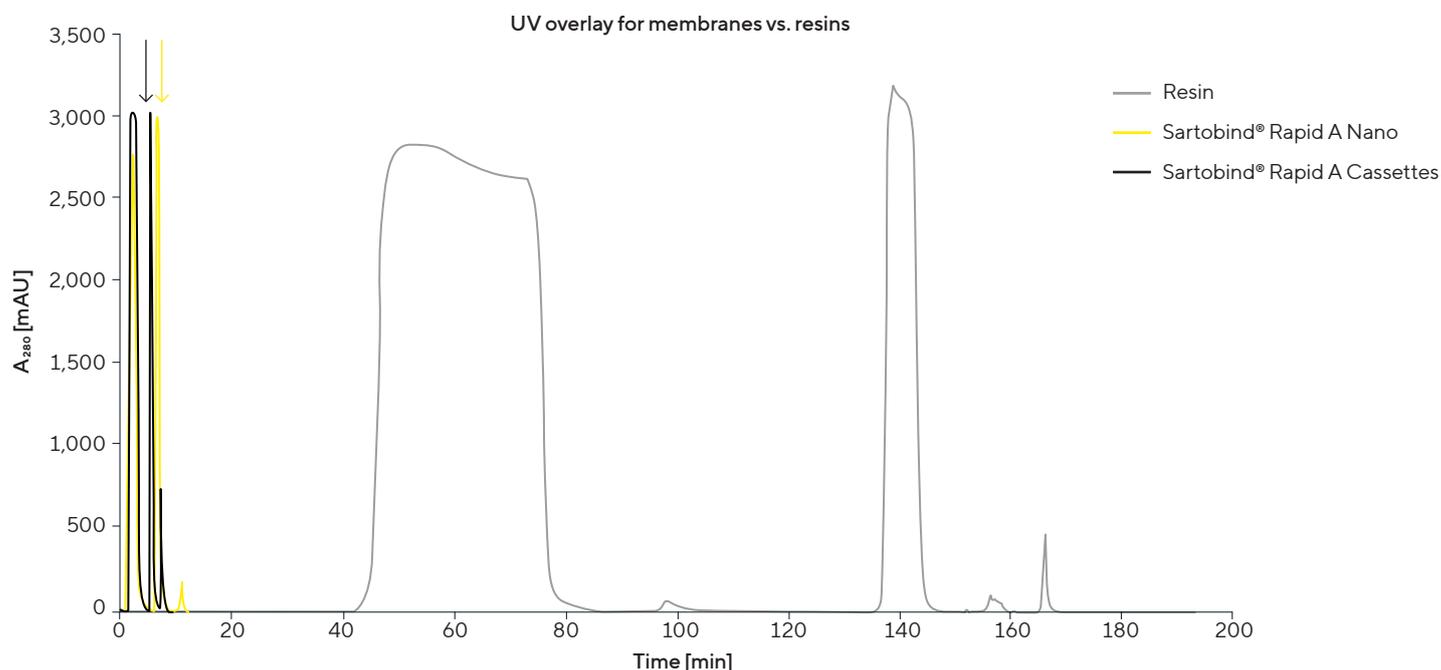
The optimized Sartobind® Rapid A mAb capture process achieved wash buffer consumption comparable to that of resin-based processes, thereby eliminating a main drawback of membrane-based Protein A chromatography. In parallel, reducing wash buffer volumes significantly increased productivity from 139 g/L/h to 201 g/L/h, representing a relative gain of 45% compared with the non-optimized Sartobind® process. Compared with resins, the optimized membrane-based process achieved ~20-fold higher productivity (Figure 2).

Figure 2: DoE optimization reduced wash buffer use to resin level and increased Sartobind® Rapid A productivity by 45% compared with the non-optimized membrane process (Sartobind® Rapid A Nano).



The higher productivity of membrane-based mAb capture compared with resin-based capture is generally attributed to substantially shorter residence times. Consequently, the cycle time of the non-optimized Sartobind® capture process was already approximately 15-fold shorter than that of the resin-based process (12.9 min vs. 195 min). Applying the reduced wash buffer volumes from the DoE model at a constant flow rate further decreased the cycle time to 9.8 min, corresponding to a ~20-fold faster cycle compared with resin (Figure 3).

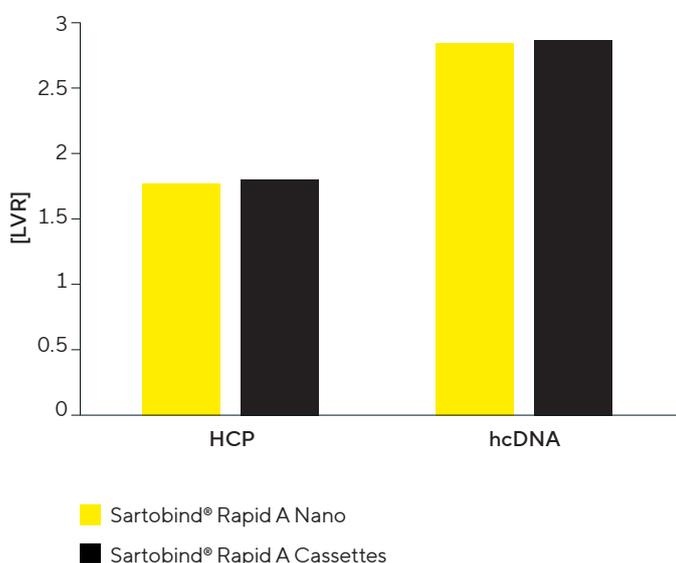
Figure 3: DoE-optimized Sartobind® Rapid A capture reduced cycle time from 12.9 min to 9.8 min, achieving a ~20-fold faster process than resin-based capture (195 min)



Consistent host cell impurity clearance

HCP and hcDNA removal were fully maintained when DoE-optimized conditions were directly transferred to process scale using two Sartobind® Rapid A cassettes (0.8 L MV each; 1.6 L total MV), confirming linear scalability in terms of impurity clearance (Figure 4).

Figure 4: Consistent HCP and hcDNA clearance (LRV) after scale-up of the DoE-optimized Sartobind® Rapid A mAb capture process from Nano scale (1.2 mL MV) to Cassette scale (1.6 L total MV)



Sartobind® Rapid A achieves quality comparable to resins with major performance benefits

Comparing the results of the DoE-optimized Sartobind® Rapid A process with traditional resin-based mAb capture highlights the superior performance of the membrane system. Sartobind® Rapid A cassettes achieved a higher yield (95.4% vs. 92.5%) and dramatically increased productivity (201 vs. 10 g/L/h) at a similar loading density. Buffer consumption was essentially identical (1.31 vs. 1.29 L/g). Product quality was fully maintained, with slightly improved monomer content (94.9% vs. 94.1%), comparable HCP clearance (1.82 vs. 1.92 LRV), and slightly higher hcDNA reduction (2.92 vs. 3.20 LRV). Taken together, Sartobind® Rapid A combines product quality comparable to resin chromatography with faster and more efficient processing (Table 2).

Table 2: Overview of critical process parameters, key performance indicators, and CQAs achieved with the DoE-optimized Sartobind® Rapid A mAb capture process compared to a traditional resin-based process

Value	DoE-optimized Sartobind® Rapid A	Resin
Load density [g/L]	35.0	35.0
Yield [%]	95.4	92.5
Productivity [g/L/h]	201.0	10.0
Buffer consumption [L/g]	1.31	1.29
Monomer content [%]	94.9	94.1
HCP reduction [LRV]	1.82	1.92
hcDNA reduction [LRV]	2.92	3.20

Cost analysis: Sartobind® Rapid A outperforms a resin-based process by 11.1 USD per gram of mAb

The CoGs analysis was applied to a typical downstream purification process using either the optimized Sartobind® Rapid A or a standard resin-based capture. The scenario considered five batches per year, each processing 1,800 L of feed material with an mAb titer of 8.7 g/L. Total downstream yields were set at 72% for the membrane-based and 70% for the resin-based capture process (Figure 5, Table 3).

The analysis revealed total savings of 11.1 USD per gram of purified mAb (total CoGs 208.9 vs. 220.0 USD/g mAb) when using Sartobind® Rapid A. Capture costs were lower for Sartobind®-mediated mAb capture (resin: 67 USD/g mAb; membrane: 53 USD/g mAb), whereas subsequent virus inactivation and anion exchange chromatography costs were slightly lower for the resin process. These advantages, however, only partially offset the substantial savings achieved by the optimized Sartobind® capture step of 14 USD per gram of mAb (Figure 5).

Considering the slight differences in total yield, five batches with resin-based mAb capture deliver ~54.8 kg mAb annually, whereas Sartobind® Rapid A increases the output to ~56.4 kg. Together with lower CoGs, this translates into annual savings of ~280,000 USD at higher product output, or up to ~600,000 USD when normalized to the same yield (Table 3).

These results clearly highlight the economic benefit of implementing Sartobind® Rapid A for mAb capture in downstream purification. It is important to note that these CoGs represent a conservative estimate based on a low number of batches per year for clinical material supply, which explains the relatively high values in this example. Substantial reductions in CoGs would be expected when transitioning from clinical to market supply due to the higher number of batches per year.

Figure 5: CoGs analysis assuming single-use downstream processing of the output from a 2,000 L bioreactor (1,800 L working volume) operated for five batches per year to produce (pre-) clinical material

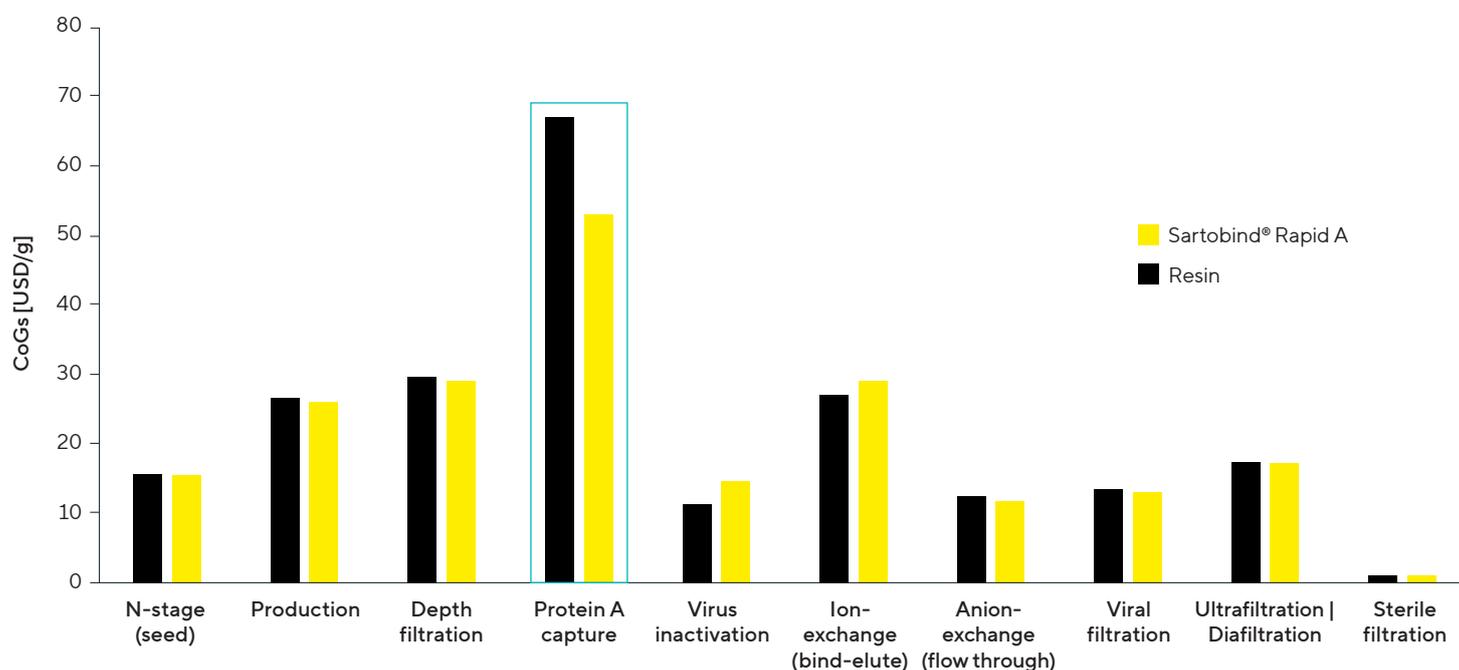


Table 3: CoGs analysis comparing single-use downstream processing (DSP) of feed material from a 2,000 L bioreactor (1,800 L working volume, 8.7 g/L mAb) operated for five batches per year, incorporating either the DoE-optimized Sartobind® Rapid A or a traditional resin-based mAb capture process

Scenario	CoGs [USD/g mAb]	Batches/year	DSP yield [%]	DSP total yield [kg]	Annual CoGs [USD]	Normalized annual CoGs [USD]
Resin	220.0	5	70	54.8	12,056,000	12,056,000
Sartobind® Rapid A	208.9	5	72	56.4	11,776,000	11,447,000
Membrane advantage	11.1	n/a	2.9	1.6	280,000	609,000

Table 4: Overview of key process and performance parameters for mAb capture using non-optimized and DoE-optimized Sartobind® Rapid A membrane processes compared with a non-optimized and a theoretically optimized resin process

Value	Sartobind® Rapid A Nano 1.2 mL (non-optimized)	Sartobind® Rapid A Cassettes 1.6 L (optimized)	Resin 4.7 mL (non-optimized)	Resin 4.7 mL (theoretically optimized)*
Cycle time [Min]	12.9	9.8	194.6	186.8
mAb/cycle [mg]	35.8	52,510	145.6	145.6
mAb/cycle normalized to 1 L stationary phase [g]	29.8	32.8	31.0	31.0
Buffer/cycle [L]	0.07	69	0.19	0.18
Buffer/cycle normalized to 1 L stationary phase [L]	58.3	43.1	40.4	38.3
Buffer consumption [L/g _{mAb}]	2.01	1.31	1.29	1.23
Productivity [g _{mAb} /L/h]	138.8	200.9	9.6	10.0

* Values based on theoretical calculations, not experimentally determined.

Summary of key process parameters and comparison with a theoretical resin optimization scenario

Table 4 summarizes key process and performance parameters achieved for mAb capture using the non-optimized and DoE-optimized Sartobind® Rapid A membrane processes, compared with the non-optimized resin process. To broaden the analysis, a theoretically optimized resin process was also included to illustrate its performance under ideal conditions. Direct comparison between the different formats was enabled by normalizing mAb yield per cycle and buffer consumption per cycle to 1 L of the stationary phase. Even when assuming a theoretically optimized resin process with reduced cycle time and buffer use, productivity and overall process speed remained clearly below Sartobind® Rapid A membrane-based mAb capture, underscoring the inherent kinetic advantage of membrane chromatography (Table 4).

Discussion

The growing demand for therapeutic mAbs requires purification technologies that combine high productivity, cost efficiency, and process simplicity to enable the efficient production of these powerful therapeutics. While resin-based chromatography remains a well-established standard in downstream processing of mAbs, it is limited by longer cycle times, higher system complexity, and larger facility footprint. In contrast, membrane chromatography offers a rapid, simple, scalable, and ready-to-use alternative, particularly suited for manufacturing environments requiring high-throughput production. However, this format typically

requires higher wash buffer volumes, which need to be balanced against its significant productivity advantages.

Using a DoE approach, we demonstrated that Sartobind® Rapid A enables mAb capture with wash buffer consumption comparable to traditional resin-based chromatography, while maintaining excellent HCP and hcDNA clearance. Although the DoE model was based on data from a small-scale mAb capture application (1.2 mL MV), it was directly transferable to process scale (1.6 L MV) due to the linear scalability of Sartobind® Rapid A, with process performance fully maintained. This scalability confirms the robustness of the process and represents a critical advantage during the development phase of commercial biomanufacturing processes.

Minimized washing further reduced the cycle time by approximately 3 min to 9.8 min, compared to 195 min for the resin process. This translates to a productivity of 201 g/L/h vs. 10 g/L/h for the resin, highlighting the substantial impact of Sartobind® Rapid A on manufacturing efficiency and throughput.

A theoretical CoGs assessment considering the entire downstream process confirmed lower production costs for the process incorporating the optimized membrane-based mAb capture compared to the resin-based process (208.9 USD/g mAb vs. 220.0 USD/g mAb). A yearly scenario with five 1,800 L batches at an 8.7 g/L mAb titer demonstrated annual savings of up to 610,000 USD, underscoring the strong economic and operational advantage of Sartobind® Rapid A, even before accounting for the substantial time savings achieved through accelerated processing.

Conclusion

The Sartobind® Rapid A process delivers high-throughput mAb capture with comparable impurity clearance, significantly higher productivity, reduced process complexity, and lower manufacturing costs than conventional resin-based methods.

By reducing cycle time from hours to minutes and simplifying downstream operations, membrane chromatography supports:

- Accelerated time-to-market
- More efficient utilization of manufacturing assets
- Cost-effective supply of biotherapeutics

Eliminating the former limitation of higher buffer consumption further strengthens the overall economic case. With approximately 20-fold higher productivity compared to the resin process, ~5% direct CoGs savings, and seamless scalability, Sartobind® Rapid A provides a strong incentive for the biopharmaceutical industry to further expand the use of membrane adsorber technology. Enhanced efficiency and reduced production costs ensure a rapid return on investment.

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