Simplifying Progress

High Productivity Drives Cost-Effectivity

Capture Chromatography for Biologics Development and Manufacturing

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Current Industry Approaches at Capture Chromatography are Unproductive and Incur High Cost, Risk, and Time

Resins, in particular resins with protein A ligands, have been the workhorse for mAb capture for the past several decades, because they result in >95% purity. Protein A media effectively reduces most of the host cell proteins and DNA from upstream. Due to the high purity which can be achieved after one single purification step, protein A based chromatography media will stay the tool of choice for monoclonal antibody purification for the foreseeable future.

Resins are small porous beads which have small channels with diameters of 50–200 nm leading to a diffusive mass transport. Diffusion is a slow process and requires time which leads to low productivity. Productivity is a parameter to measure how much product is processed per Liter of chromatographic media in a certain time and therefore gives an indication of how productive a unit operation is. Typical resins have productivity in the range of 10–20 g/L×h, which is relatively low and typically requires large processing times downstream when implemented at manufacturing scale. Current approaches to overcome this productivity bottleneck include designing processes with higher resin volume to be able to process the required product in shorter time or opting for multi-column chromatography which can increase the productivity by 3 to 5-fold.

1. Longer ROI Associated With Protein A Resins Makes the Process Uneconomical

In downstream processing (DSP), one of the most expensive steps is capture chromatography (Figure 1), with respect to the cost of goods (CoGS).

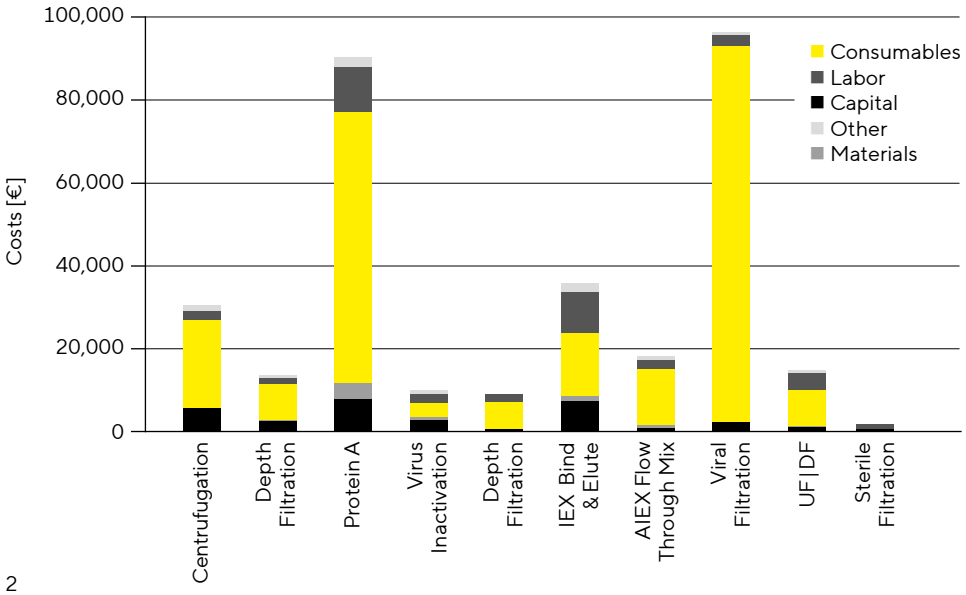
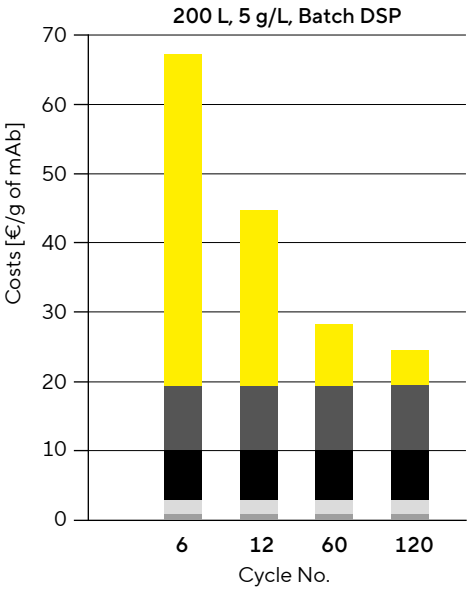


Figure 1: *CoGS Split for a 2,000 L, 10 g/L Batch DSP With Resin-Based Capture Chromatography.*

To make the process more economical at the capture step, the resin needs to be used to its lifetime, which becomes especially challenging for molecules in (pre-) clinical phase. A resin-based column that requires a large investment is typically intended to produce many batches in relatively quick succession, meaning that the cost can quickly be recouped. However, the calculations change drastically in clinical production. At this stage, batches of biologics are normally produced in lower quantities and over longer time periods. This means that large capital investments and CoGS involved in the production process can take time to pay off. These are often greater, as more manufacturers opt for pre-packed columns to reduce the required efforts and risks related to packing columns in-house. Nevertheless, due to stability and quality concerns, resins in pre-packed columns can often not be used for their intended lifetimes. As a result, they have higher CoGS, and the pre-packed columns may need to be un- and re-packed, which further increases the labor cost and eliminates the benefits of choosing these in the first place. In Figure 2, which is a plot for a 200 L process at 5 g/L specifically focusing on the capture step, cost effectivity can be only achieved when the media is used for its intended lifetime.



	6	12	60	120
Consumables	47.8	25.3	7.2	5.0
Labor	9.3	9.3	9.3	9.3
Capital	7.2	7.2	7.2	7.2
Other	2.0	2.0	2.0	2.0
Materials	0.9	0.9	0.9	0.9

Figure 2: *Chromatography Media Becomes More Cost-Effective as Consumables Reach Their Intended Lifetime.*

2. Risks Associated With Column Handling and Re-Use of Resin

In addition to cost, there are several risks associated with resin-based chromatography for biologics production. As previously mentioned, resin-based processes additionally require a large capital investment (such as columns, packing skids, slurry tank, storage room, etc.) which are recouped gradually with re-use. In the case of clinical | commerical manufacturing when batches are produced over (longer) time intervals, equipment must be stored in an integral manner with a suitable buffer in a temperature-controlled environment. This introduces additional risks such as leakage, buffer expiry or exchange, bioburden, cross- or carry-over contamination, degradation, human error, etc. In addition, activities leading to and after storage such as column packing pose risks such as packing failures, cracking of resins due to over-compression, etc. that can have a significant impact on the scheduling, batch quality (risk of batch failure), resource utilization and ultimately costs. Risks such as bed cracking would ultimately require that a resin is retired before its intended lifetime and that additional funds will be required to purchase new chromatography media with long lead times which potentially delays milestones to clinic | commercial.

3. Significant Time Investment for Lifetime Studies and Batch Readiness

Current capture processes using resins are inefficient as they suffer from long cycle times (2 – 4 hours) due to diffusional limitations. If the intended lifetime of such a resin in commercial manufacturing is 200 cycles, which by the way is very hard to reach due to the above-mentioned risks, performing lifetime studies will take 400 hours (Figure 3a; lifetime study of 200 cycles with 2 hours per cycle).

There are additional steps associated with resin-based columns such as attaining batch readiness that can further increase the time investment. For example, column packing, unpacking, and repacking is required during the start and end of a campaign, which can add over 24 hours to the mAb capture step. Each time a column is packed it is subject to additional testing. Not only does this take time, but test failures mean that columns must be repacked, which further adds to the time investment. Cleaning in place (CIP) after each unit operation is an extremely important step when using resin-based technologies. From Figure 3b, it can be seen when operating the column for the first batch of a campaign, around 70% of time is spent on activities to achieve batch readiness (column packing, set-up, cleaning) while the actual run time is only 30%. Every step in the mAb capture process is subject to quality systems that must be documented and maintained. More steps therefore require more time dedicated to extensive paperwork.

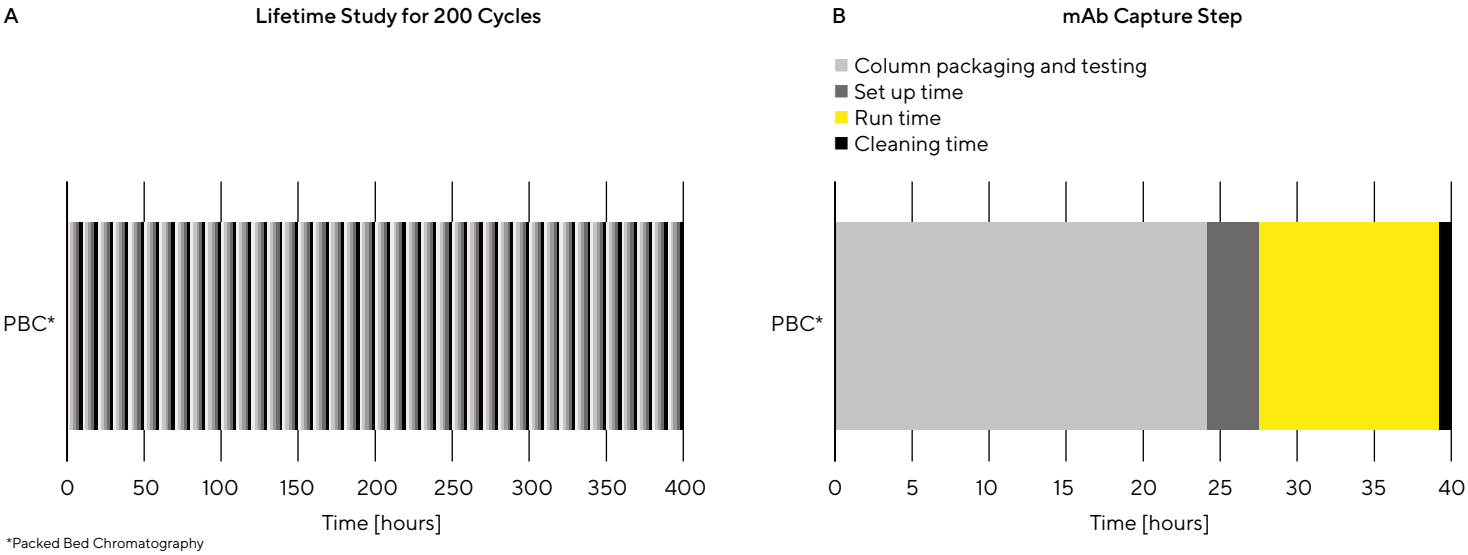


Figure 3: *Resin Lifecycle Management Requires Significant Time Investment.*

Intensify to Simplify: High Productivity With Rapid Cycling Chromatography Improves Process Economics and Mitigates Risk

Rapid Cycling Chromatography (RCC) is possible when a chromatography matrix delivers good binding capacities at short residence time. As a result, the cycle time can be shortened from 2 – 4 hours to 10 – 15 min, and ≥10× higher productivity can be achieved (Table 1).

	Packed Bed Chromatography-Media	Rapid Cycling Chromatography-Membrane
No. of devices used	1 column	1 device
No. of cycles per batch	3 – 6	30 – 150
Cycle time	> 2 hours	10 – 15 minutes
Productivity	10 – 20 g/L×h	> 150 g/L×h

Table 1: *How RCC Compares to Bed Chromatography.*

Simplifying Drug Development and Manufacturing With RCC

Case Study 1: High Productivity, Reduced Risk and Comparable CQA with Sartobind® Rapid A Operated in One-Batch, One-Membrane

Users of Sartobind® Rapid A benefit from improved productivity versus other technologies. Resin-based protein A capture can produce between 10 and 20 g/L×h. At larger scales, the capture step alone can take between 8 and 24 hours, which represents a bottleneck for the subsequent steps and affects the facility output. Membranes such as Sartobind® Rapid A can have vastly improved productivity. It is possible to see a 10- to 15-fold increase in productivity compared to packed bed affinity resin operated in batch mode (see Figure 5). This significantly increases the output achieved in one typical 8-hour shift. High productivity leads to short cycle times, which in turn enables full utilization of the membrane within one batch. In contrast to columns, this eliminates the risks and time associated with lifetime studies, column packing, handling, storage, etc. for each subsequent batch with the one-batch, one-membrane (1B1M) approach (Figure 4).

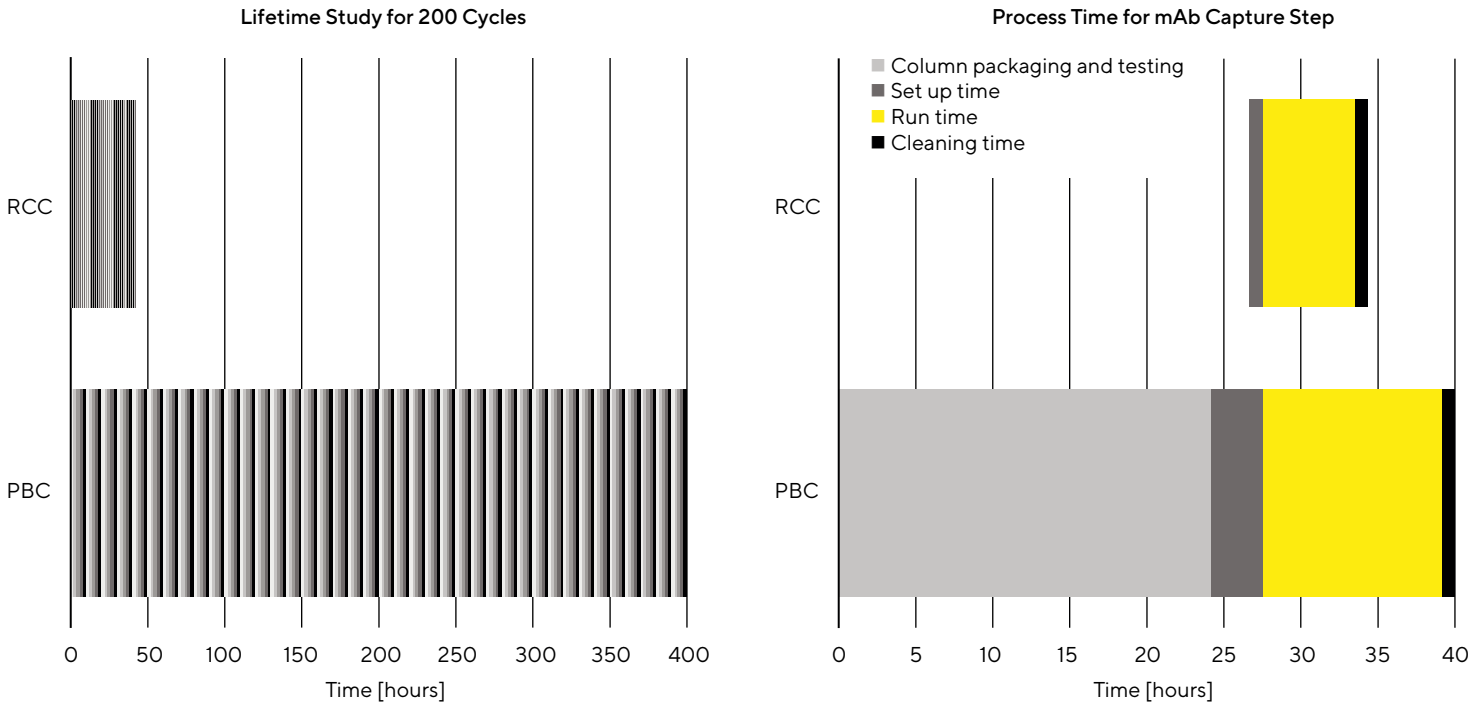


Figure 4: *Time Savings During Lifecycle Studies and the Unit Operation.*

Process parameters and critical quality attributes (CQA), such as yield and HCP removal, are on par with a resin-based affinity process, while DNA removal (higher by approximately 1.3×) and reduction in leached protein A ligand (lower by up to 60%) fare much better with Sartobind® Rapid A when compared to traditional resins (Figure 5) thus adding a positive impact to product quality.

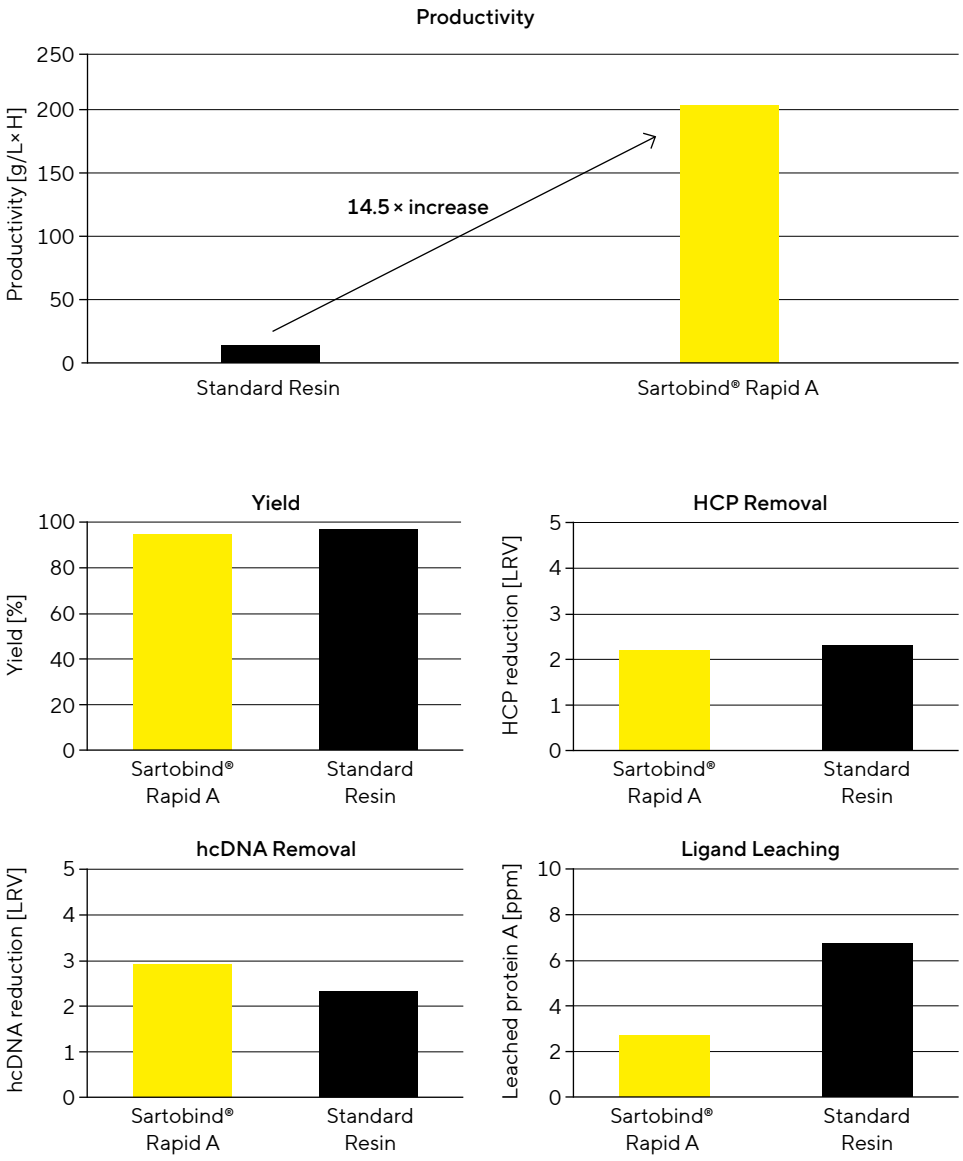


Figure 5: *Comparison of Different Quality and Process Attributes as Well as Productivity for Traditional Resins and Sartobind® Rapid A.*

Case Study 2: Reduction of Overall Process Cost by Full Lifetime Utilization of the Chromatography Consumable Within One Batch

At clinical scale, CoGS for protein A media are more of a cost driver because the chromatography media is underutilized, and the intended lifetime is not reached. This invariably leads to multiple columns piling up in cold rooms and occupying space until they are ultimately used or must be relocated. Underutilization and prolonged storage can also increase bioburden risk, as mentioned in the previous chapter.

Sartobind® Rapid A is fully utilized within one batch before being discarded. As a result, it circumvents the above-mentioned challenges, allows to recoup the investment after one batch, offers >30% of savings on the overall process cost at clinical scale or in low batch number processes (Figure 6) thereby bringing cost-effectivity to biologics development and manufacturing.

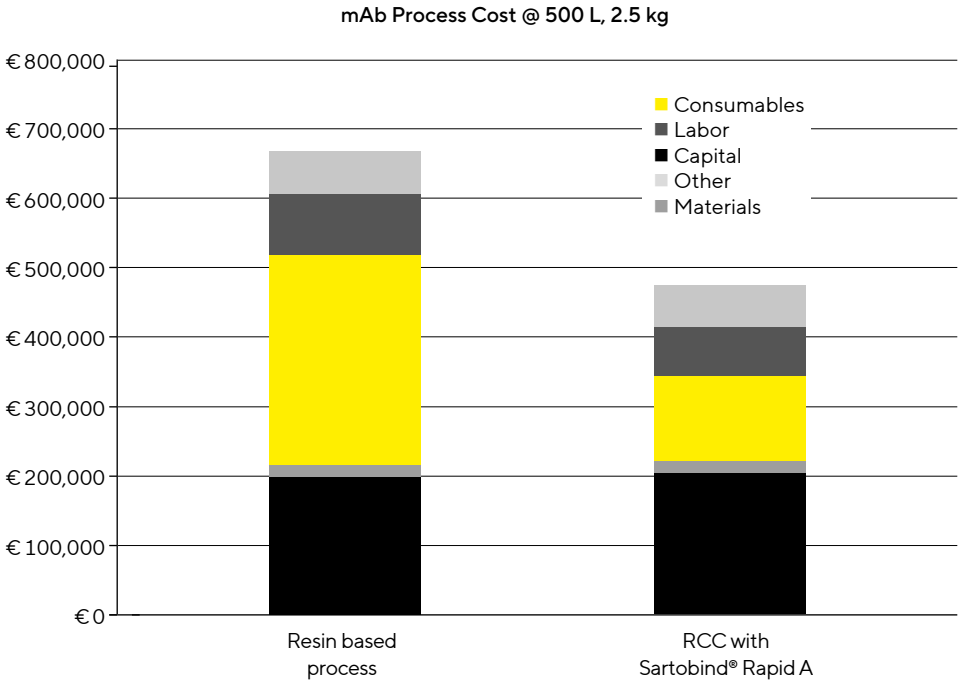


Figure 6: *Summary of Cost Reduction at Clinical Scale by Implementing Sartobind® Rapid A, and Process Cost Breakdown Showing That RCC Is More Cost Effective Than Processes Using Resins.*

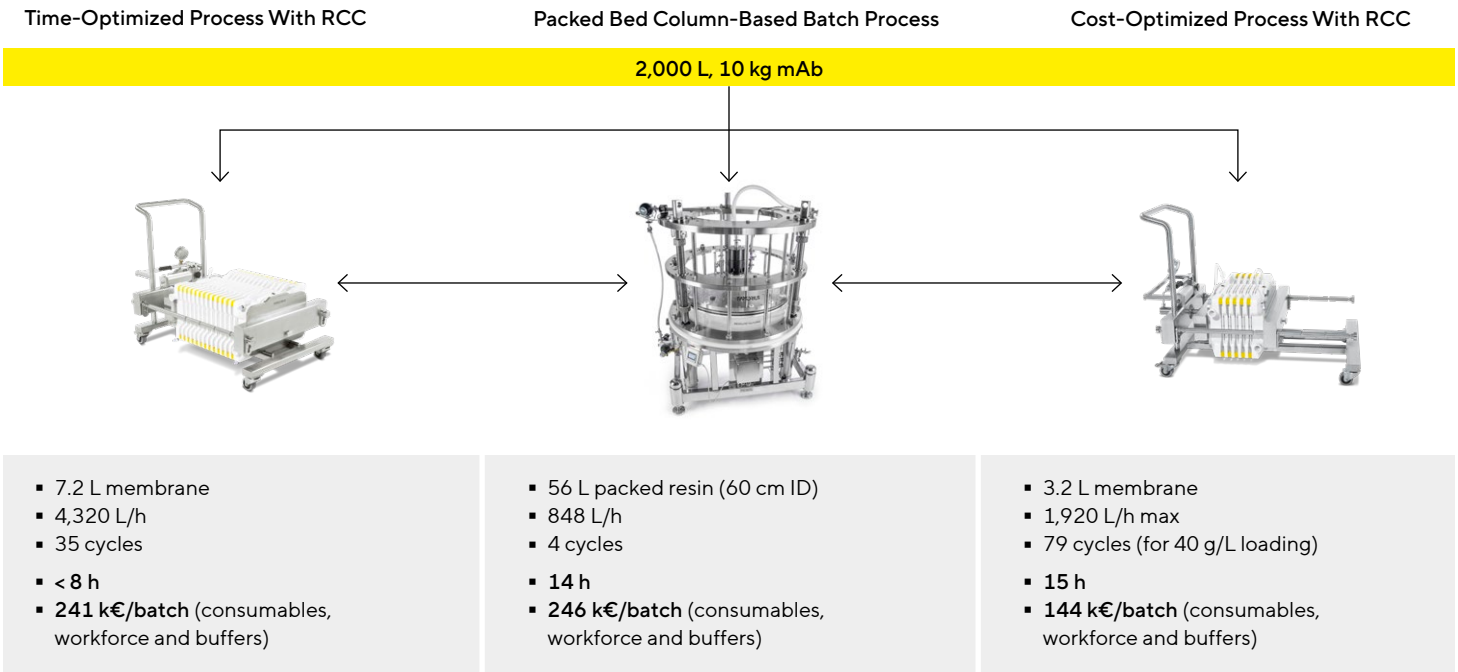
Case Study 3: Scalability, Flexibility, and Time-Savings at Commercial Scale

Scaling up from PD to manufacturing is an important consideration for any process as this can help shape PD and streamline the transfer to production from the onset.

Several features of Sartobind® Rapid A lend themselves to smooth scale-up. First, it is a very flexible platform that can easily adapt to different volumes and masses. Depending on the goals of a production batch, it is possible to design a faster process or a more cost-optimized process (Figure 7). Compared to a standard packed-bed chromatography step which utilized 56 L of media to process 10 kg mAb over 4 cycles which results in a run time of 14 hours. The CoGS for this capture step are around 246 k€ per batch including only consumable cost, workforce, and buffer.

Using Sartobind® Rapid A can allow processes to be run based on a certain target time. As an example, if the process should be realized within one 8-hour shift, one can process 10 kg of mAb mass over 35 cycles which requires 8 cassettes (equal to 7.2 L of membrane volume). The CoGS in this case would be in the same range compared to the resin-based process, but the membrane is better utilized in this scenario.

The second option with high productive membranes is to design a cost-optimized process. In this case, a smaller membrane volume (3.2 L) is used, and a higher cycle number needs to be reached (79 cycles). This enables better utilization of the membrane and a reduction of CoGS by 40%.



*Costs include consumables, hardware, workforce and buffers. Calculation made for clinical phase 3, 5 batches produced in a year

Figure 7: *Rapid Cycling Chromatography Provides Flexibility Regarding Process Time and Cost.*

Scale-up is also simplified with the Sartobind® Rapid A product range, allowing the production of small batches of several liters with a single membrane and large batches from 2,000 – 12,000 liters using the modular cassettes format, which are directly scalable from smaller capsule formats. This enables easy prediction and mapping of performance from PD to full-scale manufacture. Further scalability is simplified as it can be easily achieved based on capacity while flow rates, pressure behaviour, and bed height are kept constant.

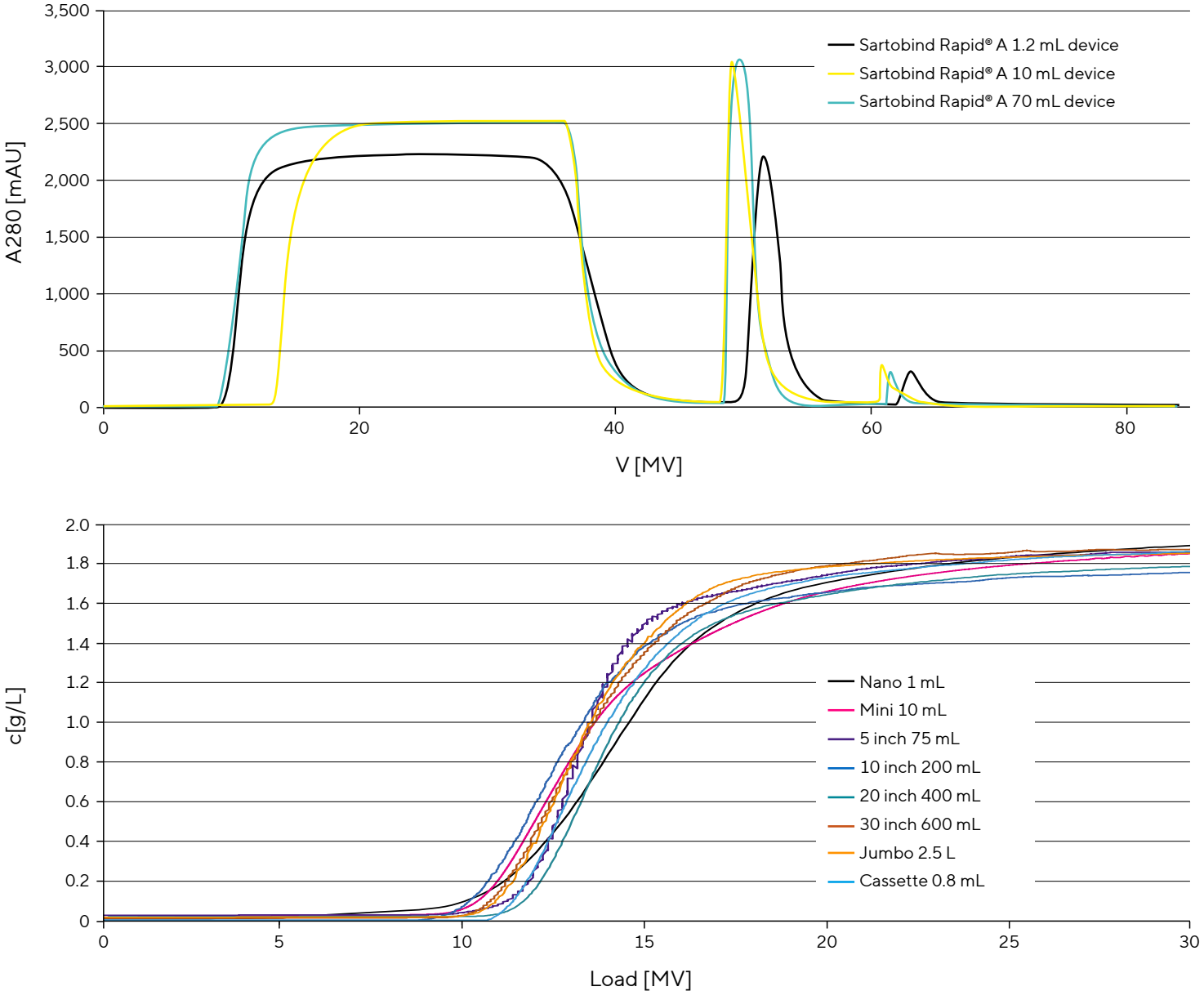


Figure 8: *Overlay of UV Chromatograms for 3 Different Device Sizes of Sartobind® Rapid A, and UV Traces of Breakthrough Curves With Sartobind® Q for All Device Sizes From Nano to Cassette.*

Paradigm Shift in Capture Chromatography With Membrane-Based Rapid Cycling Chromatography

Protein A affinity-based ligands have proven to be the workhorse at the capture chromatography step in effectively purifying the mAb from impurities coming from the cell culture process. However, its being increasingly accepted in the industry that using them in resin-based chromatography matrices comes with a drawback of higher process and business risk, lower productivity leading to higher cost, and ineffective lifetime utilization (particularly pre-commercial). With alternative membrane-based rapid cycling chromatography such as Sartobind® Rapid A one can effectively intensify the process to obtain high productivity (10 – 15×), improved product quality, cost-effectivity (>30% savings), and reduced risk, thereby having a positive impact to the overall efficiency of the facility during development and manufacturing phases.

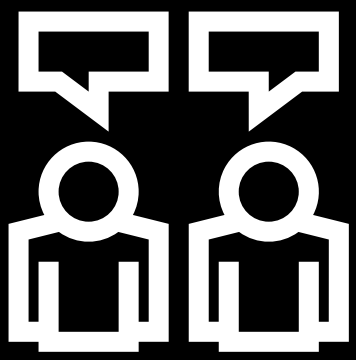
Though adoption of membrane adsorbers at the capture chromatography step could be perceived as a disruptive technology, they have been successfully adopted at the polishing steps and are increasingly becoming the platform of choice for newer molecules. Feasibility analysis, technology evaluation, change management, scale-up and successful implementation can be achieved effectively by leveraging on protocols and packages developed by solution providers as well as through active collaboration between the biopharmaceutical developers and suppliers.

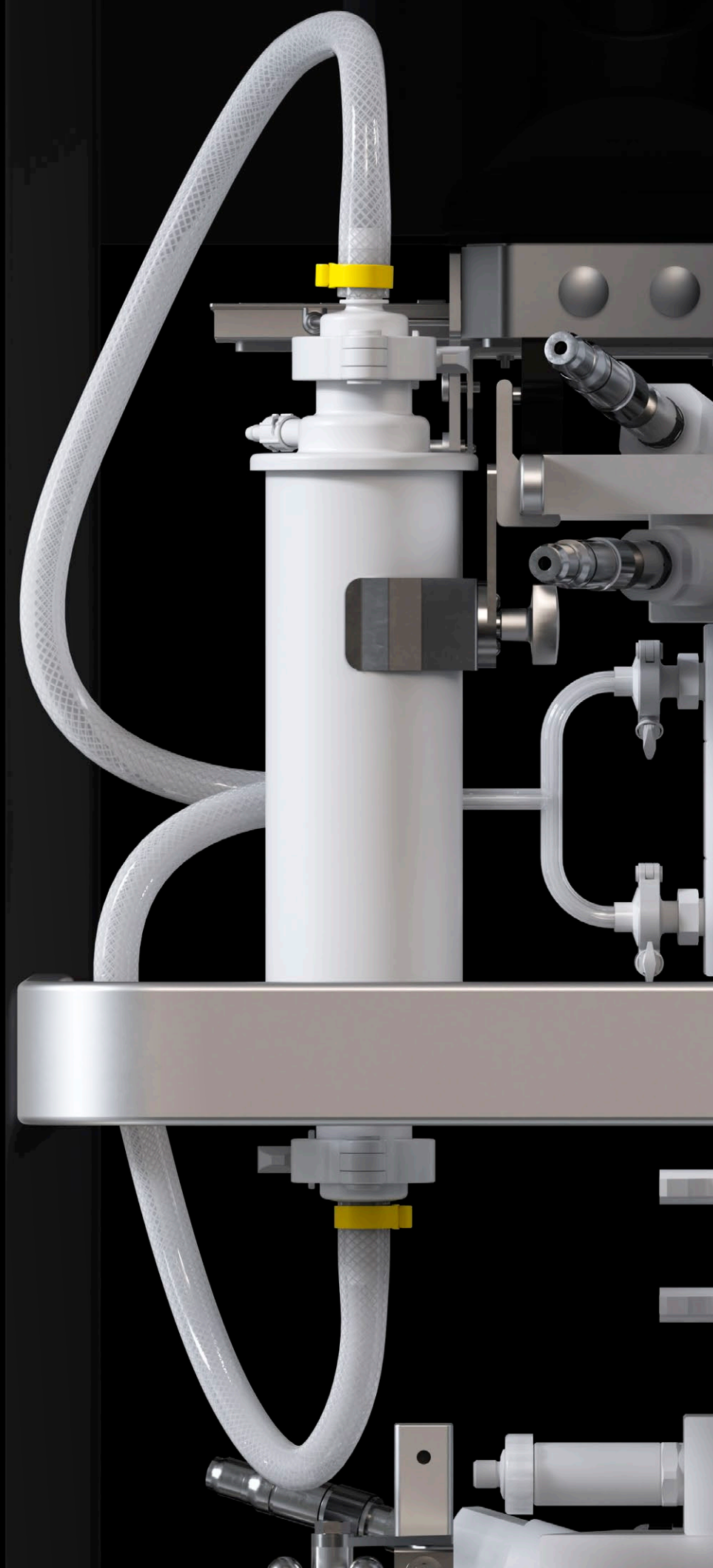
Want to Evaluate Sartobind® Rapid A for Increased Process Productivity?

Sartobind® Rapid A will help your team develop a thoughtful antibody capture process in PD and have a positive impact at all stages from MS&T to production and procurement. The technology is both simple to implement at a larger scale, and to evaluate at the bench.

Contact us today to learn more about Sartobind® Rapid A. Our team is on-hand to answer any questions and to provide technical guidance and support, including set-up and protocols.

For more information, visit
www.sartorius.com/sartobind-rapid-a





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Dr. Ricarda A. Busse joined Sartorius in February 2018 as a Product Manager for Membrane Chromatography.
She has a PhD in biology | biochemistry from the Georg-August University of Goettingen. She also holds an MBA from the European Fernhochschule Hamburg in General Management, where she specialized in digital and international marketing.

She has 8+ years of experience in the biotechnology and bioprocessing industry. Prior to joining Sartorius, she worked as Product and Marketing Manager for affinity chromatography solutions used for recombinant proteins at IBA Lifesciences. During her time as a doctoral candidate at the Max Planck Institute of Biophysical Chemistry, Geottingen, she worked on upstream and downstream process optimization of recombinant proteins from bacterial, mammalian and insect cell cultures.

Ganesh Kumar
MS, Integrated Solutions Manager, Sartorius

Ganesh started at Sartorius in 2016 as a Process Engineer | Consultant and was one of the key contributors to the development of the conceptual design platform to design end-to-end process platforms in SU facilities.
Today he fills the role of Integrated Solutions Manager. As part of the Integrated Solutions team at Sartorius, he actively works with clients to conceptualize, design, and deliver process solutions and platforms at clinical | commercial manufacturing stage for production of protein-based and cell | gene-based therapies.
He holds a Master of Science in Bioprocess Engineering from Technical University Hamburg-Harburg, Germany.

Ganesh started his career at Lonza, Singapore, where he was actively involved in the tech transfer, validation, and large-scale commercial manufacturing of blockbuster mAbs. Over the years, he has actively collaborated | led projects on process positioning, acquisitions, building the technical platform, solution packages and establishing strategic customer collaborations for process intensification.
He has over nine years of experience in the biopharmaceutical industry, both as an end-user and a solution provider.
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