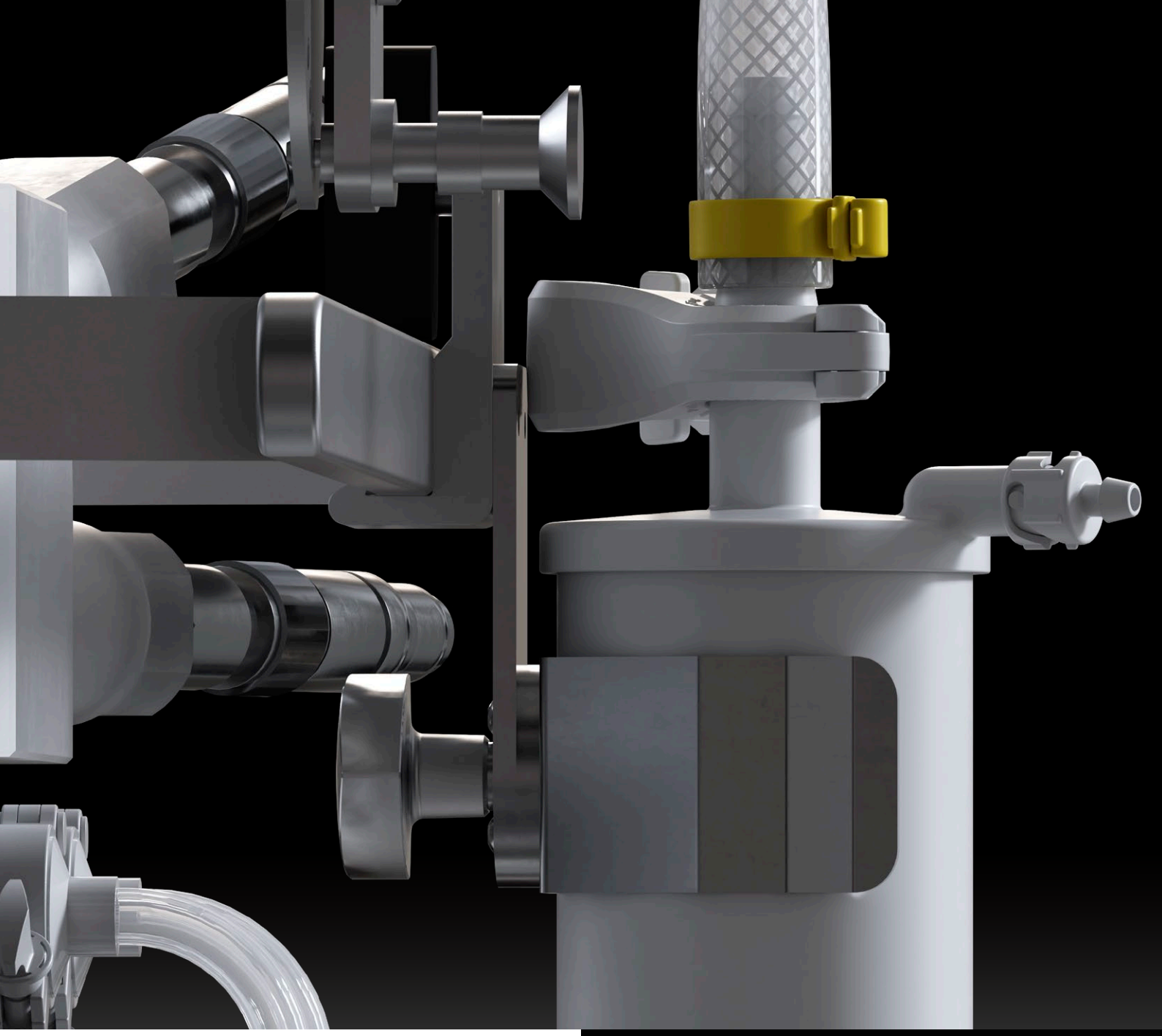

Simplifying Progress

Intensification Through Process Simplification

A Disruptive, Scalable, and Robust Capture Solution with Sartobind® Rapid A

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Introduction

Monoclonal antibodies (mAbs) are an extremely successful class of therapeutic agents for a wide range of diseases. Improving and scaling their production to be able to produce larger quantities more cost effectively is an important goal for the pharmaceutical industry. There are several hurdles to scaling a mAb production process which must be overcome. For example, the need to quickly amortize the entire production plant weighs in many of the strategic decisions occurring during manufacture, meaning fast turnarounds and highly productive processes are essential. That being said, the quality of the finished product cannot be compromised, so any solutions to improve productivity must perform comparably to established methods.

These challenges are also coupled with an industry trend towards orphan drugs and more personalized medicine: treatments are tailored for smaller patient groups, allowing to treat them with the right product. This leads to smaller antibody batch sizes (often only serveral liters up to <2000 L), where flexible manufacturing options are required. This shift effectively allows production plants to become multiproduct facilities to increase the overall throughput of the facility, which opens new revenue streams and opportunities to amortize the plant more quickly. To realize the opportunities provided by a multiproduct facility, new production solutions are required to accommodate all scales in a flexible way. This is partly linked to hardware and the way chromatography capture is performed. For example, large resin columns with long cycle times that take long periods of time to prepare and break down are not amenable to quickly changing production in a multi-product facility. Utilizing packed bed columns for mAb capture requires a large footprint, which impacts the overall facility design and floor space utilization.

Membrane chromatography technologies such as Sartobind® Rapid A provide an exciting new path towards scalability with shorter cycle times and a smaller production footprint. Considering alternative technologies to those currently in use may be attractive, however their implementation requires very close alignment with PD and procurement.

Considerations on Process Alignment

In general, simpler processes cause less problems when scaling, meaning that it is important that this simplicity is reflected in all development stages leading up to manufacturing. Simplification in PD means that technology transfer to manufacturing will be faster and seamless. For example, column packing, testing, and cleaning are all essential to the mAb capture process when using resins, but these steps can be eliminated if resins can be replaced with a simpler modality such as membranes. Removing these steps can make the mAb capture process more streamlined.

Simplification in procurement leads to better economies of scale when sourcing raw materials as well as making it easier to manage the supply chain. Complex methods with many different buffers and components are at risk of becoming delayed if one component cannot be sourced, or if supplies run low. However, if the number of components required can be reduced to a core number of readily available products that are simple to use and store, then supply chain issues and delays can be reduced.

Aligning PD and Manufacturing

The key to aligning PD and manufacturing is finding solutions to purification challenges that will easily scale. Membrane chromatography is already widely used for mAb polishing since it provides easy scale up, fast processing, and reduced buffer consumption. With Sartobind® Rapid A, membranes are now entering the mAb capture market providing a range of advantages. Firstly, there are many different device sizes available, ranging from 1.2 mL devices for process development to several liters of membrane volume for commercial production scale (Figure 1). In each production scale, the productivity is kept at a >10-fold increased productivity compared to resin-based processes. Membranes such as Sartobind® Rapid A are provided in ready-to-use formats and are very easy to implement for any production scale. This simplicity works both in PD as well as manufacturing, which helps make technology transfer go as smoothly as possible.

	96 Well Plate	Nano	Mini	5" Capsule	10" Capsule	Cassette	Cassette Assembly
Bed Volume	19 µL/well	1.2 mL	10 mL	75 mL	200 mL	800 mL	0.8 – 10 L
Bed Height	0.8 mm	4 mm	4 mm	4 mm	4 mm	4 mm	4 mm

Figure 1: *The Sartobind® Rapid A Product Portfolio Includes Screening Devices (96 Well Plate) As Well as the Scalable Devices Ranging From Nano to Cassette.*

Aligning Manufacturing and Procurement

When procurement processes go well, you hardly notice them. However, delays and missing inventory can significantly affect a manufacture operation causing unscheduled downtime and a loss in facility utilization. Carefully designing the manufacturing process can reduce the pressure on procurement and minimize the risk of downtime or delays caused by inventory shortages.

Production runs using resins require a lot of material that needs to be ordered months in advance, from columns and related spare parts to resins and buffers. This can be a significant problem if a resin needs to be changed sooner than expected. Of course, backup resin can be purchased and stored but this is expensive and significantly increases the footprint of the production facility with the need for purpose built cold rooms to store the additional resin. This leads to planning constraints, since resin unpacking and repacking are generally done as part of the column maintenance, often with the intervention of external companies. During clinical trials, prepacked resins can be used to avoid the packing constraints. But ordering those generates higher costs and longer lead times. Finally, they are limited in scale and transporting packed resins leads to risks of bed instability

This can be simplified with membrane and products like Sartobind® Rapid A. To give an illustration of the size differences, 65 L of packed resin can be replaced by 4×0.8 L cassettes. This means that by using membranes, the storage requirements of having backup chromatography equipment are not as high. It is also often faster to order, transport, and hand over smaller units that do not need any significant assembly. Ordering smaller quantities of chromatography media generally expediates lead times.

Another important factor for controlling costs is a reduction in wasted media. For each packing, up to 10% of the resin volume needed is added to fill the pipes used to deliver the resins and buffers to the column. Membrane cassettes can be a valuable alternative to remove the need for this extra chromatography media (caused by column packing operations) and resulting costs.

Ultimately, using a small pre-packed format brings strong benefits to manufacturing supply chain, enhances plant flexibility and reduces consumable lead time.

How Does Sartobind® Rapid A Improve Productivity?

Improve Facility Throughput

Efficient productivity is essential in manufacturing. Using Sartobind® Rapid A can significantly increase manufacturing efficiency and reduce time to amortization. One obvious way to increase the productivity of a chromatography capture process is to reduce the hands-on time related to manufacturing. Most hands-on interventions will cause production to stop. Therefore, reducing the number of interventions (as well as the downtime per intervention) can significantly improve productivity.

Implementing membrane chromatography is a good way to minimize handling. With a product like Sartobind® Rapid A, a relatively small device is installed very easily and used for a high cycle number in one batch without the need for replacement. If the production plant is using agile methodologies for production, they may implement a one-batch, one-membrane approach on a single-use system, meaning that cleaning steps are eliminated. The ready-to-use membrane is fully utilized after one production run. All column-related operations (packing, unpacking, maintenance, CIP, HETP) are removed which leaves more time in the plant to produce batches. Also, all validation studies (cleaning, shelf life) are significantly reduced as one single purification cycle takes only 10 minutes with membranes.

A significant productivity boost that comes from using membranes in place of traditional chromatography capture methods lies in the higher flow rates they can accommodate (residence time decreased by 20-fold). This gives the potential to either purify more product in a shorter amount of time, or at the same time but on very small consumable (Figure 2).

Figure 2 : *Time versus Cost Optimized Processing With Rapid Cycling Chromatography*

Reduce Facility Footprint

If a production facility is packing its own columns, then it requires additional GMP space and often a dedicated room with high ceilings. This effect on footprint and room design also impacts facility build time and costs since GMP factories are expensive to build and maintain.

The storage of columns can also increase the building footprint. Columns, resin containers and the large tanks used for packing take up a lot of storage space. Furthermore, all of this must be stored in a cold room to maintain the quality of the raw materials and decrease the risks of bioburden. The additional cold storage and packing facility can be eliminated (or downsized) if a plant moves over to a chromatography modality, like membranes. Membranes do not require a specialized packing room and the one-batch, one-membrane concept removes the need for storage while minimizing bioburden risks.

Of course, pre-packed columns could, in theory, eliminate the need for a packing room up to a certain scale. However, this doesn't always happen in practice. Pre-packed columns further increase CoGS and their lifetime is so long that if problems arise, it can incur a significant cost. At that stage, it is not economically viable to exchange a resin column for a new one, so the ability to re-pack a column becomes an essential safeguard in case anything goes wrong.

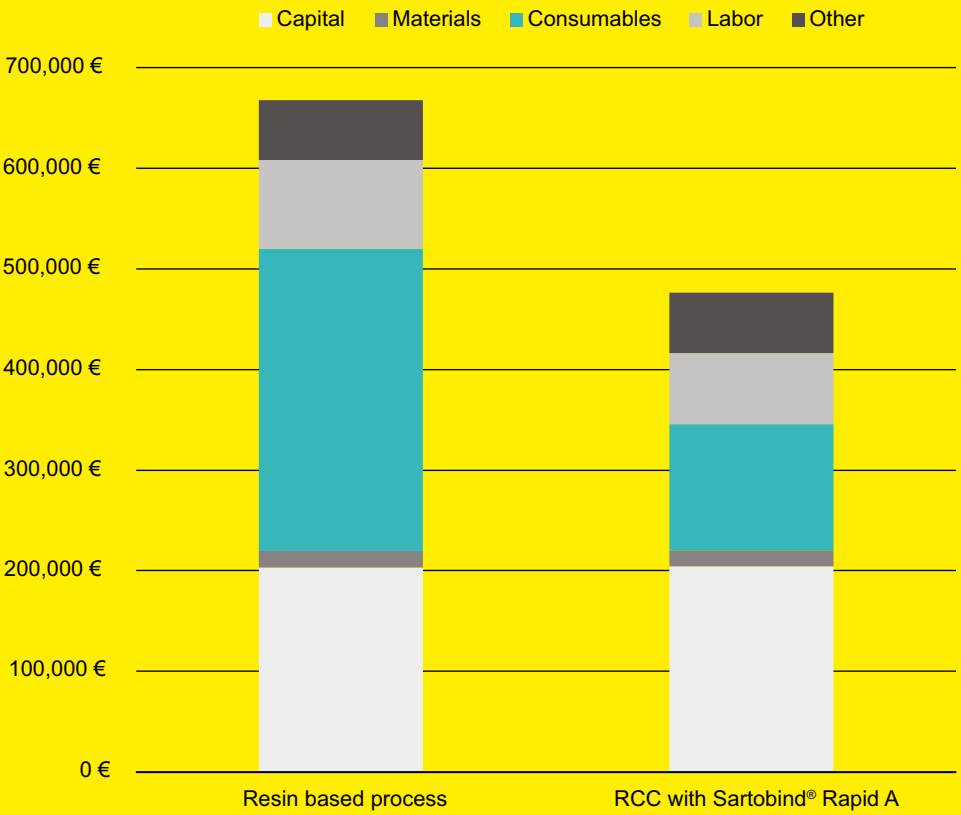
Lower Hardware Investments

On the day-to-day, hardware means maintenance and the more hardware there is in a plant, the higher the maintenance bill will be. Reducing hardware can therefore lower the cost to run a production plant. If you are building a new plant from scratch, there could be dramatic savings simply by reducing the amount of hardware that is needed. To begin with, this would reduce the capital outlay and equipment lead time to set up production. However, there is an additional benefit as we discussed before. Less hardware (such as columns, buffer tanks, packing stations and equipment like forklifts or other lifting tools) means there is less space needed to store and use this hardware. In the case of columns, we previously identified that GMP packing rooms could be removed and cold storage could be significantly reduced. This in turn has other cost implications, for instance, the reduction in use of electricity due to a smaller operation with decreased cold storage requirements.

Reduce Consumables Costs

Protein A resin is a key contributor to consumable costs in mAb processes (Figure 3). Resins need to be reused many times (more than 100 cycles) to be cost efficient, which is not compatible with clinical phase manufacturing or multiproduct facilities. The use of small membrane volumes is more cost-efficient for molecules with less than 300 kg yearly demand. Indeed, the full membrane lifetime can be used within one batch, amortizing more efficiently each liter of membrane. The costs linked to validation studies are also drastically reduced (no cleaning validation or shelf-life study required). Finally, the membrane bed is not unstable which avoids unplanned repacking, and the single-use nature alleviates bioburden issues which can lead to resin and product loss.

Thanks to all these advantages, it has been shown that affinity capture costs for a 500 L clinical phase process can be reduced by 30% using Sartobind® Rapid A. Changing to a modality like membranes can therefore bring high-cost benefits, even at larger scale.



Clinical scale scenario: prepacked columns reused over 3 bachtes each 5 cycles

Figure 3: *Comparison on Overall Process Cost (mAb Process Cost @ 500 L, 2.5 kg)*

Bridge Batch and Continuous Processing

Determining which production method (batch or continuous processing) makes the most sense, ultimately depends on factors such as the targeted production throughput and the finished product requirements. Continuous processing can be an efficient solution to intensify a process through different ways of handling chromatography media. First option is to use columns or membranes in parallel, in batch mode (Batch multi-column chromatography or "B-MCC") to ensure continuous loading. A second option is the simulated moving bed (or S-MCC) which puts two columns in series to fully saturate them, while operating other columns in parallel. This typically leads to columns with reduced bed height and short residence times. Since Sartobind® Rapid A offers quick cycling time and reduced bed height in ready-to-use format, it is very easy to integrate in B-MCC or continuous processes.

Indeed, with membranes, batch and continuous processing are very similar. A cycle with Sartobind® Rapid A takes around 10 minutes (Figure 4). Purification of the whole mAb mass could be done as a batch process. When run at a high cycle number, it can effectively run as a continuous chromatography capture process. It's possible to run 200 – 300 cycles over the lifetime of a Sartobind® Rapid A membrane which can be scaled based on binding capacity and forecasted processing time.

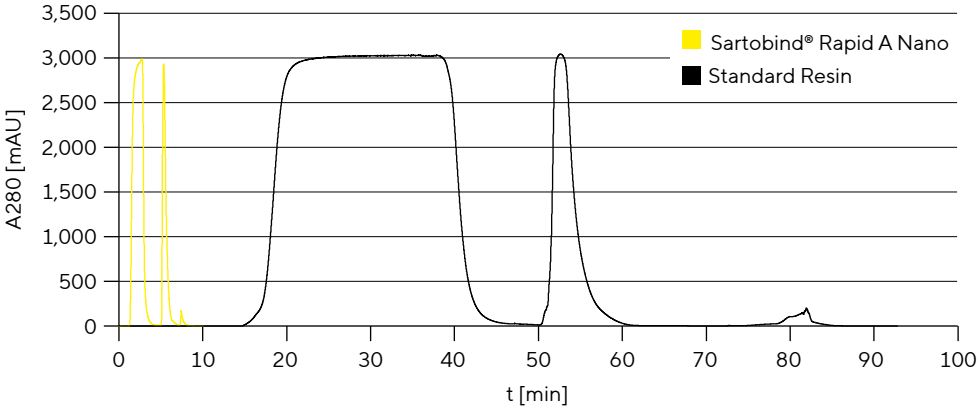


Figure 4: *Comparison of Cycle Times of Sartobind® Rapid A and a Standard Resin.*

Case Study – Lifetime Testing

Using Sartobind® Rapid A to run Rapid Cycling Chromatography (RCC) can significantly reduce the time spent on lifetime studies. With an RCC cycle time of 12 minutes, a 200-cycle lifetime study can be completed in 40 hours. The equivalent study in a packed bed column (PBC) setup has an average cycle time of 2 hours making a lifetime study of 200 cycles take 400 hours to complete (Figure 5).
The ability to complete lifetime testing in a short amount of time is advantageous for facilities looking to scale out the number of mAb products they produce.

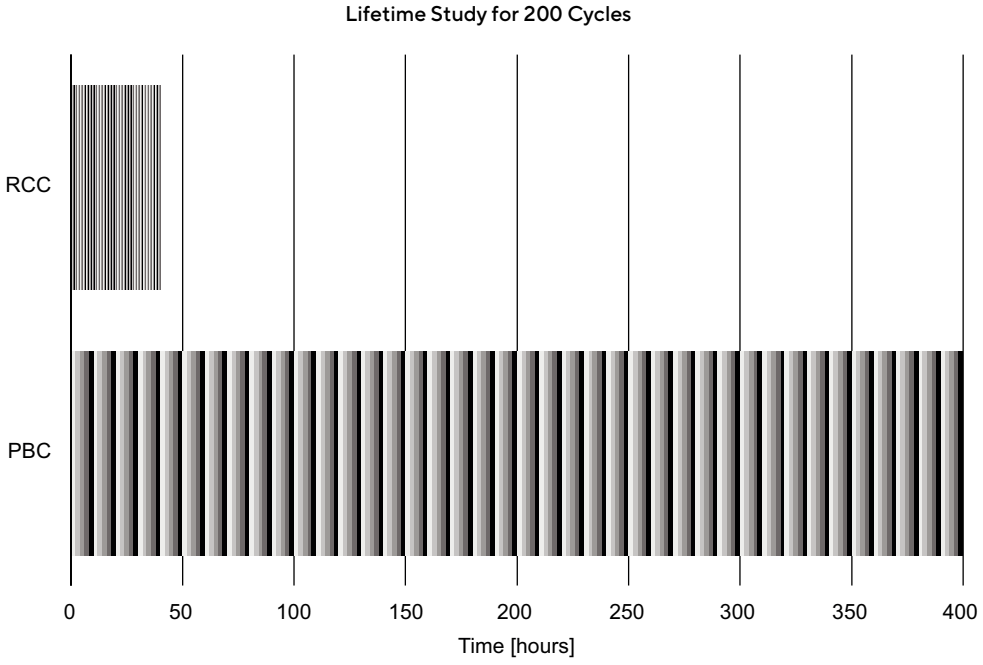


Figure 5: *Comparing the Time to Complete a Lifetime Study for RCC and PBC. RCC Cycle Time Is 12 Minutes and PBC Cycle Time Is 2 Hours in This Example.*

Conclusion

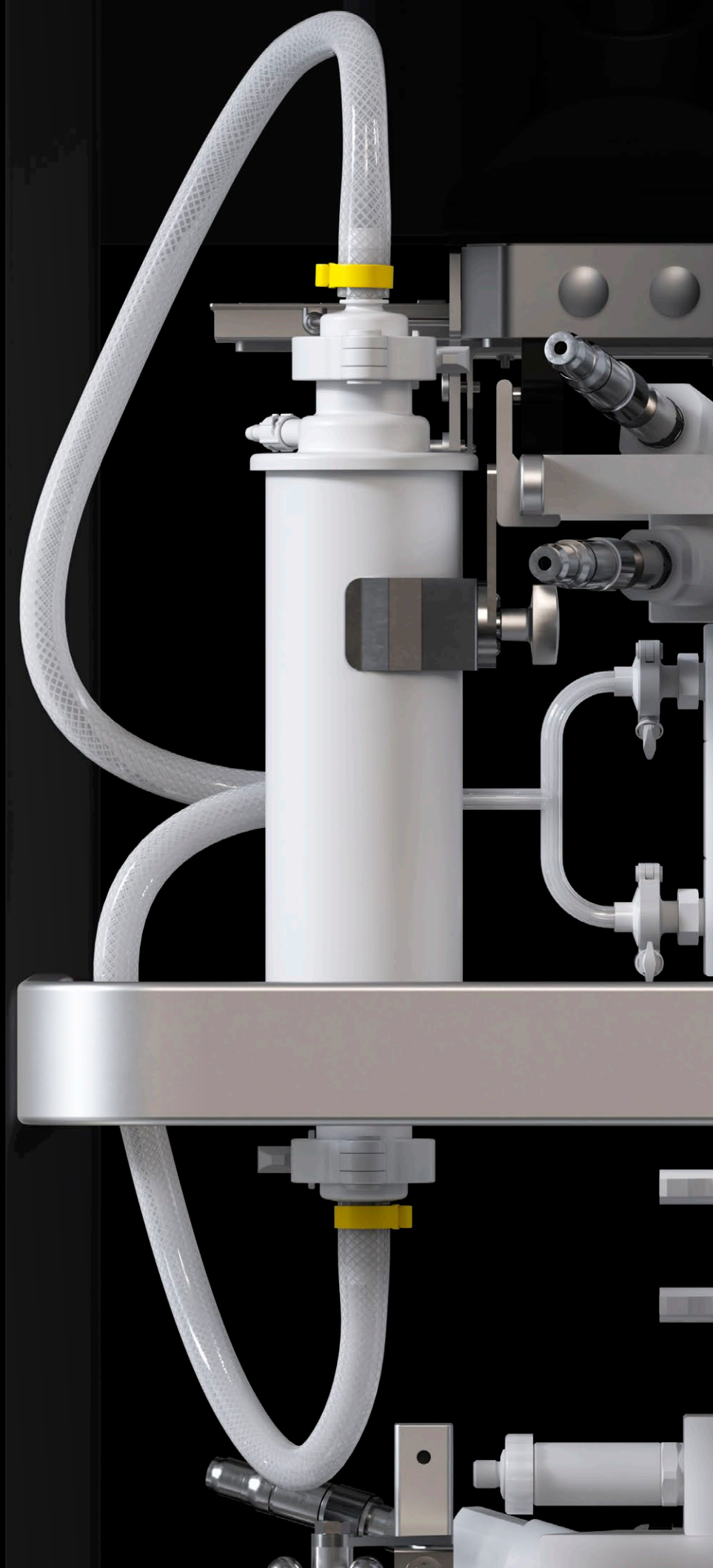
In closing, Sartobind® Rapid A is a real game changer in mAb manufacturing. It can increase plant productivity based on its fast flow, by removing column-related operations, minimizing validation efforts and by enhancing flexibility. It also reduces the costs for clinical phase manufacturing or multiproduct facilities by downsizing the media and making the best use of its lifetime. It streamlines the supply chain by ordering standard and relatively small, ready-to-use products. Finally, some of the risks that can lead to production downtime or expensive batch losses (contamination, bed instability) are eliminated. The Sartobind® Rapid A membrane technology opens the door for full membrane-based processes which will revolutionize the industry.

Test Sartobind® Rapid A For Yourself

There is so much at stake when it comes to improving manufacturing processes. If this whitepaper has shown you that Sartobind® Rapid A can make a difference in your processes, then the next stage is to try it out.

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



Author Bio

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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.

Geoffrey Pressac
Manager of Field Application Specialist Chromatography SE, Sartorius

Geoffrey Pressac has been working for Sartorius since January 2016, where he is Manager of South Europe Chromatography Field Application Specialists. He holds a Master's degree in biotechnology from Polytech Marseille.

Between 2016 and 2020 he worked as Application Specialist supporting the full downstream portfolio and since May 2020, he has been focused on chromatography. Since February 2022, he leads the South Europe team which supports customers on a wide range of topics like process development, DOE, scaling up, as well as training in systems and troubleshooting. He has experience in purifying both proteins and large molecules like exosomes, pDNA and a wide range of viruses. Before Sartorius, he worked for 3 years as Area Sales Manager at Texcell, a CRO providing viral safety services to support biopharmaceutical development.

Xindao Mao
Product Manager Chromatography Systems, Sartorius

Xindao joined Sartorius in December 2019, where he is Product Manager Chromatography Systems. He holds a Master's degree in chemical engineering from RWTH University Aachen, Germany.

Today, Xindao manages chromatography skids applied to different technologies such as RCC, MCC and single-use chromatography. Before joining Sartorius, he worked as Corporate Product Manager at IKA-Werke. In this position, he managed the global business of several product groups in laboratory and analysis technology and successfully led the global launch of several key products.

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