

Membrane Adsorbers

A Cutting Edge Process Technology at the Threshold

Uwe Gottschalk, Stefan Fischer-Fruehholz, and Oscar Reif

Membrane chromatography — or the synonymously used expression *membrane adsorption* — is an essential process platform technology. After some 20 years of development with drawbacks, disappointments, and crucial innovations, the current generation of membrane adsorbers plays a central role in today's biotech processes amid numerous economic and regulatory challenges. Efficient development and use of this technology is an important strategic factor as the biotech industry matures and faces consolidation. Modern membrane adsorbers address current trends in state-of-

PRODUCT FOCUS: PROTEINS AND VIRUS PRODUCTS

PROCESS FOCUS: DOWNSTREAM PROCESSING: ION-EXCHANGE AND AFFINITY CHROMATOGRAPHY

WHO SHOULD READ: PROCESS DEVELOPMENT MANAGERS, DOWNSTREAM PROCESSING MANAGERS

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LEVEL: INTERMEDIATE



Membrane adsorber technology is entering biopharmaceutical production suites
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the-art downstream processing: full development pipelines with manufacturing capacity limitations, process integration to overcome complex supply chain scenarios, growing cost awareness, high quality demands, and other driving forces toward higher efficiency and productivity. Multiple- and single-use membrane adsorbers build the basis for the most efficient separation of biopharmaceuticals and the removal of unwanted process-related or endogenous impurities. Various application examples set the stage for fast purification-train assembly from modular, predeveloped unit operations allowing a standardized, seamless process transfer with reduced engineering costs and reliable economic calculations.

This is a short overview about the present capabilities and

limitations of membrane adsorber technology in protein and virus purification using Sartorius membrane adsorbers. For reviews of membrane chromatography, see references 1 and 2.

THE PROCESS VIEW

Of central concern in process performance is the ability of membrane structures to cope with the growing demands of the feedstream in biotech manufacturing. Such demands result from a clear trend toward very large-scale applications that require optimized throughput and must accommodate significantly increasing expression levels in the upstream. In cell culture, fermentation is setting the pace with rapid progression of cell line and technology development; routine production of

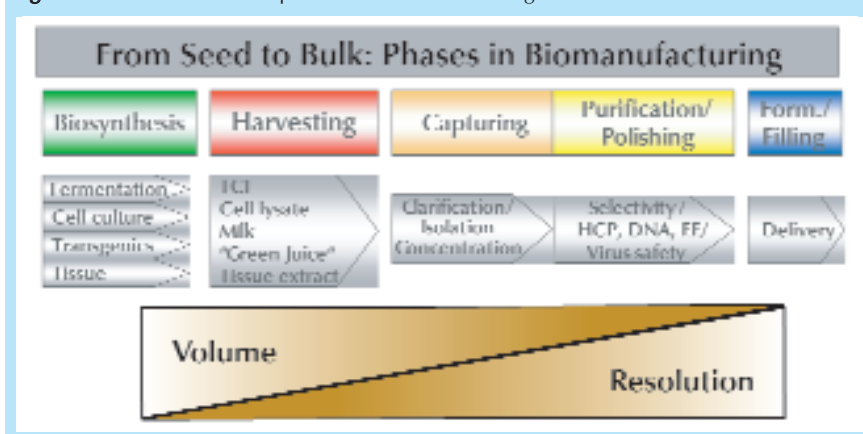
glycosylated proteins in the 1–3 g/L range is becoming feasible. This is further reinforced by advances in microbial fermentation and access to transgenic options.

Innovative concepts are welcome because downstream processing contributes up to 80% of the total production cost of a biopharmaceutical purification (3). Bringing products to market faster and improving process economics helps manufacturers compete successfully. For example, the batch yield of a product after ten production steps with a 95% yield per step results in a purification yield of 60% for the complete downstream process. With 90% yield per step, the overall yield drops to 35%. Further, with a supposed price of \$250 per dose and a given batch yielding 10,000 doses at 60% purification yield, the decrease of value would be from US\$2.5 million to \$1.45 million — a loss of \$1.05 million.

Modern large-scale downstream processes for secreted biomolecules derived from fermentation follow a streamlined concept of cell removal, capturing, intermediate purification, and polishing. A new trend is for the capture step to play an increasingly important role in removing more than 90% of bulk impurities (Figure 1).

It is now widely accepted that the ideal capture step quickly isolates a product from the feedstream. Harvesting is usually the first nonsterile process step. Because the feed solution becomes contaminated as it matures, speed in column loading is extremely important. Primary selection criteria for media used in the capturing step therefore focus on efficiency, yield, concentration factor, and clearance of major contaminants. Because

Figure 1: From seed to bulk: phases in biomanufacturing



dynamic capacity under physiological conditions is central to the screening process, results are often optimized for conductivity and contact time (specific process parameters).

Additional polishing steps ensure clearance of viruses and other infectious agents and remove key impurities such as host cell proteins, media components, aggregates, product variants, nucleic acids, endotoxins, and proteases. In any case, every batch of material must meet end-product specifications. Robust and reliable processes are the basis for comparability of different production versions, scales, and manufacturing sites for complex biotech products such as recombinant proteins, monoclonal antibodies, and virus particles.

Trends in bioprocess engineering and fermentation development are prompting continuous improvement in downstream processing operations. Despite the complexity of biotech processes, there is room for innovation using integrated unit operations, automation, and rational design of facilities and equipment. During the recovery phase, the combination of clarification (cell removal) and capturing composes an ideal scenario.

TECHNICAL BACKGROUND OF MEMBRANE ADSORPTION

The limitations of preparative low-pressure chromatography result from packing large-scale columns with coarse resins. Large particles create diffusion limitations (especially for macromolecules) and have a negative effect on resolution that increases with increasing flow rates.

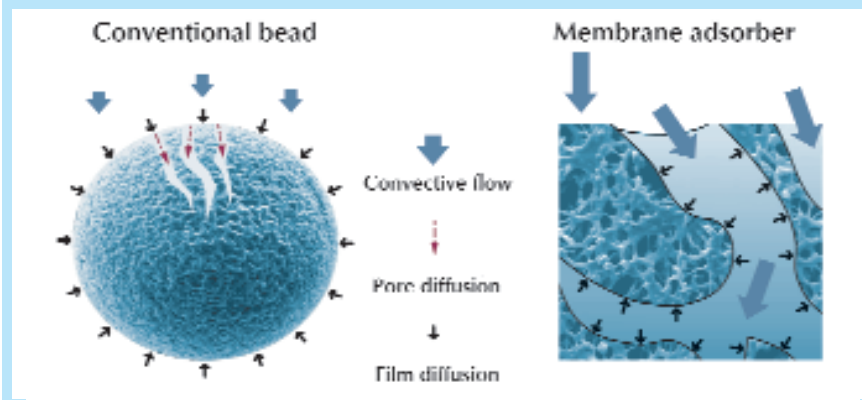
Some 10 years ago, perfusion chromatography addressed this problem with newly designed resins. In perfusion chromatography, the convective flow of the mobile chromatographic phase accesses the core of particles (flow-through pores) to provide high linear flow rates of more than 1000 cm/h during routine processing. These are attempts to mimic the natural hydrodynamic properties of membranes, although still at least one order of magnitude below their actual performance limits.

The highest convective flow rates and mass transfer rates at low back pressures are reserved for membranes that reflect breakthroughs in batch cycle times and therefore overall process performance. Membrane pore sizes of 0.45 (or >3) μm are two orders of magnitude above those of gels. In addition, the ratio of bed

Table 1: Data of Sartobind ion-exchange MultiSep 50 cm (20 inch) standard modules

Module size	Membrane bed height (mm)	Membrane bed volume (L)	Nominal membrane area (m ²)	Nominal number of layers	Nominal flux (L/min × 0.1 MPa)
MultiSep 15-50	4	0.56	2	15	10
MultiSep 30-50	8	1.1	4	30	5
MultiSep 60-50	16	2.1	8	60	2

Figure 2: Comparison of existing transport phenomena in conventional beads and membrane adsorbers



surface to bed height is 10–100 times larger than in columns. The chromatographic adsorber bed of Sartobind MultiSep modules is formed by stacking 15, 30, and 60 membranes to bed heights of 4, 8, and 16 mm. A 15-layer 560 mL (2 m² membrane area) Q module generates a flux of 10 L/min at 0.1 MPa (Table 1). Because of the relation between linear flow and pressure, flux may increase up to 60 L/min at 0.6 MPa.

Downscaled MA 75 Luer Lock units (15 layers, 75 cm², flow rate at 0.1 MPa >27 mL/min) are used for the initial experiments. It is possible to scale up directly to process 15-layer modules. Although it is easy to connect several units by the Luer Lock connectors up to the desired number of layers, it would be advantageous to construct 30- and 60-layered small-scale units instead. Membranes available at this time offer high flow rates and sufficient binding capacities. Current options with >3 µm pore size include ion-exchange and iminodiacetic acid metal chelate membranes. Affinity or coupling membranes such as epoxy- and aldehyde-activated membranes or protein A are available in the 0.45-µm pore size. The highest binding capacities for proteins such as lysozyme or bovine serum albumin (BSA) are presently available on the strong ion-exchanger in the range of 30 mg/mL (0.8 mg/cm²).

A disadvantage at this time is the fact that the manufacturer produces

only one adsorber membrane with one pore size for each ligand. As the number of applications grows, we will observe the same differentiation to a variety of membrane pore sizes that we have seen in the history of conventional chromatography media.

An intrinsic property of macroporous and microporous membranes is that transport phenomena are convection driven (rather than dependent on the pre- and intraparticle diffusion of solute molecules in beads). That fact compensates for the generally smaller available surface and makes scale-up and processing of very large feedstream volumes much easier than with conventional packed bed chromatography. Binding sites in adsorbers are exposed to the molecules within short diffusion distances (film diffusion), whereas 90–95% of bead ligands will be reached only by large diffusion distances and pore diffusion (Figure 2).

Studies using confocal microscopy on the intraparticle protein transport in porous bead-type adsorbents demonstrate that it takes hours even under static conditions before a diffusion-controlled process leads to protein uptake in the core of chromatography resins, whereas the internal surfaces of adsorber membranes in the flow-through pores are accessible by convective transport at a much faster rate (4, 5).

Even second-generation adsorbers on which polymer chains have been grafted to multiply potential binding sites (and therefore binding capacities) demonstrate only minor

contributions of additional rate-limiting diffusive effects. At extremely high flow rates with three-dimensional adsorptive layer structures, it is possible to keep the mass transfer high without significant loss in resolution. The space-time yield of such high-capacity adsorbers can be about six times higher, with a constant dynamic capacity over a wide range of flow rates compared with polymer-based chromatography resins (6). The open membrane structure combines the advantages of excellent flow characteristics (and thus productivity) with the high selectivity of classical chromatography.

CAPTURE WITH MEMBRANE ADSORBERS

Membrane chromatography achieves its full potential in the fast and efficient processing of large amounts of liquid. Membrane adsorbers meet all requirements needed in a capture step, recovering large volumes with rather dilute proteins — in most cases not the main constituents.

In most biotech processes, the handling of a diluted feed stream is associated with high manufacturing costs. The most important task is bringing that volume down as quickly as possible. The feasibility of membrane adsorbers for fast and efficient capture has been demonstrated by numerous examples. Among these applications are the preparative purification of human serum albumin from human plasma (7), continuous large-scale purification of bovine lactoferrin (8), ion-exchange chromatography of monoclonal antibodies (9), large-scale purification of oligonucleotides (10), and virus purification (11). In all those examples, the evaluated membrane adsorbers proved superior compared with traditional chromatography in time-yield performance, flow-independent binding capacity, and short cycle time.

Whether or not membranes are the right choice for a bind-and-elute separation is assessed case by case, depending on a number of process-related parameters: product and matrix, operation lifetime of

sorbent, number of cycles, cost of goods, validation, cleaning effort, and so on. Because to date membranes cost more than resins capacity-wise (measured with small proteins at low flow rates), they need to be operated as multiuse devices and in a format exploiting their hydrodynamic advantages.

Meanwhile, process type adsorber systems based on cylindrical module geometry with up to 100 m² are becoming available (12). With a combination of different adsorber modules in parallel or serial connections, key parameters such as breakthrough behavior and (low-) flow resistance can be optimized. Scale-up by combining individual modules provides a large window of operation, reduces investment, and increases flexibility.

Figure 3 shows a cross-section of the Sartobind MultiSep cylindrical module and a capsule. In these modules and capsules, the membrane adsorber is rolled up to form the chromatographic bed. The feed (red) enters the module from the top and is distributed by a central dead-volume-reducing core to the internal membrane channel. Then the solution passes the membrane layers axially. The eluate arrives at the external channel (blue) and is collected at the outlet. Flow is from inside to outside to prevent any deterioration of the module at high flow rates. By contrast, the capsule is constructed similar to a filtration capsule and can be discarded after a single use.

In a typical experiment with multistage equipment, 60 g of hemoglobin could be purified from bovine blood in a single step (adsorber size 16 m², cycle time seven minutes). The theoretical productivity of such a unit with a 4.3-L bed approaches tons of protein per year. Up to 1000 cycles have been performed on small-scale equipment without loss of performance. Even elution with linear gradients is easily possible by increasing resolution as a function of the number of membrane layers.

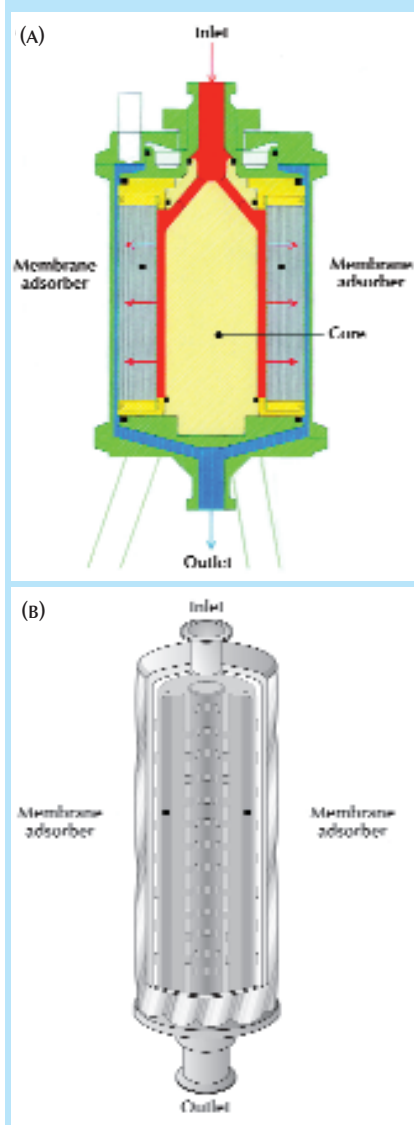
Adsorbers can reduce size

exclusion effects typically observed during conventional chromatography of molecules larger than 100 kDa. Comparable but slightly lower capacities on membranes measured with small standard proteins increase when looking at large molecules such as genomic DNA or even viruses (Table 2).

DNA-binding capacity on membranes is much higher (and faster) than on beads and is accepted for economic DNA removal from pharmaceutical antibodies (13). To measure that capacity, a monoclonal antibody dissolved in a 10-mM phosphate/250-mM NaCl buffer (pH 7.25, 25 mS/cm at a concentration of 0.63 mg/mL) was spiked with 25 µg/mL of DNA isolated from CHO cells. A total of 900 mL was run through a Sartobind Q 100 anion-exchange unit (area 100 cm²) at a flow rate of 30 mL/min. A small continuous increase of the 254-nm line, starting at 620 mL of effluent, indicated breakthrough. The dynamic binding capacity for the membrane (275 µm thick) was determined to be 156 µg/cm² or 5.6 mg/mL. The dynamic binding capacity for an anion-exchange bead matrix — Q Sepharose FF (Amersham Pharmacia Biotech, Uppsala, Sweden) — in a chromatography column of 7 cm by 1 cm was determined at 0.6 mg/mL of DNA at a flow rate of 78 mL/h (13).

For viruses, membrane ion-exchange chromatography seems to be the only practical option (11). The analytical ion-exchange chromatography of adenoviruses on membranes is already a standard offered by a number of manufacturers. The “Small-Scale

Figure 3: Cross section of cylindric Sartobind MultiSep Membrane Adsorber module system (A) and a SingleSep capsule for single-use contaminant removal (B)



Adenovirus Purification Protocol” box presents a typical protocol for small-scale purification of adenoviruses using Sartobind Q 5 (5 cm² area).

Those results are shedding a different light on cost

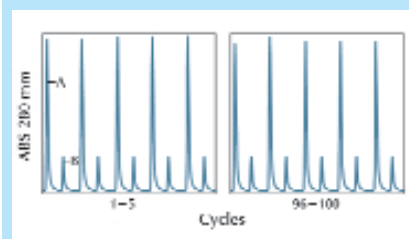
Table 2: Comparison of the dynamic binding capacity for DNA on a membrane adsorber and on a bead-type strong anion exchange matrix.

	Flow rate mL/hr	DNA µg/mL	Binding capacity mg/mL
Sartobind Q 100 (100 cm ² = 2.8 mL)	1800	25	5.6
Q-Sepharose FF (8.6 mL)	78	25	0.6

SMALL-SCALE ADENOVIRUS PURIFICATION PROTOCOL WITH SARTOBIND Q 5

1. Amplify adenovirus in HEK 293 cells grown on three 100-mm dishes with 10–12-mL medium.
2. Once nearly all the cells are detached, collect the medium and cells in a 50-mL conical tube. Keep at -20°C until purification.
3. Thaw and freeze totally three times. Make sure that temperature of solution will not be higher than room temperature (RT) at any time in thawing.
4. Centrifuge at 3500g for 10–15 minutes to pellet cell debris.
5. Prefilter through a $0.45\text{-}\mu\text{m}$ filter
6. Add same volume (or weight) of adenovirus dilution buffer (20 mM Bicine 0.6 M NaCl, pH 8.4, adjusted with HCl, at RT) and filter medium and buffer.
7. Prewet one Sartobind Q 5 (Luer Lock connectors) with 2–5 mL saline.
8. Filter through all the medium and buffer (color is supposed to be purple) with one Sartobind Q 5 attached with 10-mL syringe and 18 gauge needle.
9. Wash with 30 mL adenovirus washing buffer (10 mM Bicine 0.4 M NaCl, pH 8.4 at RT) and remove all the liquid from membrane.
10. Elute the adenovirus with 1 mL adenovirus elution buffer (10 mM Bicine 0.61 M NaCl, pH 8.2 at RT) by pushing slowly using a 1-mL syringe.
11. Count particles by measuring OD with 0.1% SDS PBS. A typical yield will be $0.7 - 1 \times 10^{12}$ particles/mL.

Figure 4: 100 Purification cycles of human IgG on Sartobind protein A; each cycle contains two major peaks: A = flow-through is mainly serum albumin; B = IgG fraction eluted with 0.1 M glycine at pH 2.3



considerations. When a process requires very high flow rates, and the target molecule is large enough (or if it is a virus particle), an economic calculation clearly favors membrane adsorption technology.

Affinity membranes are a subgroup of membrane adsorbers. Here the thermodynamics of adsorption are determined not only by the overall flow characteristics, but also by an underlying bioaffinity interaction between ligand and target molecule. Because separation should occur under physiological conditions, the recommended association constants are above certain critical values. For affinity

chromatography of antibodies, protein A membrane adsorbers based on polysulfone and regenerated cellulose were evaluated in a recent study (14), which revealed good selectivity for human IgG and a reusability performance in repeated adsorption-elution cycles.

Figure 4 presents the result of a typical repeated cycling experiment with a laboratory-scale unit and a monoclonal antibody from $0.45\text{ }\mu\text{m}$ of prefiltered human plasma. Loading and elution is performed within seven minutes on a Sartobind recombinant protein A analytical unit (three layers, 9.3 cm^2). Elution was achieved with 0.1 M glycine at pH 2.3. The first large peak of each cycle represents the flow-through of unbound proteins, mainly human serum albumin; peak B represents the eluted IgG fraction. Cycles 1–5 and 96–100 are shown. The constant peak sizes of the eluted IgG fraction also represent a stable linkage of the protein A ligand on the matrix.

POLISHING WITH MEMBRANE ADSORBERS

If the target protein is the major constituent of the feed, then

impurities such as DNA, viruses, or host cell proteins are very efficiently removed in a polishing step.

Established cell lines for the production of glycosylated proteins contain infectious viruses or virus-like particles. In addition to those endogenous agents, mammalian cells are susceptible to process-related infections with adventitious viruses. Several independent safety measures must be taken to ensure that a downstream process can clear a potential virus load. Retrovirus titers must be determined in the bulk harvest, and regulations require that the purification process demonstrate an overall virus reduction potential far above that determined level in the ensuing virus validation studies. Other critical impurities of biotech processes include DNA, infectious agents of the prion-disease type, and other host-cell-derived impurities such as endotoxins and proteins. When the protein is the major constituent of the feedstream, unwanted contaminants must be removed efficiently in a polishing step.

The traditional unit operation for removal of trace contaminants such as DNA, host cell proteins, endotoxins, and infectious agents has been flow-through chromatography. Typically, traces of DNA require only a small amount of resin relative to the volume of process solution. Because of flow-rate and pressure limitations in conventional chromatography, these steps require large columns, with the associated drawbacks of hardware investment, column packing, validation efforts, and additional handling. By comparison, a small, disposable in-line membrane adsorber unit with no regeneration and validation requirements and a breakthrough capacity independent of flow rate is clearly advantageous. Load-to-volume ratios of chromatography steps versus membrane adsorption in a polishing situation differ by a factor of at least 100.

Several authors have reported a DNA breakthrough capacity for membrane adsorbers that was constant over a 4–9 pH range and

at conductivities <40 mS/cm, with complete removal of typical DNA levels and a 23-fold process time reduction compared with chromatographic beads. Besides the superior pressure–flow relation, benefits included ease of handling for set-up and a considerable yield improvement (9, 13). In large-scale experiments of 2000-L and 12,500-L batches of a cell harvested monoclonal antibody purified by a Protein A column (Table 3), the DNA burden was cleared to the detection limit with Sartobind Q (13). Excellent removal rates have also been reported for proteases and endotoxins (15).

In addition, disposable membrane systems can remove typical host-cell-protein loads even under worst-case conditions, as demonstrated under normalized economic conditions (cost per kg of antibodies processed per hour).

Membrane adsorption represents a robust step for virus clearance. The virus-reduction potential of strong anion- and cation-exchange membranes has been documented in a number of experiments, in one of which a clearance validation for a registered monoclonal antibody was performed. Typical model virus loads were reduced by about four logs under downscaled process conditions (16) as listed in Table 4.

LIMITATIONS AND FUTURE WORK

Despite some major limitations of classical chromatography — such as the high pressure drop of a packed bed, long cycle times, and scale-up problems with conventional chromatographic supports — this technology represents the industry standard for most downstream separations. Classical distribution chromatography with pulse injection, high-end capacity separations especially of low molecular weight components, and applications that require high-end resolution with HPLC-type equipment will probably remain in the area of column chromatography. Complementing rather than replacing column chromatography is the next logical step.

Table 3: Sartobind Q used in process scale manufacturing of 2000 and 12,500 liter batches to clear DNA below detection limit

	Batch Size	Number of Batches	Average DNA after Affinity Purification Step (pg/mg protein)	DNA Concentration after Sartobind Q (pg/mg protein)
Sartobind Q MultiSep 15-06 (15 membrane layers, 6 cm height, 70 mL bed volume)	2000	8	168	<8
Sartobind Q MultiSep 15-50 (15 membrane layers, 50 cm height, 560 mL bed volume)	12,500	3	187	<4

Table 4: Virus clearance under downscaled conditions with Sartobind Q

Viruses	Size (nm)	Clearance by Sartobind Q Run 1, Factor (log ₁₀)	Clearance by Sartobind Q Run 2, Factor (log ₁₀)
SV-40: Simian Virus 40	45	1.25 ± 0.46	1.34 ± 0.43
Reo-3: Reovirus Type III	75–80	4.07 ± 0.50	3.62 ± 0.42
MuLV: Murine Leukemia Virus	80–110	3.80 ± 0.39	4.40 ± 0.56
PRV: Pseudorabies virus	150–250	3.97 ± 0.44	3.88 ± 0.38

For membrane adsorbers, the efficiency of flow distribution, and hence use of the accessible surface, remains a challenge. Inefficient flow distribution as well as lower surface-to-bed volume ratios lead to lower binding capacities of membrane adsorbers than with beads. Developments are progressing to overcome those limitations through intelligent combinations of filter elements. Modern adsorbers show breakthrough curves that are indistinguishable from packed-bed separations. Despite broad success and applicability to various separation tasks, and although the first pharmaceutical made using membrane adsorbers has been approved by the FDA (16), membrane adsorption is still in its infancy — compared with more than 60 years of practical experience in chromatography — as a separation technique. Chromatography and filtration — two mature and irreplaceable unit operations — are coming together,

and membrane adsorption may be the perfect synergistic match for both capturing and polishing of biomolecules.

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Corresponding author **Uwe Gottschalk** is head of GMP protein manufacturing for Bayer AG, Friedrich-Ebert-Str. 217-333, D-42096 Wuppertal, Germany, 49-202-36-7704, uwe.gottschalk@bayerhealthcare.com; **Stefan Fischer-Fruehholz** is product manager (stefan.fischerf@sartorius.com) and **Oscar Reif** is vice president of R&D and technology (oscar.reif@sartorius.com) at Sartorius AG, D 37070 Goettingen, Germany.

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