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Solving cost and supply challenges in biopharma downstream processing

Monoclonal antibodies (mAbs) are the dominant therapeutic modality in the biopharmaceutical industry, representing the largest sector of the market [1]. As of 2022, more than 100 mAb therapies have been approved by the FDA – over twice as many as had been approved only 5 years ago [2].

Behind the rapid rise and longstanding market dominance of mAbs are the high levels of specificity and affinity with which the pharmaceuticals bind to their targets, as well as the variety of therapeutic areas the biologics can address.

As the demand for mAbs and other therapeutic proteins has increased, so have concerns over cost and supply. Downstream processing – which accounts for roughly 60 percent of the cost of producing a biologic drug and often takes place over a period of weeks – is particularly challenging because it has not improved and scaled at the same rate as upstream processing has [3]. This is largely due to the complexity of downstream processing, which involves the movement of biological materials through a series of unit operations that include multiple chromatography steps. The complex stage presents numerous opportunities for improvement [3]. Of downstream processes, buffer management and chromatographic purification operations in particular are areas that are ripe for interventions to increase efficiency and scalability.

BUFFER MANAGEMENT

Buffers play a key role in chromatography purification steps in terms of both efficiency and purity. By stabilizing the pH of a mixture, some buffers help proteins bind to ligands while others – called elution buffers – help to separate out byproducts. As the biomanufacturing industry moves toward continuous bioprocessing and as titers resulting from upstream processes increase, the importance of and demand for buffers in downstream chromatography steps likewise continue to increase. Improving buffer efficacy and efficiency can happen in multiple ways, from optimizing buffer management processes by selecting the appropriate formulation to improving buffer performance through the use of additives.

In-house buffer preparation has been the dominant choice for years [4]. Established methods for in-house buffer preparation, such as the use of WFI (water-for-injection)-grade water in the hydration of powdered buffers in steel tanks, are appropriate for generating large amounts of buffer. However, the large footprints and high amounts of labor required for such methods make buffer outsourcing an appealing option. Outsourcing buffer management often comes with the added benefit that the burden of ensuring quality and consistency in buffer materials is shifted to the supplier [5].

Though it remains practical to manage certain kinds of buffer preparation in-house, outsourcing offers significant benefits by reducing the necessary capital, labor and footprint and by ensuring scalability and a reliable supply chain. Alternatives to traditional buffer preparation methods include the procurement of hydrated buffers, delivered as ready-to-use buffer solutions or concentrated buffers, or pre-weighed, ready-to-use, powder supplied in Direct Dispense bags helping streamline the biopharma manufacturing process [4]. Beyond this, workflow improvements largely depend on buffer preparation methods selected for a particular process or scale. Large-scale manufacturing – such as the production of mAbs, vaccines and recombinant proteins – and small-scale manufacturing – such as cell and gene therapy applications – have vastly different buffer needs, all of which can be accounted for through thoughtful collaboration between manufacturers and their suppliers.

The importance of this collaboration is demonstrated by the decision-making calculus involved in choosing between, for example, 1x buffers, buffer concentrates and buffer stocks. 1x buffers are ready-to-use and can be attached directly to the column. This ease of use, however, is balanced by concerns about the large amount of space such buffers require for storage. This is further complicated by the fact that some manufacturers, such as those developing new products, may not need enough buffer to justify the space and inventory issues generated by the use of 1x buffers.

For such manufacturers, multi-component buffer concentrates may make more sense. Those concentrates are intended to be used in conjunction with in-line dilution (ILD) skids. They reduce the warehouse space required compared to 1x buffers, but other issues arise. For example, multi-component concentrates tend not to generate cost savings, and the use of one concentrate in multiple process steps requires careful calculation and increases process complexity.

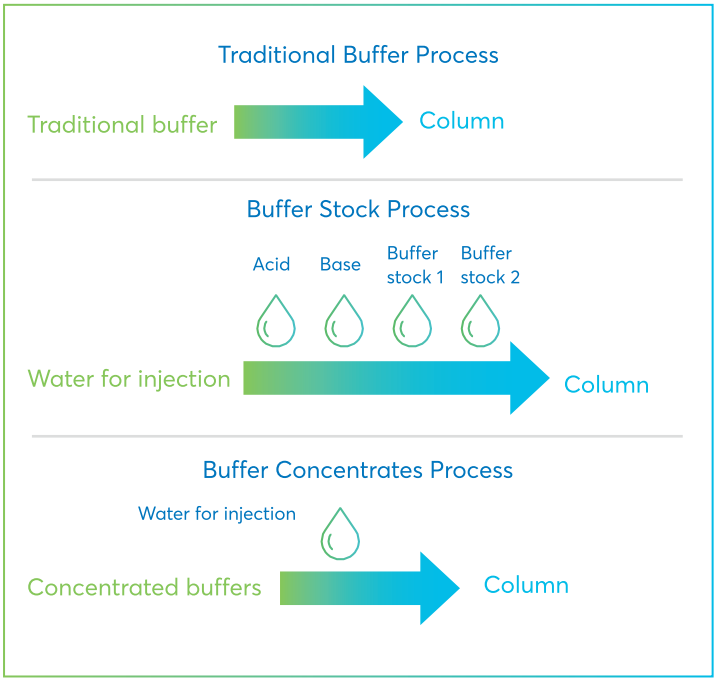

Fig. 1: Buffer handling strategies using liquid raw materials process visual.

Buffer stocks, single-component concentrates, are the most flexible of these three options, designed to be used in conjunction with WFI water, acids and bases in a buffer stock blending system. These single-component concentrates can be purchased in higher-concentration preparations than multi-component buffer concentrates, and therefore require less space and minimize shipping costs. However, buffer stocks tend to require higher capital costs (see figure 1) [8].

The varied benefits and detriments of each of these buffer preparations can be most easily navigated with the help of a supplier with the process expertise to help their customer identify the optimal solutions for their workflow's needs.

Another area of interest for the enhancement of buffers used in chromatographic purification involves the use of additives that improve the retention of and selectivity for proteins in the chromatographic medium. For example, in hydrophobic interaction chromatography (HIC) – a common polishing step in monoclonal antibody purification processes – additives are used to modulate hydrophobic interactions and improve separation efficiency, which by extension improves throughput [3]. Similarly, additives might be employed to enhance the ability of elution buffers in affinity chromatography to dissociate bonds between proteins. The use of buffer additives, ready-to-use buffers and single-use fluid handling systems to enhance efficacy are still being fine-tuned, but the optimization of the chemistry of chromatographic resins is showing itself to be one of the most effective ways to improve recovery while normalizing or even reducing production costs [3].

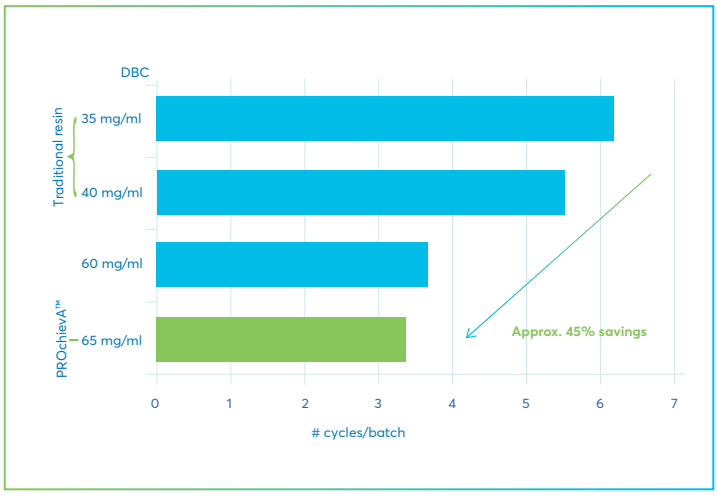

Fig. 2: Effect of DBC on theoretical number of cycles per batch.

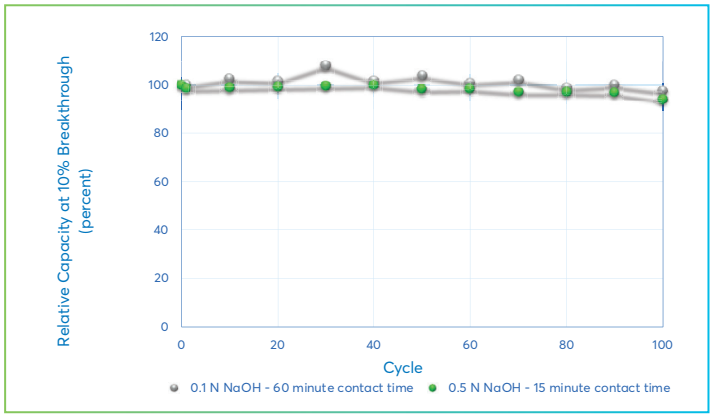

Fig. 3: Resin life of PROchievA. All testing conducted at 2° C to 8° C.

CHROMATOGRAPHY

While the general improvement in upstream process titers in the biopharmaceutical industry is advantageous in many ways, it also burdens the downstream chromatographic steps that were originally designed to process smaller amounts of proteins [6]. Improved buffers are not enough to accommodate higher titers, so enhanced resins must also be part of an optimized downstream workflow.

Because of its near ubiquity in the downstream processing of antibody products, protein A affinity chromatography provides insight into potential improvements in the chromatographic aspects of the downstream processing of therapeutic proteins. For decades, protein A chromatography has been the gold standard for protein capture due to its specificity. This step alone provides up to 99% yield after capture [1]. However, protein A is expensive, and its frequent use leads to further expense in two ways. First, without thorough cleaning, impurities left in the column can interact with protein A and cause fouling. If harsh solutions are used to clean the columns, however, another challenge presents itself in the reduction of resin lifetime [6]. Furthermore, protein A ligands may leach from the resin, further increasing the purification burden on subsequent processing steps that are already overburdened due to the failure of downstream processes to improve at the same rate as upstream processes.

Multimodal or mixed-mode chromatography – in which ligands in the resin interact with the protein product in multiple ways – has gained attention as a way to optimize downstream chromatography steps in recent years. However, tailored ligands are perhaps the biggest recent change in the chromatographic purification of proteins [7]. Tailored ligands can significantly improve resin stability and selectivity and increase dynamic binding capacity, enabling resin to process more protein per cycle. For example, the J.T.Baker® BAKERBOND® PROchievA™ resin, a recombinant protein A affinity chromatography resin that uses a novel proprietary ligand, can reduce the number of cycles needed by 45% and the amount of buffer consumed by almost 40% (see figure 2) [6]. In addition to these significant performance boosts over traditional protein A affinity resins, BAKERBOND PROchievA has a high alkaline stability, which extends the resin lifetime even when the column is cleaned with sodium hydroxide (see figure 3) [6].

Tailored ligand-based resins, therefore, can significantly reduce process cost over time, especially with large batch sizes, through increased throughput and decreased resin and buffer consumption [6]. The high purity these resins achieve also reduces the burden on subsequent steps.

Finally, buffer management cannot truly be optimized without the implementation of quality support systems. Traditional sampling methods are destructive, risk contamination of buffer components and waste time. With side sampling and non-destructive identification technologies such as Raman ID compatible packaging, however, there is no need for physical sampling. This not only decreases risk but enables heightened operational efficiency [8].

DATA AGGREGATION AND THE FUTURE OF DOWNSTREAM PROCESSING

While the improvement of purification process materials like buffers and chromatography resins will be crucial for the continued alignment of downstream capabilities with upstream output, raw material availability is an issue that should not be ignored. Emerging technologies will enable biopharmaceutical companies to aggregate and analyze process data [9]. Having the resulting information available could allow companies to anticipate variations and understand their impact, minimizing batch failures while heightening supply-chain visibility [9].

Because of this, even though real-time evaluation is not yet possible, emerging technologies that allow companies to monitor their processes and track raw material quality over time have the potential to inform process efficiencies and supply chain decisions. While the use of data to refine process parameters is a comparatively simple process involving batch repetition, characterizing raw material variability involves the use of a variety of datasets. For example, the use of certificate of analysis data for all raw material lots manufactured, manufacturing in-process data, in-test actuals for conforming specs and stability testing interval data can enable biopharma manufacturers not only to assess but also to predict the performance of raw materials and therefore choose the most impactful workflow interventions [3].

In line with these opportunities, digital solutions can be developed that map the potential for variability in different raw materials and

the potential impact of such variability. This is done through the aggregation and analysis of stability interval testing of downstream components. Though bringing this technology to bear in ways that can valuably inform process and materials decisions is difficult, it demonstrates the potential to minimize batch failures by increasing the understanding of variations' impacts.

CONCLUSION

Demand for therapeutic proteins has never been higher, and the biopharmaceutical companies and their raw materials' suppliers must collaborate effectively throughout the development and manufacturing processes for biologics. Cost control or even reduction, raw material availability, process efficiency and speed-to-market are all potential areas for improvement in the downstream processing of therapeutic proteins. While these goals may be obvious, their attainment is less so. The investigation of new, state-of-the-art materials will be crucial, but so will the development of process efficiencies and raw material solutions. Often, such solutions are dependent on the specific needs of a customer and their process, and providing data-driven solutions that best serve a workflow with the most efficient selections of raw materials and process improvements will necessitate a close relationship between those researching and producing therapeutic proteins and their downstream material suppliers. The resulting combination of knowledge – spanning insight into the precise needs of a particular product to expertise in process chemistries and raw material performance, as well as supply chain issues and end-to-end workflow efficiencies – will be key to the generation of downstream solutions. This collaboration enables suppliers to meet their customers' needs for tailored solutions and high-quality materials so that biologics producers can achieve the speed-to-market that today's biopharmaceutical industry demands.

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Nandu Deorkar is Senior Vice President, Biopharma Production Research & Development for Avantor. He is responsible for innovation strategy and planning, and execution of new products and technology development. During his more than 25-year career in research & development, Dr. Deorkar has been leading teams working on various aspects of upstream and downstream bioprocessing, single-use systems, chemical/polymer R&D, drug development, formulation, drug delivery technologies, process development and technology transfer. He has published more than 30 articles and holds more than 20 patents. Dr. Deorkar received his Ph.D. from Indian Institute of Technology, Mumbai, India, and a MBA in Marketing from Fairleigh Dickinson University, Madison, NJ, USA.

With decades of experience in therapeutic protein bioproduction and a comprehensive product portfolio, Avantor offers customers the expertise and materials needed to develop new biologics. Our process experts can streamline workflows and help select the right materials with a focus on quality. Avantor is committed to supporting our biopharma customers so they can move science forward and get life-changing therapies to the people who need them.

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