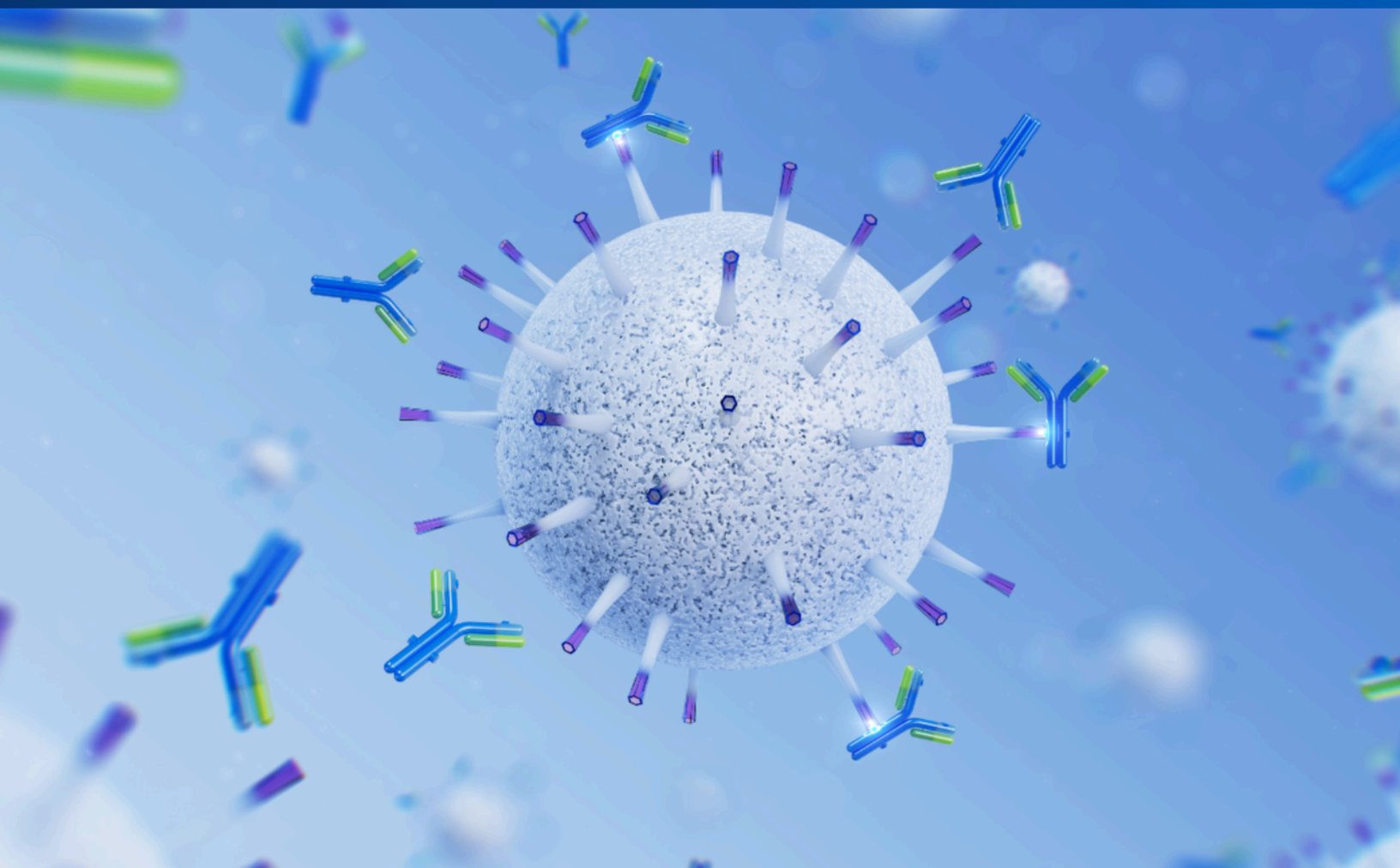




PRODUCT TRANSITION GUIDE

Legacy Protein A Resins to Praesto™ AP+80

Enabling Confident Resin Transitions:
Critical Attributes for Cost Reduction in
Biosimilar and Generation II Manufacturing



The Industry Drive Towards Reducing Cost of Goods for mAb Production

In the ever-evolving landscape of global drug manufacturing, cost efficiency has become a paramount concern.

Governments worldwide are striving to reduce pharmaceutical costs for target populations and alleviate the overall tax burden of healthcare. This drive necessitates lowering the manufacturing cost per dose while maintaining efficacy and regulatory compliance. However, the heavily regulated nature of bioprocessing workflows and the need for compatibility with downstream processes add layers of complexity to these improvements.

In the realm of monoclonal antibody (mAb) drug manufacturing, there is a significant push to reduce the cost of individual workflow steps, including the chromatographic capture and polishing processes that are integral to mAb purification. As part of broader efficiency drives in drug manufacturing, reducing the cost of unit operations in commercial manufacturing is a key focus. Many manufacturing processes have long lifetimes, meaning that chromatography resins developed and adopted at the outset of a particular mAb commercialization may be superseded by newer, more efficient, and lower-cost alternatives. Generation II processes using modern resins are designed to reduce costs and increase productivity.

The development of biosimilars, which are official variants of commercial drugs produced by alternative manufacturers, presents an additional opportunity to reassess the manufacturing process with the aim of reducing costs. However, changes from the established workflows introduced with the parent drug can lead to increased complexity and regulatory burdens. Therefore, it is ideal if the changes are minimal while still achieving cost reductions compared to the original process.

Transitioning from one resin to another in a bioprocessing workflow, whether in biosimilar development, updating your processes or as part of a Generation II project, is a complex undertaking with many potential pitfalls. Swapping out capture and polishing resins in a downstream process involves several critical considerations to ensure that the new resins maintain product quality and process efficiency¹.

This article discusses how Ecolab's Praesto AP+80 has been developed to facilitate adoption into commercial processes by addressing some of the key considerations that govern the implementation of a new resin.

TABLE 1 Comparison of the characteristics of AP+80 to Competitor B or legacy agarose.

Characteristics	Praesto AP+80	Competitor B
Matrix	Highly cross-linked agarose	Highly cross-linked agarose
Ligand	Alkaline stable protein A – Pentamer	Alkaline stable protein A – Tetramer
Particle Size (d50v- μ m)	80	85
Dynamic Binding Capacity*	Up to 60 mg Ab/mL (6 minutes residence time)	Up to 60 mg Ab/mL (6 minutes residence time)
Pressure Flow	400 cm/h (30 ID x 20 BH cm) with a pressure less than 2 bar.**	500 cm/h (30 ID x 20 BH cm) with a pressure of less than 2 bar.***
pH Stability (working)	3–12	3–12
pH Stability (CIP)	2–13	2–13
Cleaning Agent	0.1–0.5 M NaOH	0.1–0.5 M NaOH
Delivery Conditions	20% Ethanol, 2% benzyl alcohol upon request	20% Ethanol, 2% benzyl alcohol upon request

*Capacity determined in a 0.66 x 10 cm column with human polyclonal immunoglobulin G at 6 minutes residence time with a PBS loading buffer.

** Determined in a BPG300 with an inner diameter of 30 cm and bed height of 20 cm using deionised water at 20°C.

***Determined in an BPG300 with an inner diameter of 30 cm and bed height of 20 cm using buffers with the same viscosity as water at 20°C.²

Resin Selection for Biosimilar and Generation II Development

There are many factors to consider when selecting an alternative resin for an established chromatographic process, whether as part of a 'generation II' or a biosimilar project. Developing a firm understanding of the impact of the change in these areas will lead to an informed choice as to whether the change is necessary or desirable.

In assessing resin performance, here are the factors that must be considered.

Dynamic Binding Capacity

When selecting a new resin, it is important that it has the same or better binding capacity than the current resin. A reduction in binding capacity will not only reduce the yield per run but have a knock-on effect across the workflow, for example, requiring more cycles per batch, which in turn means more operator hours. Critically, the resin should be assessed for the target mAb under the same loading conditions, flow rates and concentrations as are currently used for a true representative comparison.

TABLE 2 Protocol for dynamic binding capacity determination for polyclonal human IgG and monoclonal human IgG1.

Step	Buffer	CV
Equilibration	Phosphate buffered saline, pH 7.0–7.4	5
Sample Load	Loading to 50% breakthrough – hIgG and mAb at 5 g/L respectively.	N/A
Intermediate Wash 1	Phosphate buffered saline, pH 7.0–7.4	3
Elution	100 mM sodium acetate, pH 3.0	3
Regeneration	100 Mm Acetic Acid	3
CIP	0.1 M NaOH	3
Equilibration	Phosphate buffered saline, pH 7.0–7.4	5

Figure 1

Dynamic Binding Capacity

At 10% breakthrough for polyclonal human Immunoglobulin G on Praesto AP+80 and Competitor B over a range of residence times.

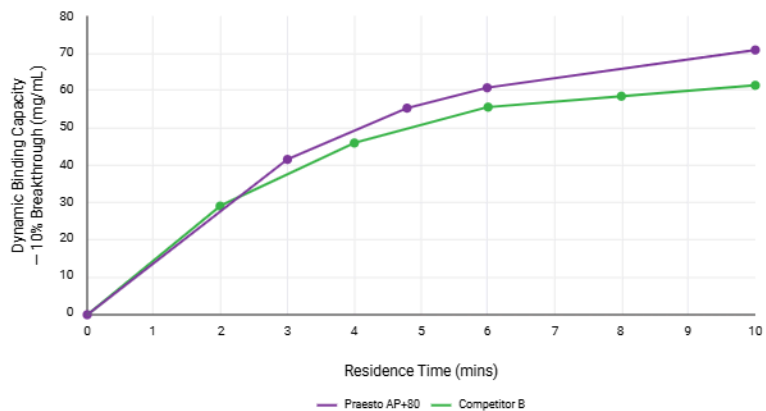
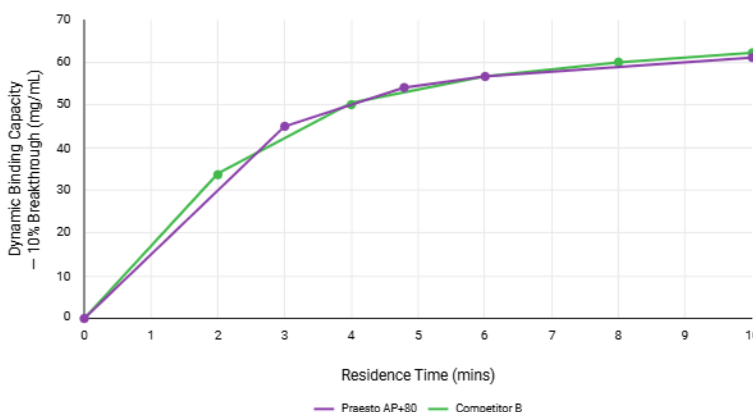


Figure 2**Dynamic Binding Capacity**

At 10% breakthrough for a monoclonal antibody (IgG1) on Praesto AP+80 and Competitor B over a range of residence times.



Elution Conditions

With the established resin will come a set of optimized elution conditions that have been adopted into the current manufacturing process. Ideally, these same conditions will be used with the new resin to minimize change, so it is therefore important that these conditions do not adversely affect the yield, activity, or quality of the mAb at the end of the process. The goal would be to integrate the new resin seamlessly into existing workflows, including the currently employed elution conditions. If elution profiles need to be adjusted, the effect of this on the downstream workflow needs to be carefully assessed.

Praesto AP+80 binds similarly to Competitor B, to the Fc region of human Immunoglobulin G antibodies. Praesto AP+80 has increased affinity to the VH3 region compared to Competitor B. However, elution pH and elution pool volumes have been shown to be similar.

It is important to screen the optimum elution for the target molecule with regard to optimal elution CV, purity, and process-related impurity removal. Please refer to the [Praesto AP+80 Instructions For Use](#) for recommended screening conditions.

TABLE 3 Typical protocol used for manufacturing mAbs applied to the purification of Human IgG1 mAb using Praesto AP+80 and Competitor B or legacy agarose resin.

Phase	Buffer	Column Volumes	Residence Time (mins)
Equilibration	100 mM PBS, pH 7.2	5	6
Sample Load	IgG1 mAb	Loaded to 80% of DBC10%	6
Chase	100 mM PBS, pH 7.2	5	6
Wash 1	20 mM Tris, 1 M NaCl, pH 8.0	5	6
Wash 2	100 mM PBS, pH 7.2	5	6
Elution	100 mM sodium acetate (pH 3.0, 3.5)	5	6
Strip	100 mM acetic acid, pH 3.0	5	6
CIP	100 mM sodium hydroxide	3 + 15 mins static	6
Equilibration	100 mM PBS, pH 7.2	5	6

Figure 3

Recovery/Yield Percentage

From protein A capture of an IgG1 mAb for Praesto AP+80 and Competitor B eluting at pH 3.0, pH 3.5, and pH 3.7.

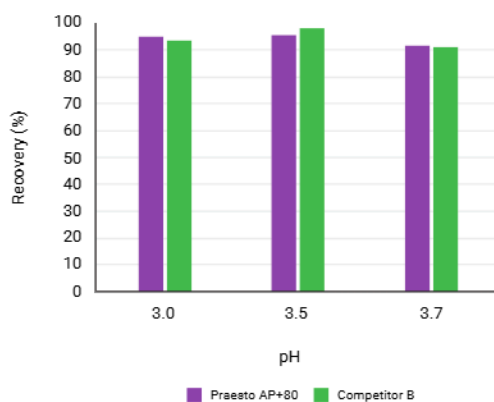


Figure 4

Elution Volume

From protein A capture of an IgG1 mAb for Praesto AP+80 and Competitor B eluting at pH 3.0, pH 3.5 and pH 3.7.

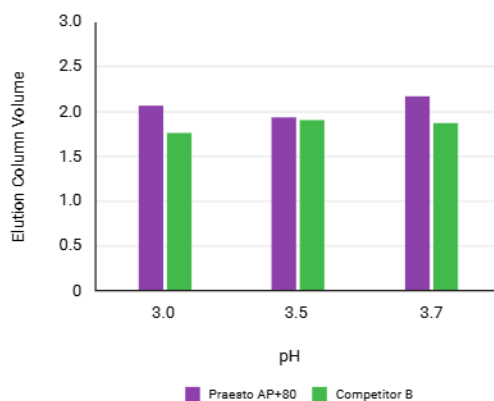
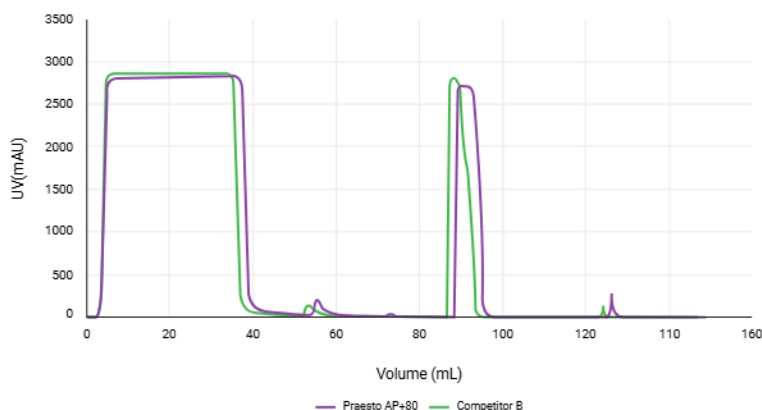


Figure 5**UV Chromatogram**

From protein A capture of an IgG1 mAb for Praesto AP+80 and Competitor B eluting at pH 3.0.



Selectivity

It is important to assess the resin's selectivity for the mAb of interest and other impurities, such as host cell proteins, DNA, and aggregates. A large change in the impurity profile will have an impact further down the workflow, as other polishing resins may need to work harder to achieve the same impurity profile in the final product. It is also important to ensure that the new resin does not capture other unrelated proteins, that could undermine the yield and final product purity.

Here, we demonstrate the similar performance of Praesto AP+80 and Competitor B regarding recovery, elution, and impurity clearance.

TABLE 4 Typical protocol used for manufacturing mAbs applied to the purification of Human IgG1 mAb using Praesto AP+80 and Competitor B or legacy agarose resin.

Phase	Buffer	Column Volumes	Residence Time (mins)
Equilibration	Phosphate buffered saline, pH 7.4	5	6
Load	HCCF – IgG1 mAb at 8.5 g/L	Loaded to 80% DBC10%	6
Wash 1	20 mM sodium phosphate, pH 7 + 500 mM NaCl	5	6
Wash 2	50 mM sodium acetate, pH 6.0	5	6
Elution	50 mM sodium acetate, pH 3.5	5	6
Strip	100 mM acetic acid, pH 2.9	5	6
CIP	0.1 M NaOH	3	6
Equilibration	Phosphate buffered saline, pH 7.4	3	6

Figure 6

Dynamic Binding Capacity

Of an IgG1 mAb at 6 minutes residence for Praesto AP+80 and Competitor B.

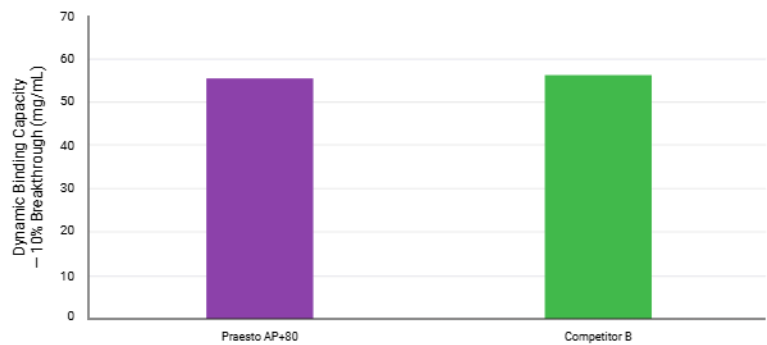


Figure 7

UV Chromatogram

From protein A capture of an IgG1 mAb for Praesto AP+80 and Competitor B eluting at pH 3.5.

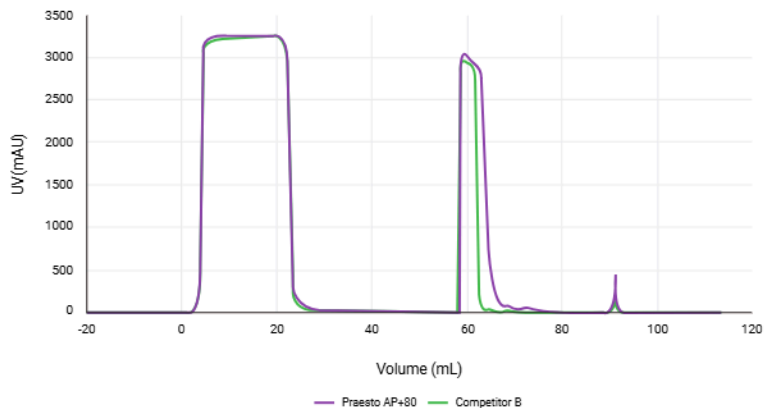


Figure 8

Recovery/yield (%) from three cycles of protein A capture of an IgG1 mAb for Praesto AP+80 and Competitor B.

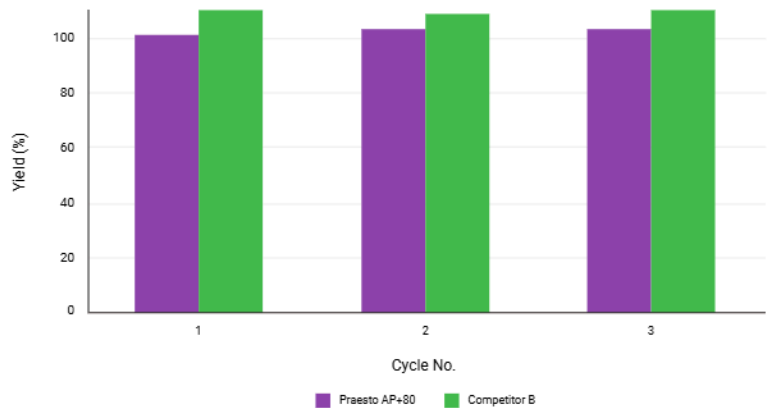
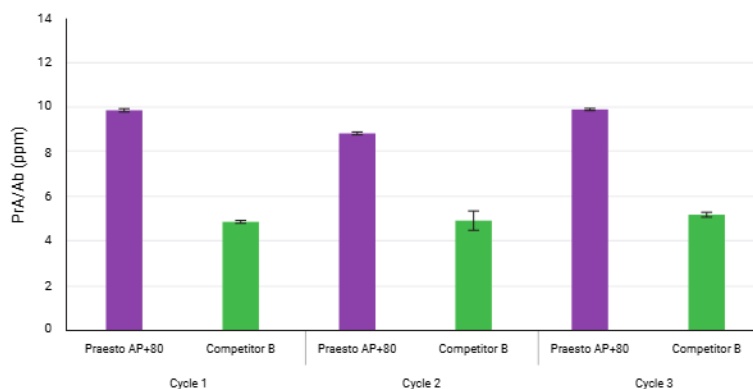
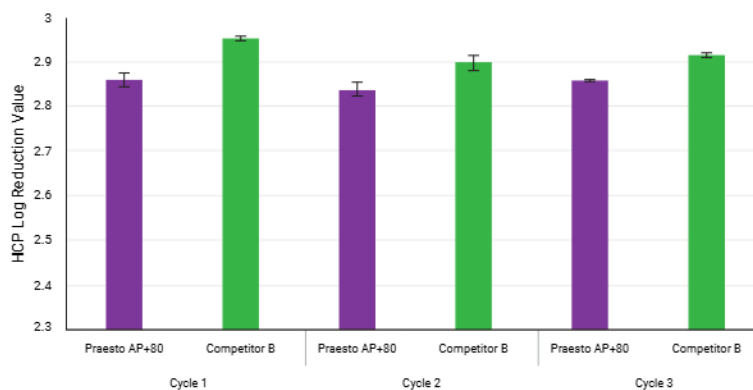


Figure 9

Protein A leakage from three cycles of protein A capture of an IgG1 mAb for Praesto AP+80 and Competitor B.

**Figure 10**

Host cell log reduction value from three cycles of protein A capture of an IgG1 mAb for Praesto AP+80 and Competitor B.



Durability and Lifetime

A key to overall process economics is the durability of the resin to both the damaging characteristics of the process, such as the presence of proteases in the feed, and to necessary procedures, such as the caustic conditions employed during typical 'cleaning in place' steps. It is vital to evaluate how many cycles the new resin can sustain without significant loss in performance, as a drop in this characteristic compared to the incumbent resin will significantly affect operational costs. It is, therefore, particularly vital to establish the long-term viability of the resin compared to the current material.

Sodium hydroxide (NaOH) is commonly used in bioprocessing as an industry standard for cleaning in place. Sodium hydroxide exhibits high efficiency in removing bound proteins, nucleic acids, and lipids from bioprocess resins, alleviating the risk of fouling on heavily burdened Protein A columns. 0.1 M NaOH is typically sufficient; however, higher concentrations can be used periodically for challenging harvests.

Figure 11

Relative dynamic binding capacity at 6 minutes residence for Praesto AP+80 and Competitor B after successive 20 hour static holds in 0.1 M NaOH.

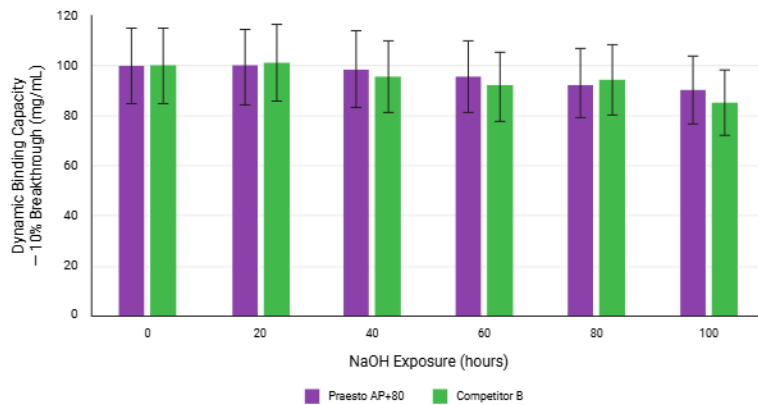
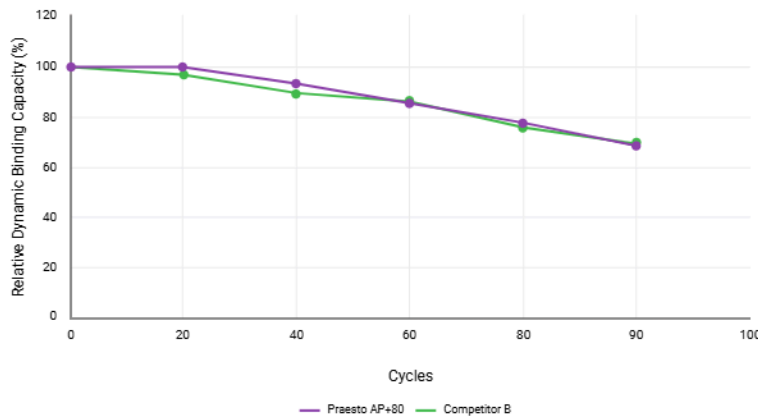


Figure 12

Relative dynamic binding capacity at 6 minutes residence for Praesto AP+80 and Competitor B after cycling under blank conditions with a 30 minute CIP in 0.5 M NaOH.



Process Scale-Up

Ultimately any new resin selected for a commercial process must perform both at laboratory scale and at the large scale used in manufacturing. Ensuring that the resin delivers consistently across all scales is critical to avoiding variations in large batch processing that can be costly to remedy. This is perhaps one of the key factors when assessing a new resin candidate and it is essential to conduct both small-scale studies and pilot runs where possible to ensure performance before full implementation.

The flow and pressure properties of bioprocess chromatographic resins are critical when designing a downstream purification process. Development work starts at the laboratory scale using relatively small column dimensions. However, the high linear flow velocities that can be achieved at the laboratory scale cannot always be used at the process scale.

During process development work, columns are typically between 0.66 to 2.6 cm inner diameter. At such narrow diameters, the resin is well supported by the column wall. This support rapidly decreases with increasing column diameter and is known as the “wall effect”. The wall effect supports the packed bed from additional compression and subsequent collapse as the flow increases. As the diameter of the column is increased, the drag force of the resin bed caused by the volumetric flow through the bed counteracts the wall effect. The wall effect is very significant at column diameters below 30 cm but is still relevant for large manufacturing columns of 1 m and wider.

The decreasing support of the resin bed from the column wall not only lowers the maximum flow at a particular pressure that can be achieved but also results in higher optimum compression of the resin bed when compared to the laboratory scale.

Figure 13

Pressure vs. Flow

Of Praesto AP+80 packed in a BPG300 column to 20 cm bed height. Pressure flow was performed using deionized water at 20 °C.

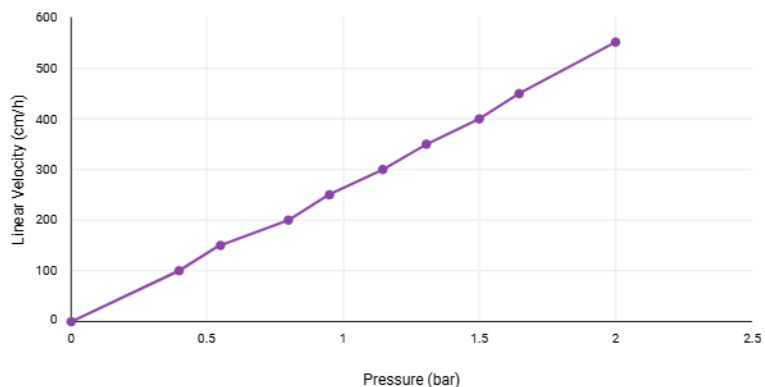
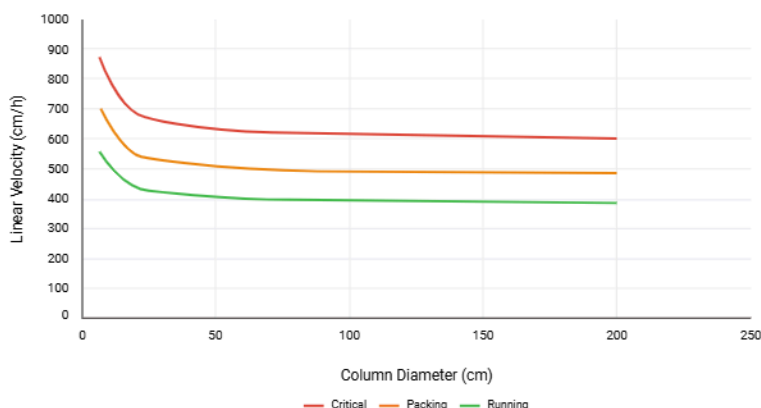
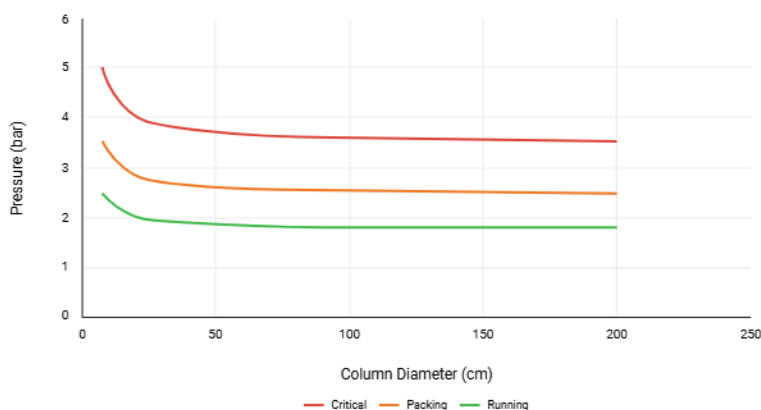


Figure 14**Linear Velocity Expectation**

For Praesto AP+80 on extrapolation of column diameter at a 20 cm bed height in a solution of viscosity of 1 cp at 20 °C.

**Figure 15****Pressure Expectation**

For Praesto AP+80 on extrapolation of column diameter at a 20 cm bed height in a solution of viscosity of 1 cp at 20 °C.



Please refer to [Praesto AP+80 Process Scale Column Packing Instructions](#) and [Praesto AP+80 Laboratory Scale Column Packing Instructions](#) for column packing instructions.

Regulatory Compliance

Before any resin can be introduced into a commercial pharmaceutical manufacturing process, it is essential that it meets all the relevant regulatory standards (e.g., FDA, EMA) required for biomanufacturing. Without this, it will not be possible to file the new resin with the appropriate authorities. As part of this process, the vendor of the new resin should be assessed on their ability to supply appropriate documentation for traceability and compliance audits, and security of supply which ensures their reliability as a long-term partner for drug manufacturing. Praesto AP+80 regulatory support file is available upon request.

Toxicological Information

Praesto AP+80 recombinant Protein A Ligand (supplied by Repligen) is used for the manufacture of Praesto AP+80. Following searches on Toxnet and the Pesticides Action Network (PAN), there are no known toxic effects for this ligand.

Impact on Product Quality Attributes

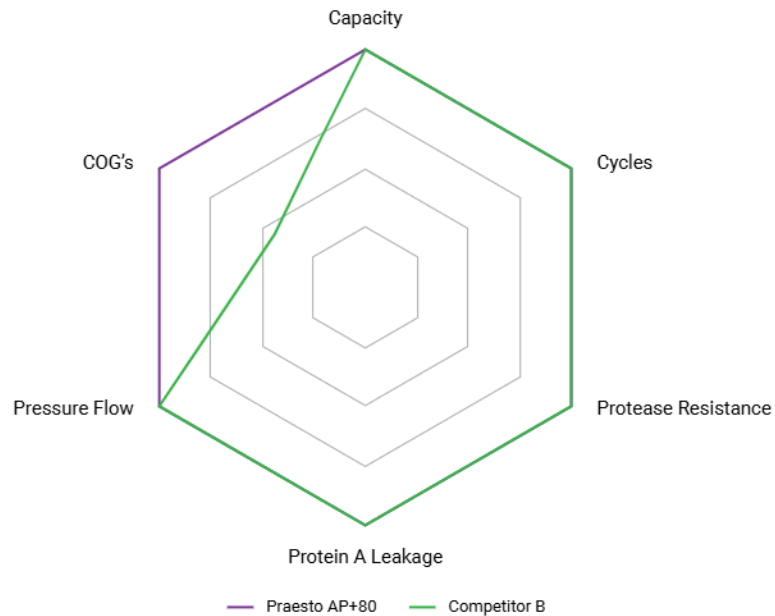
Ultimately, the new resin must be able to deliver a final purified product with the same or better performance and quality attributes already established for the process. Gains in efficiency through the adoption of a new resin will be far outweighed by quality issues if the final material is compromised. As part of the overall evaluation, it is important to assess whether the substitution affects the stability, bioactivity, and proper folding of the mAb, typically working closely with the quality team to ensure performance.

Performance Metrics

Finally, as part of the overall assessment of a new resin, it is important to consider how efficiently the new resin can be integrated into existing processes and what optimization may be required. Any of the previous points may have raised changes that need to be considered when implementing the new resin. Each change must be carefully evaluated and costed to understand the effect on the entire workflow and those activities that support it. For example, an understanding of whether the introduction of the new resin offers efficiencies in processing time over the current workflow or requires additional personnel training is going to be critical.

Cost Assessment

The final consideration is cost. Before any changes are made, the goal at this stage is to accurately show that implementing the new resin and any optimization needed significantly improves the process's economics while not compromising quality or regulatory aspects.

Figure 16**Praesto AP+80 Versus Competitor B**

Conclusions

Carefully evaluating each of the factors outlined above can help ensure that the new resin not only meets cost-efficiency goals but also maintains the integrity, quality, and regulatory compliance of the monoclonal antibody production process. Although process improvements can be made, they are not the sole driver — the goal is to improve the workflow's process economics while maintaining performance and quality.

References

1. [BioPhorum Approach to the Registration of Innovative Raw Materials Using Quality by Design Principles](#)
2. [digi-19326-pdf](#)

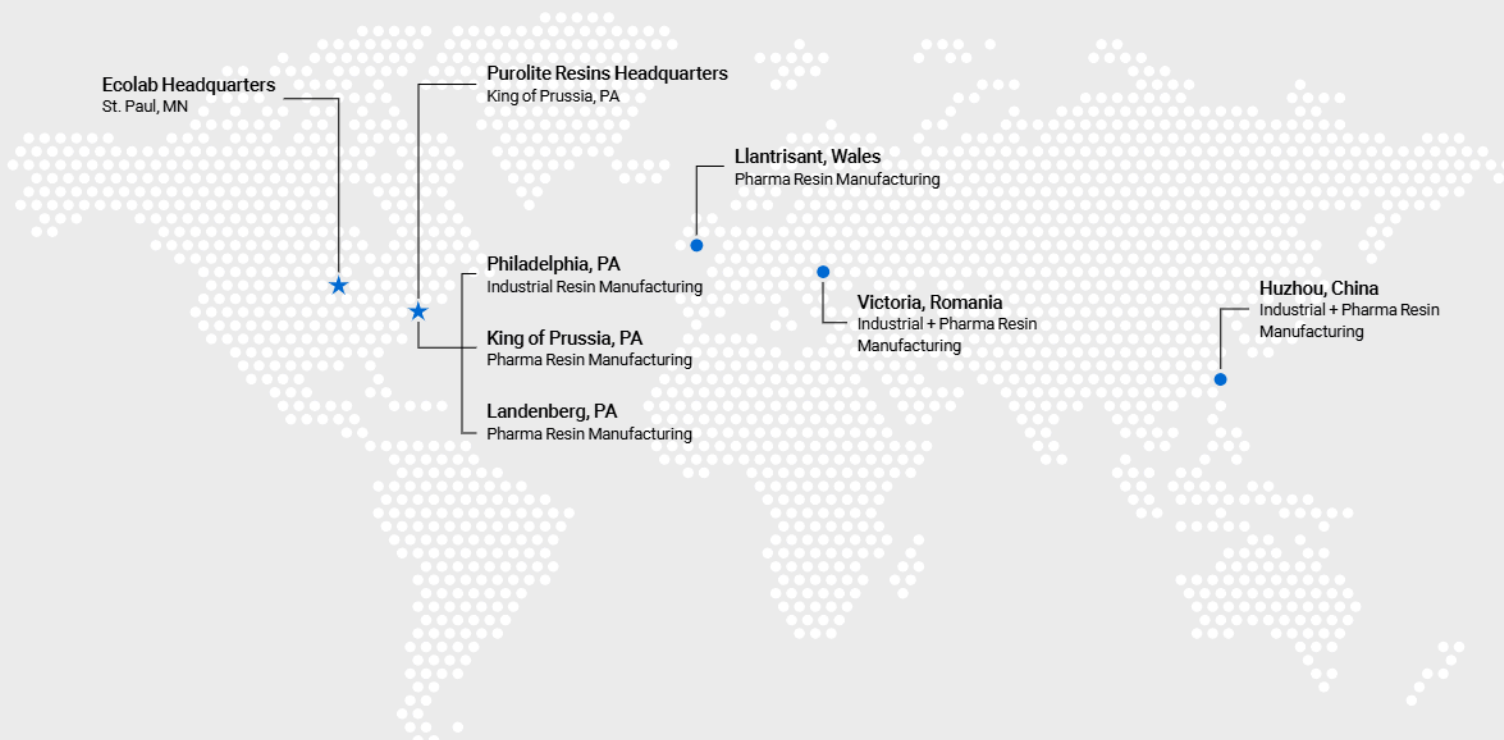
No matter the location, our expert field application team members are positioned to help you solve your technical and downstream purification challenges, together.

Offering a variety of services, we provide the guidance necessary to develop robust, scalable, high productivity purification processes for mAbs and recombinant processes using Praesto™ Jetted chromatography resins. For wherever you are in your biomanufacturing journey, we are here to help.

Ecolab is a global developer, manufacturer, and supplier of Purolite™ Resins including ion exchange, catalyst adsorbent and advanced polymers that make the world cleaner and healthier.



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