# Mastering mAb Manufacture

Experts share their tips and tricks for enhancing the production of monoclonal antibodies.

*Please click the circles to navigate*


HOW TO BEAT THE BOTTLENECK

MABSELECT PRISMA

REIMAGINE CAPACITY

# How to Beat the Bottleneck

**As the accelerating number of monoclonal antibodies on the market continues to drive higher upstream titers, chromatography resin suppliers must continually strive to improve productivity, quality and overall process economy.**

*By Kajsa Stridsberg-Fridén*

The monoclonal antibody (mAb) field has come a long way since the first therapeutic mAb was commercialized in 1986. As of today, over 60 mAbs have been approved in the US and Europe and sales of mAbs are expected to cross $125 billion by 2020 (1). As the number of mAbs on the market and in development has accelerated over the years, so too have upstream titers. With the increasing upstream titers, the constraints on downstream processing have only increased. The efficient recovery and purification of mAbs from cell culture medium is a critical part of the production process and can contribute significantly to the total manufacturing costs (2). Protein A affinity chromatography is commonly used in the process-scale purification of mAbs because it is an easy, fast and selective procedure for capturing the target protein – often resulting in a greater than 99 percent purity from complex cell culture media in a single step.

The demands of protein A resins have evolved significantly over the years and the nature of the process means that the capture step can act as a bottleneck – especially as upstream titers continue to increase. I believe suppliers must do what they can to keep pace with the constantly evolving demands of the industry. And this is why GE Healthcare Life Sciences has made the long-term strategic decision to constantly improve our protein A chromatography resins.

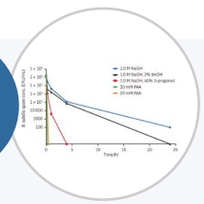
Native protein A chromatography resin first began seeing routine use in the lab in the 1980s, but approximately every five years since then there has been a new demand from the industry for further innovation – for resins with new properties to address new challenges. One of the early developments was the switch to recombinant protein A, as the industry moved towards animal-free products. Then, as production scales continued to rise in the early 2000s, we introduced the "second generation" in protein A resins, the MabSelect resin, the first in a family of products, to allow for higher throughput downstream processing.

These resins are based on a highly cross-linked agarose matrix with a recombinant protein A ligand. In 2005, GE launched the MabSelect SuRe resin that has an alkaline-stabilized protein A ligand, which allows for efficient cleaning and sanitization with reagents such as sodium hydroxide (NaOH), eliminating the need for expensive and hazardous cleaning agents. Six years later, we launched MabSelect SuRe LX to meet the needs associated with high-titer upstream processes. One of the key features of MabSelect SuRe LX is its increased dynamic binding capacity (DBC), which allowed better economies of scale. More recently, we've worked to improve the capacity of our protein A chromatography resins to address the industry shift towards continuous manufacturing. MabSelect SuRe pcc further increases capacity at short residence time, making it well-suited for applications requiring fast mass transfer as seen in continuous processes.

## Moving forward

The biopharma industry continues to face new challenges, so it is incredibly important to continue to innovate and develop new solutions to support the market. Throughout the evolution of our protein A resins, the need for greater productivity has been a constant theme, and never more so than today. That's why our latest solution, MabSelect PrismA, is designed to achieve high capacity to increase mass throughput, enabling greater productivity of current chromatography columns and systems to be improved without costly capital expenditures (see the infographic for more details). With

LINKS



**Learning Link**
*Bioburden control*

*Produced by* the Medicine Maker | *Sponsored by* GE

increased binding capacity, MabSelect PrismA allows for up to 30 percent more target mAb to be purified using current equipment; alternatively, the resin volume required to achieve a given mass throughput can be reduced.

MabSelect PrismA also seeks to address bioburden challenges with improved alkaline stability to enable more efficient cleaning and prevent growth of microorganisms and inactivate potential endotoxins. Protein A columns are more prone to contamination because of heavy impurity load and weak tolerance for common concentrations of NaOH cleaning-in-place solutions. Regulators are therefore increasingly asking manufacturers to control the sources of bioburden. Improving tolerance for NaOH will continue to pose a significant challenge for the industry in the future.

As we look ahead, it seems likely that upstream titers in mAb production will continue an upward trend. The protein A capture step does create a production bottleneck in downstream processing and it remains to be seen whether current technologies can keep pace. Another major challenge for the field is the development of next-generation antibody constructs. The industry is rapidly moving beyond conventional mAbs towards a variety of new constructs, including antibody fragments, Fc fusion proteins, bispecific antibodies and antibody-fusion proteins. These new antibody variants most often require modifications of the original mAb platform process to enable production. There might also be the potential to modify protein A to create a tailored version based on antibody structure.

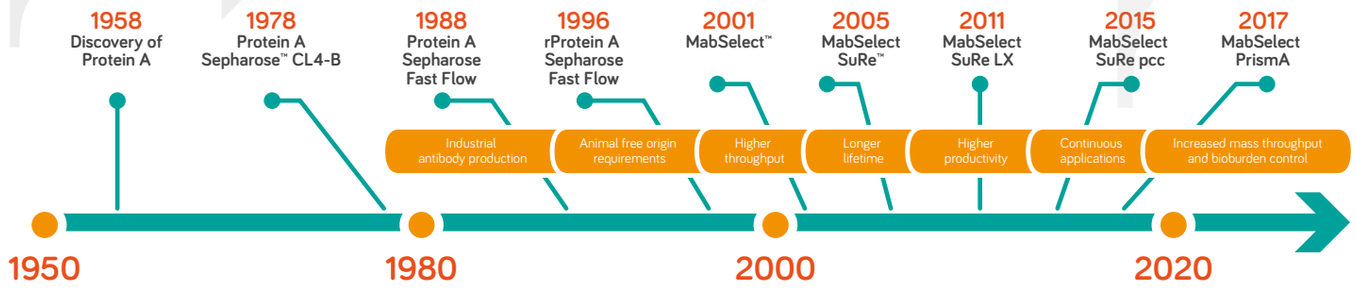
Today, we're excited to be talking about our latest chromatography resin, MabsSelect PrismA, but there is always room for further innovation and I have no doubt that we will be sharing the next step in protein A evolution and other affinity chromatography solutions down the road.

*Kajsa Stridsberg-Fridén is Senior Project Manager R&D at GE Healthcare, Sweden, and has been with the company for more than 15 years. In her current role, Kajsa is managing cross-functional projects, developing chromatography products for the biopharmaceutical market.*


*References*

1. *AA Shukla et al., "Downstream processing of monoclonal antibodies - Application of platform approaches", J Chromatogr B, 848, 28–39 (2007). PMID: 17046339.*
2. *AA Shukla et al., "Evolving trends in mAb production processes", Bioeng & Transl Med, 2, 58–69 (2017). PMID: 29313024. AA (2015).*
3. *Application note, "Significant time savings with simplified cell culturing using ReadyToProcess WAVE 25", 29111313, Edition AA (2014).*


## Evolution of GE Healthcare's protein A chromatography resins



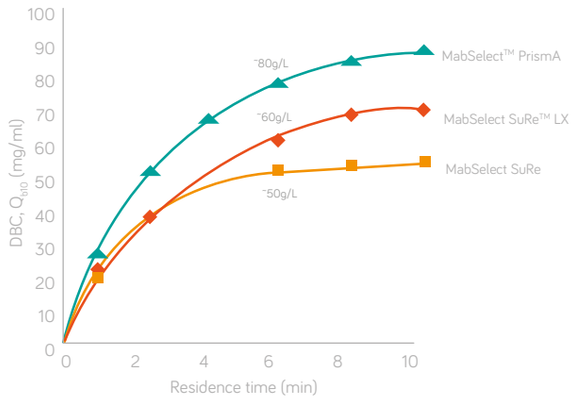

### Alkaline stability

MabSelect PrismA maintains dynamic binding capacity (DBC) when cleaning with 0.5 M or 1.0 M sodium hydroxide

**95%** of DBC retained after 150 cycles with 0.5 M NaOH

DBC retained after 150 cycles with 1.0 M NaOH **>90%**

### MabSelect PrismA has significantly increased DBC




**Use the increased capacity to reduce your consumables while keeping mass throughput constant**

MabSelect PrismA has up to **30%** increased DBC compared to MabSelect SuRe LX at 4 min residence time.

LINKS

**Video**
*MabSelect™ PrismA protein A resin: Product overview*

*Produced by* the Medicine Maker | *Sponsored by* GE

# MabSelect PrismA

**An efficient Protein A resin specifically designed to boost mAb purification capacity**

*Produced by GE Healthcare Life Sciences*

the Medicine Maker Innovation Awards 2017

2017 Innovation Award Winner

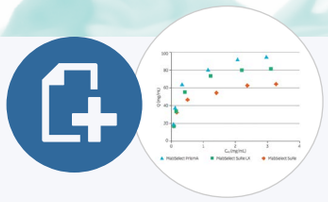

According to GE Healthcare, MabSelect PrismA can help mAb producers to improve their purification capacity by up to 40 percent thanks to enhanced binding properties. Protein A chromatography resins play a fundamental role in mAb purification efficiency thanks to their high selectivity, but the drawback is a lack of chemical resistance and the relatively low productivity of many protein A resins. MabSelect PrismA has been developed using high-throughput screening methodologies to identify and resolve weaknesses in the protein A molecule that make it susceptible to sodium hydroxide degradation – allowing MabSelect PrismA to be cleaned with a higher concentration of sodium hydroxide to better control cross-contamination and bioburden risks.

## Potential impact:

Historically, the binding capacity of Protein A resins has lagged behind other chromatography resins. GE Healthcare claims that co-optimization of the chromatography bead and the final ligand construct has given MabSelect PrismA a binding capacity on a par with other techniques. Increasing mAb purification capacity can have a significant impact on equipment decisions. If overall productivity of existing equipment is improved, capital investments in new columns and facilities can be delayed until financial risks are reduced. The increased capacity also allows the use of prepacked columns.

LINKS

**Learning Link**
*2017 Medicine Maker Innovation Awards*



**Application Note**
*Capacity anTM d performance of MabSelect PrismAproteinA chromatography resin*

*Produced by* the Medicine Maker

*Sponsored by*

# Reimagine capacity for success – MabSelect™ PrismA protein A chromatography resin

**The area of therapeutic monoclonal antibodies (mAbs) is growing rapidly, and much effort is put on intensifying processes to increase productivity and cost efficiency. Ever increasing titers in upstream production demand increased efficiency in downstream purification. GE Healthcare works intensively to help improve throughput in the large-scale manufacturing of mAbs.**

As most of today's upstream processes are of high feed concentrations, mass throughput rather than volumetric throughput is the main target for downstream process improvements. Protein A capture is the initial downstream purification step of most mAb processes. As such, the protein A capture step is subjected to large quantities of crude sample feed. To prevent protein A capture from becoming rate-limiting for the manufacturing process, high efficiency of this step is crucial. To improve performance of protein A capture, GE Healthcare has worked on optimizing both the ligand and the base matrix to develop a next-generation protein A resin that exhibits increased productivity over current protein A resins.

Co-optimization of the ligand and the base matrix is necessary, as large pores reduce steric hindrances but at the expense of available surface area, and long ligands increase the number of binding sites but can increase steric hindrances. To improve cleaning efficiency, weak points in the protein A ligand were identified and subjected to mutations to enhance alkaline stability. More than 400 different constructs were evaluated using high-throughput screening methodologies. A library of ligands was generated using a design of experiments approach, and Biacore™ surface plasmon resonance technology enabled quick evaluation of the different modifications introduced to the protein A ligand upon decision of final resin design.

## Addressing higher demands for maximized productivity

The final product, MabSelect PrismA, is built on the heritage of former MabSelect products. However, with the enhanced properties of both the agarose base matrix and the protein A ligand, MabSelect PrismA offers significantly increased capacity compared with its predecessor resins. The improved capacity allows for handling of the increasing upstream titers to resolve bottlenecks in downstream mAb processing. The high capacity of MabSelect PrismA enables an increased mass throughput per purification cycle, improving productivity of current chromatography columns and systems without costly capital expenditures. MabSelect PrismA allows for up to 30 percent more product to be purified using current equipment. Alternatively, the increased binding capacity can be used to decrease the resin volume required to achieve a given mass throughput.

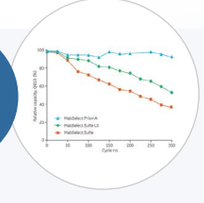
## Optimizing cleaning and sanitization for improved process efficiency

Efficient cleaning prevents impurities from building up on the chromatography column and reducing the capacity of the resin. Efficient cleaning and sanitization protocols also help prevent growth of microorganisms and inactivate potential endotoxins. A high alkaline stability of the resin enables the use of high concentrations of low-cost sodium hydroxide as a cleaning agent, supporting both cleaning efficiency and good process economy. MabSelect PrismA exhibits more than 90 percent retained dynamic binding capacity after cleaning with 1.0 M NaOH or more than 95 percent retained dynamic binding capacity after cleaning with 0.5 M NaOH between runs for 150 cycles. The significantly enhanced alkaline stability of MabSelect PrismA ensures a better process economy, while meeting the requirements of a stringent bioburden control.

*Learn more at www.gelifesciences.com/mabselectprisma*


LINKS

**Learning Link**
*MabSelect protein A resins*



**Application Note**
*Lifetime performance study of MabSelectTM PrismA during repeated cleaning-in-place cycles*

*Produced by* the Medicine Maker

*Sponsored by*