Millipore®
Preparation, Separation,
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White Paper

Strengthening your Chromatography Resin Supply Chain by Increasing Transparency and Control

Affinity and ion exchange resins are essential to the purification of monoclonal antibodies, vaccines, plasma and novel therapeutic modalities. Because of their fundamental role in manufacturing processes and the impact on drug product purity and yield, assurance of quality and supply is vital to avoid shortages which could ultimately affect patient care. Any changes in the quality of the resin can impact the impurity profile, such as the content of host cell proteins and DNA, which in turn, could affect the quality and efficacy of the medicine. Adding to the need for quality and supply chain control is the fact that chromatography resins are often sourced from a single supplier as qualification processes for new manufacturing processes are costly and time-consuming, as is replacing a resin in an existing manufacturing process.

Four Pillars of Supply Robustness and Control

Consistent quality and on-time delivery of our Fractogel®, Eshmuno® and ProSep® chromatography resins along with close, proactive collaboration with our customers enables a robust, multi-faceted supply chain program. Our program, optimized over a long history of supplying chromatography resins to the biopharmaceutical industry, includes four pillars:

- **Rigorously managed supply flows** with demand and forecasting planning, production planning, supplier management and inventory management.
- **Proactive identification and mitigation of potential risks** through capacity planning, business continuity planning, supplier risk management, disaster recovery planning, supply chain mapping and continuous improvement.
- **Continuous quality control** with our quality control programs (raw materials, in-process testing, and lot release specifications), ISO certifications, process characterization and control, as well as change control management.
- **Easy access to information** with our labeling and extensive documentation, detailed content on our website and a global team of technical and customer service experts.

Below, we explore key components of our chromatography resin supply chain program which help customers control their supply chains as they seek to ensure steady progress towards their next milestone and consistent availability of medicines for patients in need.

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Supply Chain Reliability

The reliable supply of chromatography resins depends on controlling the delivery and quality of critical raw materials and engagement with customers to accurately forecast both short- and long-term demand.

The base bead is one of the critical raw materials in chromatography resins, serving as the core and surface to which functional groups are attached. A range of base beads is available to serve as the foundation of a resin. They must meet our stringent requirements including mechanical strength and chemical resistance. To more effectively control the supply of our chromatography resin components and ensure the highest quality standards, we leverage two options: We manufacture base beads at our own state-of-the-art dedicated production facility for Eshmuno® and ProSep® resins and have established strong supply and quality agreements with a set of trusted suppliers for Fractogel® base beads and other critical raw materials. With both, we are able to successfully meet increased demand for resins as the need arises, ensure lot-to-lot consistency and enable consistent change control.

In addition to controlling the delivery and quality of critical raw materials, it is essential to accurately forecast short- and long-term demand of resins. Working in collaboration with customers, we are able to determine the need for capacity investments and facility expansions. To accomplish this, we proactively and regularly interface with our customers' procurement and supplier management teams to understand business strategies and market trends they believe will impact demand and other relevant information. It is also helpful when customers share with us the molecules for which they are using our chromatography resins and in which clinical phase; this provides additional insight into the expected buying cycles and helps us to more precisely predict demand.

Short-term demand planning (from 0 to 18 months) is accomplished by tracking ordering trends through a robust sales and operating planning (S&OP) process which includes a monthly review of demand. For long-range planning, we consider market dynamics and the product lifecycle. This planning is not only accomplished by analyzing ordering trends but also by working closely with customers to understand their specific demands which drive production schedules.

Twice a year, we also review and align on long-term projections to ensure our production and operations teams are able to match capacity with current resources or initiate an investment to meet increased demand. Similar conversations and planning take place with our suppliers.

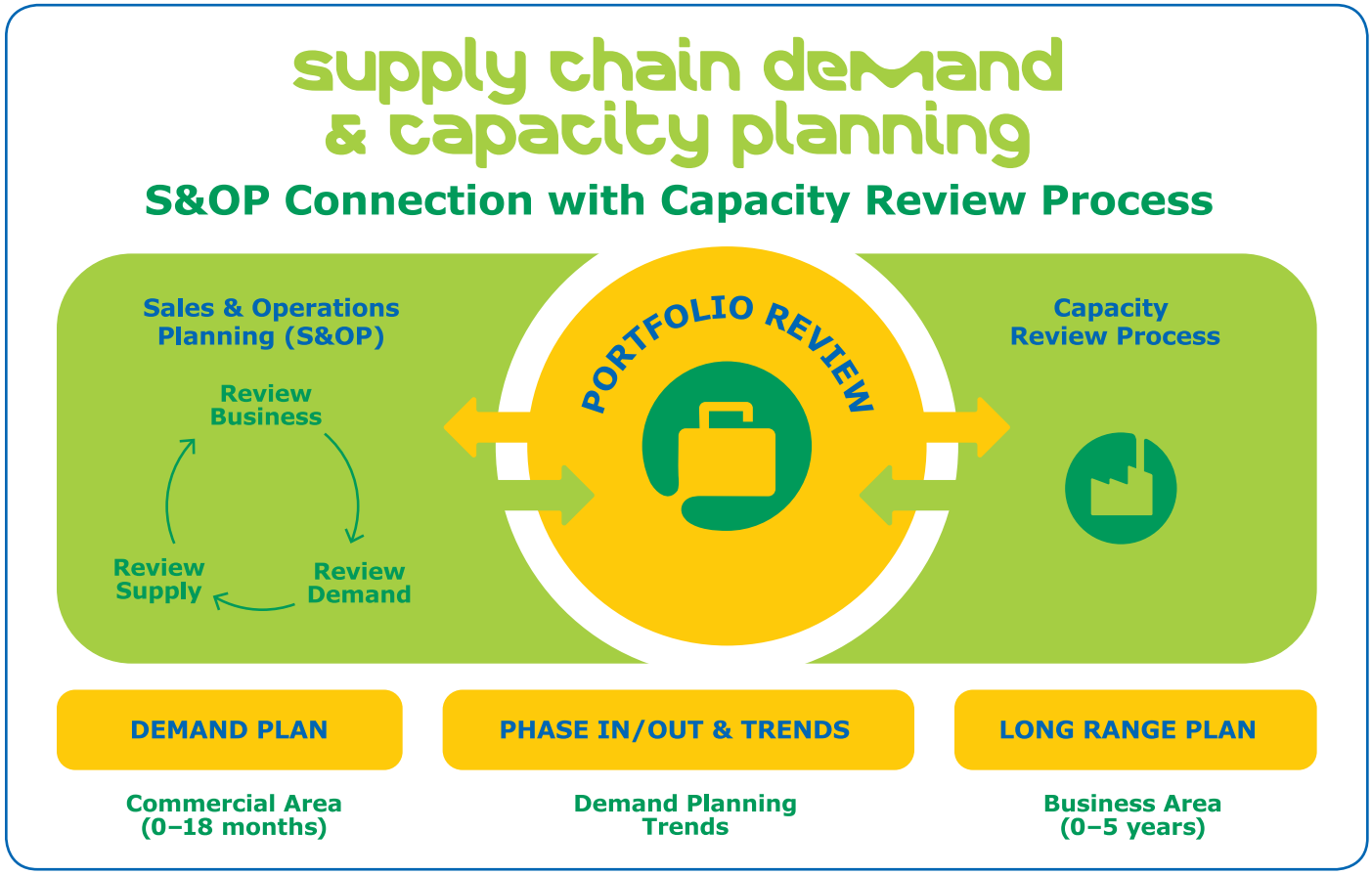

Figure 1

Short-demand planning and long-range planning in collaboration with customers enables procactive management of expected demand.

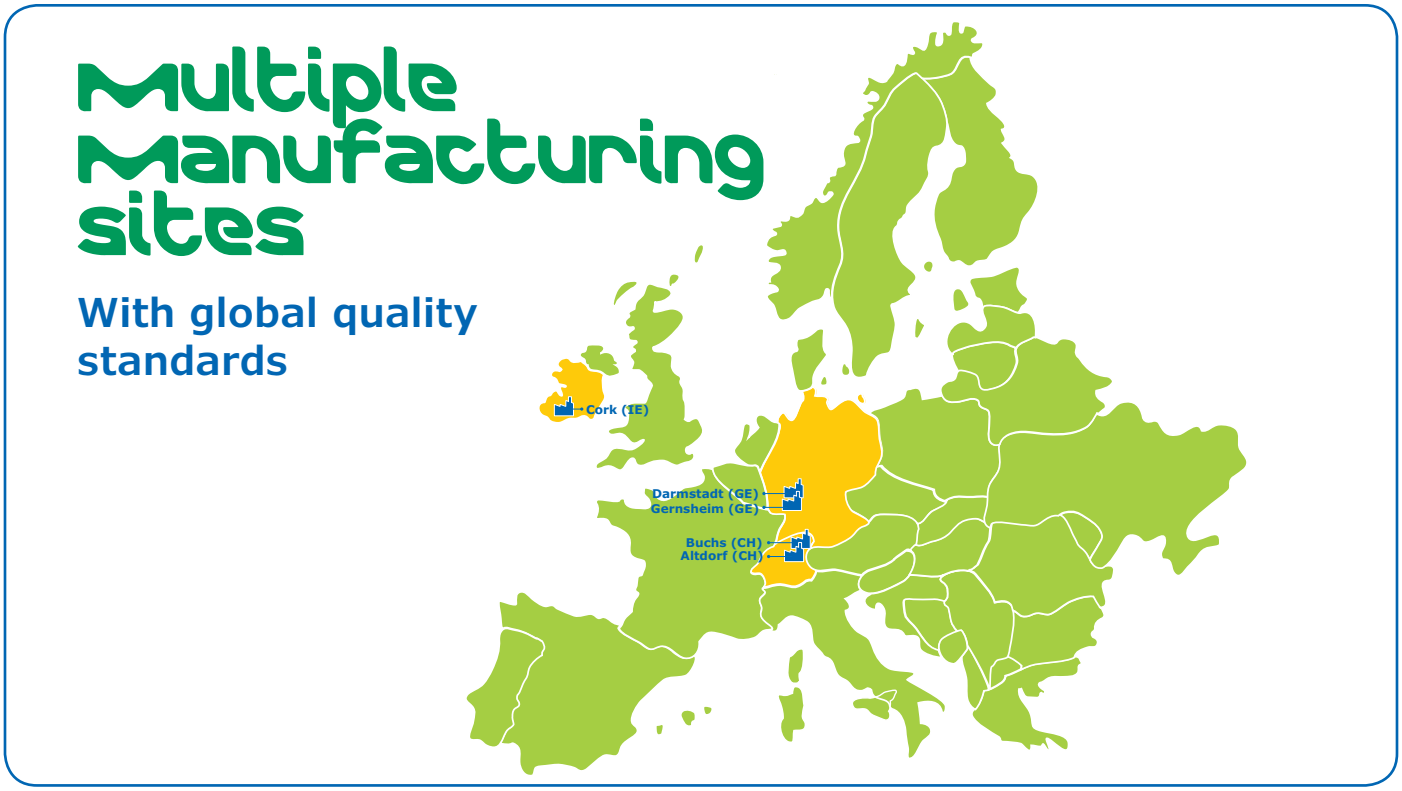

Figure 2

Multiple manufacturing plants with harmonized quality systems are approved for multiple resin production.

Supply Chain Risk Mitigation

Unfortunately, even the most robust approach to forecasting won't protect against all unforeseen events. To compensate for this, we deploy a comprehensive business continuity management program.

Our approach to business continuity follows pre-defined, formally documented policies that guide identification of risks followed by creation and implementation of appropriate risk mitigation strategies. Such strategies can include increasing the safety stock of raw materials or qualifying a second source. Our global network of trusted suppliers has also established similar contingency plans.

Business continuity also includes disaster recovery and structured plans to reduce recovery timelines, further protecting the supply of resins and customer processes. These plans define the expected time needed to rebuild stock and identify critical or time-limiting process parameters. Risk mitigation strategies also include the ability to leverage our entire manufacturing network, having a second, qualified supplier for some critical raw materials and back-up equipment which can be installed.

Our manufacturing sites in Germany, Switzerland and Ireland are suitable for multiple resin production, thanks to comparable equipment and know-how. In addition, we have a harmonized quality system throughout the global chromatography resin manufacturing network.

Customers also benefit from the close relationships and quality and supply agreements we have established with our suppliers, many of whom we have worked with for decades. When needed, our suppliers grow with us, expanding their equipment and manufacturing capacity, building safety stock as needed and maintaining global warehouses in the US, Europe and Asia. This helps to ensure our continuity of supply for our customers.

Quality Standards

Assurance of quality and lot-to-lot consistency begins at the earliest stages of our research and process development phases, when new resins and membranes are being conceptualized and designed to meet the evolving needs of our customers. We identify and use materials that will be available in the same quality and quantity when the process is transferred to production and often start with products from our own catalog where we know exactly where the material is sourced; alternatively, we select a qualified supplier capable of delivering the required quality and quantity.

The quality of raw materials selected for use in the manufacture of chromatography resins and the parameters assessed and confirmed prior to release of resins are essential to ensuring success for the end user. During product development and later as part of process robustness workflows, critical raw materials and resins undergo detailed material characterization.

Raw materials and resins also undergo extensive quality control testing which applies a set of methods used for assessment relative to predetermined criteria to confirm each component and every batch meet rigorous quality standards.

With multiple production facilities and a network of suppliers, harmonization of quality standards is leveraged to deliver important advantages to customers including:

- Availability of supplier data
- Harmonization of change control processes
- Consistency of raw material quality and performance

Because there is no GMP standard for chromatography resins such as those for APIs and excipients, we created our BioProcess Resin (BPR) Quality Marker program. The BPR Quality Marker guarantees one global quality standard for chromatography resins across all our production sites. The BPR Quality Marker defines mandatory quality and regulatory attributes governed by regulatory authorities, industry standards and/or ISO standards for chromatography resins used in biopharmaceutical manufacturing. The Quality Marker covers warehouses and production sites, documentation related to quality and regulatory topics, equipment requiring qualification and analytical methods requiring validation. The corresponding BPR Quality Manual is a globally approved and controlled document, updated as needed to align with evolving industry requirements.

An important element of these quality standards is a focus on continuous improvement of specifications and analytical methods to help ensure even greater consistency and quality across the entire manufacturing network. And while continuous improvement is an important goal, it must appropriately balance the impact of changes which can affect process performance and potentially drug product quality, safety or efficacy. To help minimize any change risks to our customers, we provide customers with the notification time needed to assess and accept the changes prior to implementation. In addition, we provide comprehensive comparability studies and offer samples from different lots to enable customers to perform additional testing.

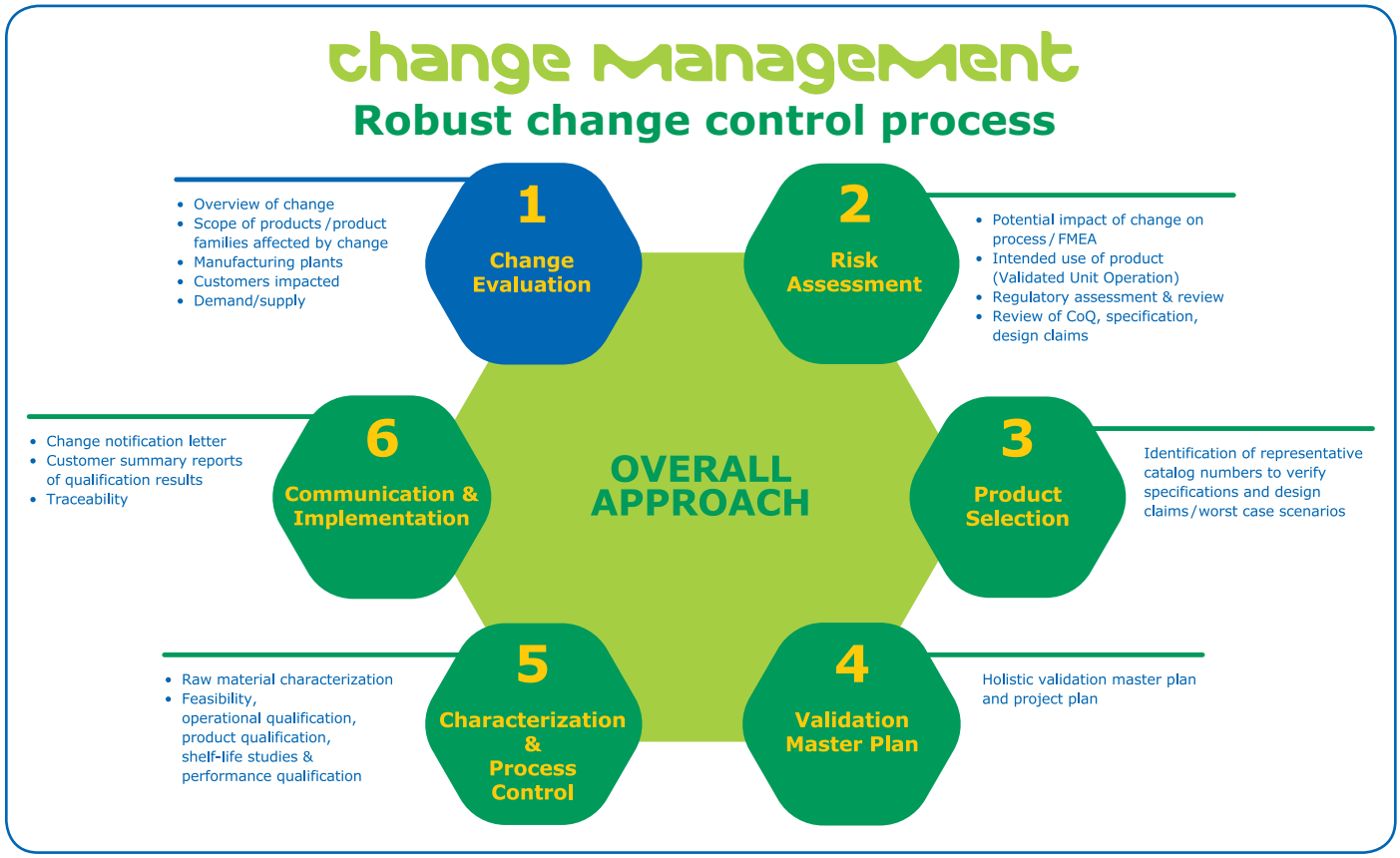

Figure 3

A proactive and comprehensive approach to change management helps minimize impact on the customer process.

Transparency of Information

For drug manufacturers, tracking down the extensive information needed to address regulatory requirements can be time-consuming, resource-intensive and costly. To remove this obstacle for our customers and help streamline their processes, our Emprove® program provides easy access to comprehensive documentation needed to support risk assessments, management and mitigation, facilitate qualification processes and expedite preparation for approval. Originally established for raw and starting materials used in biopharmaceutical manufacturing, the program is expanding to including chromatography resins. Information contained within Emprove® dossiers provide complete transparency to the entire supply chain from raw materials to final packaging and can be forwarded to regulatory authorities.

Stay Ahead with a Robust Supply Chain and Control

Patient demand for new medicines is increasing and so is the competition to develop both new and innovative treatment options as well as biosimilars. To stay ahead, biopharmaceutical manufacturers need to maximize productivity, reduce risks and enhance process performance in all areas of their workflow including purification. A critical success factor is assurance of an uninterrupted supply of quality chromatography resins.

We have created a robust and disciplined global chromatography resin supply program which leverages years of experience, market intelligence and deep product and process knowledge. The end result for our customers is confidence in the quality and reliable supply of chromatography resins to meet their specific and evolving needs.

About the authors

Nina Weis is responsible for the product management for chromatography resins at MilliporeSigma. Since joining MilliporeSigma in 2008, she has held various product management positions including cell culture media and biopharm materials. In her current position, she is responsible for the development, implementation and management of marketing strategies for preparative chromatography resins focusing on customer satisfaction and driving portfolio growth.

Julia Doreen Johann is global demand planner for chromatography resins at MilliporeSigma. She joined MilliporeSigma in 2015 and has served as demand planner for a variety of product portfolios covering different global manufacturing sites. During past years she has also worked on various strategic projects within the supply chain.

Tim Berger is a member of the chromatography marketing group at MilliporeSigma. He holds an M.S. degree in biotechnology, with a focus on bioprocess development, from Mannheim University of Applied Sciences. After joining MilliporeSigma in 2017, he completed his master's thesis on plasma purification processes and joined the chromatography R&D group focused on product development and viral vector process development. In his current position as associate product manager, he is responsible for quality and operations of MilliporeSigma's chromatography portfolio and serves as the marketing lead for development of novel modality chromatography products.

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