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White Paper

Designing Quality into Chromatography Resins to Minimize Variability

Chromatography resins and adsorptive membranes occupy a central role in the downstream purification of biologics and as such, the raw materials and processes used to manufacture these materials directly impact their performance. Assurance of quality and lot-to-lot consistency begins at the earliest stages of the research and process development phases, when new resins and membranes are being conceptualized and designed to meet the evolving needs of our customers. In this article, we speak with Dr. Michael Schulte (Head of Purification R&D) and Dr. Bertram Cezanne (Head of Chromatography Process Development), about the strategies and close collaboration employed by Merck to design quality into resins and membranes and to help customers minimize variability in their purification process.

Scientist operating in a Merck chromatography resin development lab

What types of raw materials are used to manufacture chromatography resins?

BC: We start with bead material which is modified in subsequent steps. The first step is preparation of the porous beads which are made via a polymerization reaction. We use a properly designed mixture of different reagents and additives to ensure the beads have the desired morphology and pore size and then apply a sieving process to isolate the right size distribution of beads. We develop a very deep understanding of these processes in order to have full control of the polymerization reactions and the subsequent sieving. The next step is to modify the surface of the beads by adding the necessary functionalization which will differ among various product types.

The selection of raw materials has a direct impact on the quality of the final product. Even seemingly small variations in the raw material quality can sometimes lead to significant effects on the final product. For example, the difference in chain length of a single monomer unit of a soluble polymer used as a processing aid notably impacts the resulting material. By having full control of the raw material properties and the process parameters, we can control and minimize the variability in the final product quality and process yield.

How is quality incorporated into the development of new resins and membranes at the earliest stages?

MS: We constantly monitor scientific advances, explore trends and engage with our customers to inspire ideas for new chromatographic materials that will meet the evolving needs of the industry. When we begin the research process, we are free to choose whatever

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raw materials are available, including the beads, the surface modifications and membranes. Despite this freedom, we know that even at the small scales we deal with in research, we have to identify and use materials that will be available in the same quality and quantity when the process is transferred to production. In other words, it doesn't make sense for us to start with an ultrapure raw material which we know will not be available in sufficient supply, or with the required regulatory documentation for production. We can start with products from our own catalog where we know exactly where the material is sourced; alternatively, we can select a qualified supplier we know will be capable of delivering the quality and quantity that is needed based on customer requirements.

BC: We leverage a range of stakeholders including members of Michael's R&D team, members of my process development team, and colleagues from quality assurance and control, our production sites and procurement to identify critical raw materials. A raw material would be considered critical if its technical quality has direct impact on the quality of our final products, or it could pose a business continuity risk if there is only one production line available in a high risk area. In the event of a single production line, we would partner with our supplier to ensure business continuity, as well as increase safety stock inventory and implement additional risk mitigation activities.

Explain more about how the research and process development teams work together to ensure robust processes?

MS: In research, we typically start with a 100 mL reactor/20 mL product volume and within these small volumes, we explore different variations of the process. Our goal is to find the best product at small scale, then complete the application development and first-principle characterization work. Once we have established an optimized protocol for a synthesis, we meet with Bertram's process development team and discuss moving the protocol to a larger scale and transferring into production. As the lab protocol is transferred to process development, that team also confirms raw material availability and checks for applicability of the large-scale equipment. In R&D, our biggest reactor size is 2 L which is the smallest size of reactor in the process group. We transfer at the same size and then Bertram's group scales up from 2 L to 10 L which is their standard pilot lab size. They then typically do two more scale-up steps in the pilot plant, to 150 L and 600 L, and from there, they can transfer to one of our four production sites.

BC: I think another critical success factor is that we have very strong collaboration among research, development, and manufacturing including quality assurance, quality control and supply chain. This team is collaborating along the whole process chain and the different phases of a project until launch. We also have a very strong link to our production sites to the extent that the colleagues who have run the process in development also run the first campaigns in production in collaboration with the production team.

MS: We also do job rotations with people from research coming over to development and people from development spending time in research. The better our teams work together and the more they know, results in a higher probability of success. When you start in R&D, you know the 100 mL reactor; when you've spent time in the pilot plant or in production where you have handled hundreds of liters of volume, then you have developed a completely different understanding of the challenges of your counterparts in process development.

Merck employs a continuous improvement methodology called Process Characterization and Control (PC&C; Figure 1) to help ensure superior quality, operational efficiency and a reliable supply. How is this used in the development and manufacturing of chromatography resins?

BC: To ensure the reliable supply of consistent, high quality products to our customers, we verify our production processes to consistently achieve acceptable process and product results; PC&C is an essential tool as it helps us optimize processes within experimentally confirmed ranges. The way it works is that we first define product and process requirements, such as critical quality attributes or product claims. We start with the defined specification for building prototypes. We characterize the product and develop a more detailed understanding of how the parameters of the process influence the properties of the product.

Next step, we do a thorough investigation of the parameters in that space to define what is needed to consistently meet requirements and have a thorough understanding of the process so we can reproduce the desired result. Even if there is some variability in raw materials or maybe some inherent variability due to operators or equipment, we aim to accommodate that in the process. We also consider variability in our starting materials in order to ensure a reliable quality of our products. Using these process parameters, we conduct design of experiment (DOE) studies to define the optimal process window. Once the process has been characterized, we develop and implement an improved process control plan.

MS: When we are prioritizing production processes for process characterization and control, we consider four key aspects:

1. Customer Application – How is the product used in the customer's process? Is the product categorized as critical by our customers? A more critical product is more likely to be prioritized for PC&C.
2. Yield – A process that delivers lower process yields may indicate a significant opportunity for improvement through PC&C.
3. Process Variability – Higher process variability may indicate that the process is a viable candidate for further improvement.

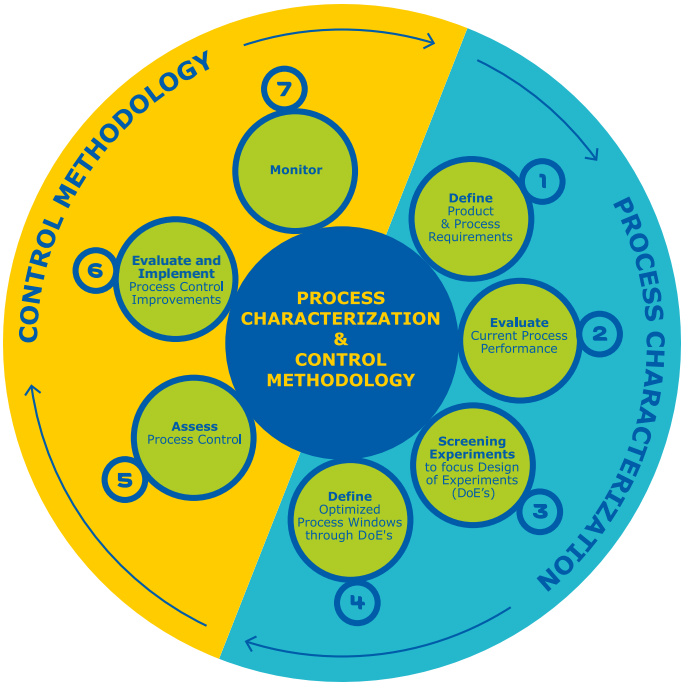

Figure 1

The process characterization and control methodology facilitate optimization of processes within experimentally confirmed ranges.

4. Plant Capacity and Utilization – A manufacturing process near or at capacity presents an opportunity to enhance process efficiencies and increase output.

As an example, we developed a production process for a chromatography resin that involved multiple chemistry steps, culminating with a test to evaluate product performance. We used PC&C to enhance our understanding and control of the process and used novel tests, which were not available when the process was originally developed, in order to characterize the process in greater detail. Using these valuable new data, we discovered correlations between the data and our process performance. With these new insights, we were able to enhance our process control. Inevitably, opportunities for continual process enhancement emerged.

As raw materials change, capacities expand, or tech transfer activities occur, we capitalize on the opportunity to leverage the knowledge gained to re-evaluate and revisit our critical process parameters for further process characterization, control, and improvement.

BC: Customers don't want variability in the product and the more we know about the process, the better we can help control the process resulting in lower variability. And the more we know about the process, the better we can assure timely delivery as process know-how and low variability are key elements of a reliable supply chain. Additionally, the more effective we are at fine tuning product properties by controlling process parameters and raw material specifications, the better we are at customizing products with a very narrow specification.

To summarize, we focus on reducing process variability and the cost of non-quality and building superior quality into operationally efficient production processes. These production processes result in higher production yields, enabling us to improve on-time delivery metrics and ultimately strengthen our supply chain for customers.

Ensuring the Quality of Raw Materials and Resin Batches

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, 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.

Raw Materials Testing

Many raw materials are incorporated into ion exchange and affinity chromatography resins including monomers for functionality and linking, porogens to create the pores, acrylate-based monomers that carry ion exchange functionality and affinity ligands. Whether incorporated into the final product or used only during manufacture, all materials are assessed using a range of analytical and physico-chemical parameters and defined by quality windows that must be met. Among the techniques leveraged to ensure quality are HPLC, MALDI, NMR, viscosity measurements, acidity measurements by titration and assessment of metal impurities.

Release Testing

Following manufacture, each batch of resin is also tested prior to release using a portfolio of methods including:

- Visual assessment via microscopy
- Physical assessment to confirm particle size and distribution as well as surface area
- Functional assessment to determine capacity of the resin, retention behavior and protein binding capacity
- Compliance assessment regarding endotoxins and microbial counts

For non-release testing, additional techniques such as NMR or MALDI-MS are employed and if new insights are derived from these approaches, they can be incorporated into the actual release testing to improve the evaluation.

About the authors

Michael Schulte is Head of Purification R&D at Merck. In his PhD thesis at the University of Münster, Germany, he developed new chiral stationary phases for chromatographic enantioseparations. In 1995 he joined Merck and since then he has been responsible for research and development in the area of preparative chromatography, including the development of new stationary phases, new separation processes, and the implementation of Simulated Moving Bed technology. In his current position, he is responsible for the development of novel stationary phases for preparative chromatography.

Bertram Cezanne is Head of Process Development Synthesis at Merck. He is a chemist by training and did a PhD in Synthetic Organic Chemistry. In 1997 he joined Merck and worked for more than 15 years in drug discovery and early scale-up, where he gained a broad experience in synthetic organic chemistry in different scales including downstream operations, such as chromatography. Since 2016 he is responsible for process development and transfer activities of various product portfolios with a strong focus on biochromatography materials. His group has very broad capabilities and know-how in process development covering organic chemistry, polymer chemistry, silica chemistry, catalysis and downstream operations.

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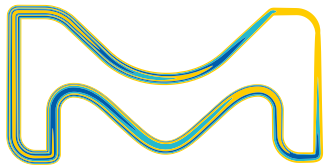

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