BioPhorum

MULTI-PRODUCT FACILITY

A practical guideline for implementing multi-product resin in biopharmaceutical manufacturing

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Since its inception in 2004, BioPhorum has become the open and trusted environment where senior leaders of the biopharmaceutical industry come together to openly share and discuss the emerging trends and challenges facing their industry.

Growing from an end-user group in 2008, BioPhorum's membership now comprises top leaders and subject matter experts from global biopharmaceutical manufacturers and suppliers, working in both long-established and new Phorums. They articulate the industry's technology roadmap, define the supply partner practices of the future, and develop and adopt best practices in drug substance, fill finish, process development and manufacturing IT.

In each of these Phorums, BioPhorum facilitators bring leaders together to create future visions, mobilize teams of experts on the opportunities, create partnerships that enable change and provide the quickest route to implementation, so that the industry shares, learns and builds the best solutions together.

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The authors would like to thank all the many friends and colleagues that have contributed over the years to the discussion and progress of implementing multi-product resin re-use.

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Abstract

Chromatography resins are used to purify biopharmaceutical products. These resins are typically dedicated to a single product due to potential product carryover risks and to avoid overly complex cleaning regimens. This strategy limits the useful life of the resin, contributing to higher material costs and resin waste which can further contribute to material shortages in situations such as a pandemic. This paper discusses strategies for multi-product resin re-use (MRR).

MRR is an area of interest for the biopharmaceutical industry. Several papers have been published on MRR including those that explore various implementation strategies and present case studies. During the COVID-19 pandemic, with shortages of materials such as chromatography resins, the re-use of resins for GMP clinical manufacturing was implemented with great success by several companies[1].

This paper gives an overview of companies that have implemented MRR along with discussion of a risk-based approach for its adoption in clinical manufacturing in alignment with ICH Q9(R1)[2]. The methodologies and controls discussed in this paper apply to all resins used for purification. However, the initial focus is on protein-affinity (ProA) resins due to their high cost, challenges associated with cleaning the feed stream of harvested cell culture fluid and the limitations of protein-derived ligand compatibility with exposure to caustic solutions used in cleaning cycles.

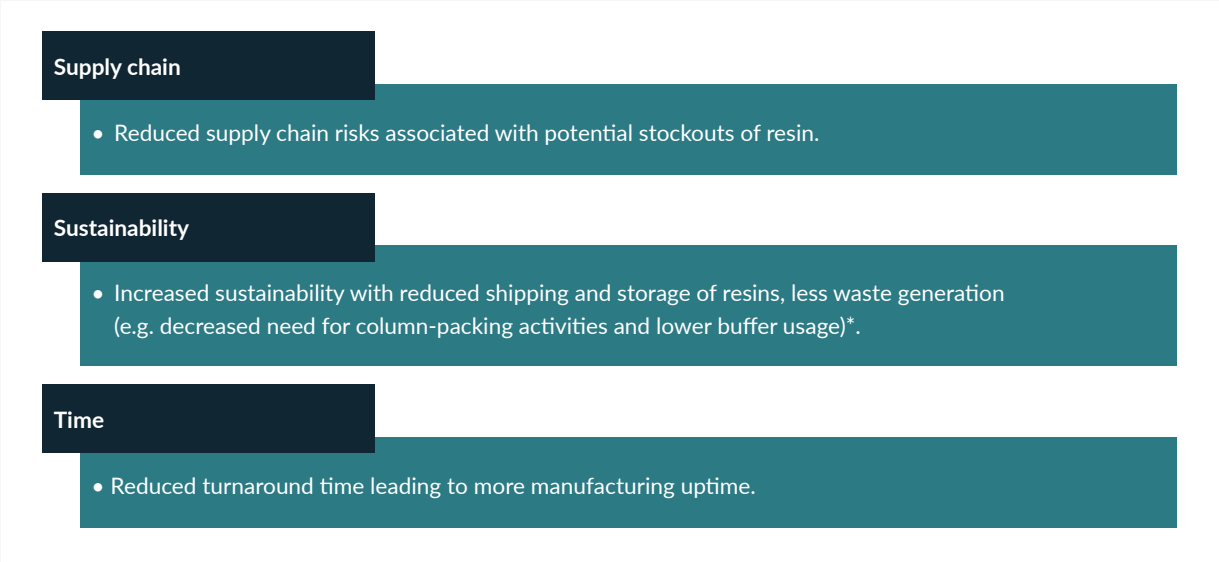
1.0

Introduction

Chromatography resins used for purifying biopharmaceuticals are generally dedicated to a single product to avoid the risk of product carryover and cross-contamination, which could compromise product safety and efficacy. In good manufacturing practice (GMP) facilities that manufacture a limited amount of any single product, this practice can result in the resin being used for a fraction of its useful life[3]. This increases the cost of downstream processing (DSP) which can account for up to 80% of total manufacturing costs, of which up to 60% are often attributed to chromatographic separation steps[4].

Therefore, restriction of resin usage to a single product, especially for clinical production, creates even higher material costs, increased turnaround time between products, and logistical problems with resin storage and testing. Ability to re-use resins across multiple products (rather than the current standard of dedicating resin to specific products) ensures full use of the resin lifetime for considerable cost savings, efficiency of operations and potential reduction of carbon footprint related to resin manufacturing (Figure 1). Re-using resins also simplifies manufacturing logistics and labor associated with less packing, unpacking and storage.

Figure 1: Advantages of MRR



* Full sustainability lifecycle assessment is still needed to understand the impact and level of any sustainability claims

The practice of dedicating product-specific resins is typically employed for all stages in clinical manufacturing. Early in the product lifecycle, the required quantity of clinical trial material is low and there is uncertainty around the technical success of the product. As a result, resins are used for a relatively low number of clinical manufacturing batches of the product and there is substantial discard of resin. Given this substantial underutilization of resin, MRR emerges as a predominantly applicable and beneficial strategy for first-in-human (FiH) manufacturing batches. This methodology could help the resin reach its validated lifetime, which can be upwards of 100 to 200 cycles depending on the resin.

A proof-of-concept methodology for extending resin re-use to multiple products is described in a series of Parenteral Drug Association (PDA) papers by Sharnez, R. et al., covering resin and column performance, product carryover and cleaning effectiveness[3, 5, 6]. During the COVID-19 pandemic, with shortages of materials such as chromatography resins, resin re-use for GMP clinical manufacturing was implemented successfully by several biopharmaceutical companies, one of which is described in the publication, Li, H. et al., 2024[1]. The implementation was restricted to specified products, and the proof of concept for resin re-use in a GMP manufacturing environment was demonstrated successfully.

MRR methodology is already in practice for both clinical and commercial drug substances that are manufactured in multi-product facilities, where product-contact equipment can either be single-use, such as bioprocessing bags, or multi-use, such as a stainless-steel vessel. The purification process may involve two or three chromatography columns depending on the ability of the process to remove process- and product-related impurities, ensuring the protein product meets required quality standards. The first step in the purification process typically includes a ProA chromatography column which separates the protein of interest from cellular components (e.g. host cell proteins (HCPs), DNA, media components and viruses) that may be present during the cell culture process. Several chromatography resins may be selected based on their properties and the matrix to be purified. Post purification, the product of interest is concentrated and buffer exchanged into the required matrix using an ultrafiltration/diafiltration (UF/DF) unit operation.

ProA chromatography is regarded as one of the most effective techniques for the capture of monoclonal antibodies (mAbs) and is a first major step in DSP in the manufacturing of mAbs. The specificity of the ProA ligand toward mAbs results in extremely effective clearance of HCPs and DNA. As a result, ProA chromatography remains a preferred step in the purification of mAbs. The high cost and efficiency of ProA resins presents an opportunity for cost reduction through multi-product use of resin, effectively increasing resin lifetime utilization.

Given the enhanced clearance capability of the ProA resin to separate and concentrate the protein of interest due to the affinity mode of separation, it is often significantly more expensive than other resins that may be used in the purification process. Additionally, because the ProA chromatography step occurs early in the purification process and deals with a complex feed stream of cell culture medium components, it poses significant challenges for resin cleaning and maintaining microbial control of the chromatography column[7]. Although the methodology in this paper can be applied to all resins, due to the unique challenges of ProA (Figure 2) this paper focuses on ProA. This paper leverages industry experience and outlines a risk-based approach to implementing MRR methodology more broadly, without compromising product quality.

Figure 2: Challenges of ProA chromatography

2.0

Current practices in the biopharmaceutical industry

Biopharmaceutical manufacturing is performed in multi-product facilities, where use of process equipment for multiple products is widely accepted and established. The methodology for multi-product equipment use ensures that existing product changeover and equipment cleaning protocols are adequate to protect the cGMP-manufactured products from cross-contamination. To date, standard practice in the biopharmaceutical industry involves single-product, dedicated use of chromatography resins and UF/DF membranes.

This paper proposes the application of multi-product equipment use methodology to multi-product use of chromatography resins.

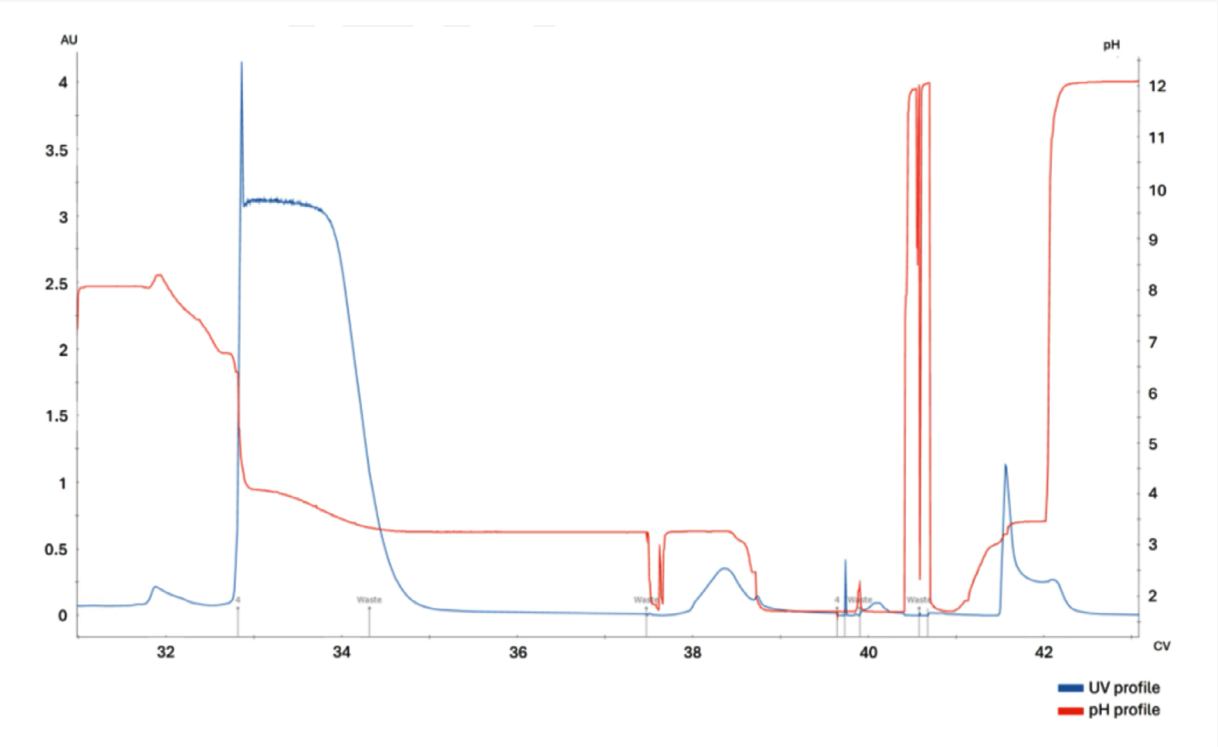
2.1 Current practice: single-product use of chromatography resin

Several chromatography resins are used in the purification process, typically operated in bind and elute or flow-through mode. The cleaning challenge may be greater with bind and elute columns to ensure that the product has been effectively removed from the column between re-use cycles. Taking ProA as the resin of interest, there are several steps for running a ProA cycle (Figure 3). The ProA affinity column binds the target product during the load step, then a high-salt wash step can be used to remove any unbound and non-specifically bound material. The product is eluted from the resin with a low-pH buffer. A strip/regeneration step (low-pH buffer) can be applied to remove any tightly bound materials from the resin, followed by a caustic solution such as 0.1N sodium hydroxide (NaOH) or higher, depending on the properties and tolerance of the chromatography resin. Within a given company, platform operating conditions are often used, based on the characteristics of the chromatography resin and vendor recommendations for pH and caustic stability. Blank/mock elution chromatography runs that mimic purification without loading protein on the column, are run at predefined intervals to verify the effectiveness of the resin-cleaning regime. Figure 4 shows a typical chromatogram for a ProA chromatography profile, where the product is eluted with a low-pH buffer, followed by stripping and cleaning with an alternate low-pH buffer and/or 0.1N NaOH, which solubilizes proteins and nucleic acids bound to the resin.

Figure 3: Typical sequence for resin re-use in a single-product process

* The blank/mock elution chromatography run is executed at predefined intervals; this may be integrated within the typical chromatography cycle or may be a standalone run post-processing campaign.

Figure 4: Typical chromatogram for a ProA chromatography profile



The extent to which chromatography resins can be re-used without adversely affecting product quality is assessed in small-scale laboratory studies. During clinical manufacturing, prior knowledge gained from platform experience with specific chromatography resins and operating conditions can be leveraged. Periodic product quality testing of the eluted product is performed to ensure that continued resin re-use does not have an adverse impact. For commercial manufacturing, usable lifetimes of the chromatography resins are confirmed by an ongoing lifetime monitoring program (US Food and Drug Administration (FDA) process validation (PV) Guidance[8, 9]). Monitoring of resin re-use at either laboratory or large scale (Figure 5) ensures there are no adverse trends with extended resin re-use.

Figure 5: Monitoring of resin re-use

Product purity

- Quality of the process intermediate is monitored during resin re-use and tested at intervals over the course of resin re-use for product-related impurities such as aggregates, DNA and HCPs.

Product yield

- Resin re-use and aging can result in a loss of performance which manifests as a decrease in yield
- An active process-monitoring program ensures early detection of declining resin performance. This is pertinent for ProA resin where fouling of the resin or ligand loss from a stringent cleaning cycle can result in a decline in yield.

Sanitary processing

- Bioburden and endotoxin monitoring can be performed on the equilibration effluent to verify the effectiveness of the resin sanitization regime.

Chromatography profile monitoring

- The product load, product elution and regeneration profiles are typically monitored to ensure typical transitions, demonstrating laminar flow, no bed channeling and stable bed pressure, which demonstrate no resin fouling or bed instability.

Column integrity evaluation

- Height equivalent theoretical plate (HETP), transition analysis (asymmetry, peak shape etc.).

Cleaning effectiveness

- A blank run/mock elution is performed at periodic intervals to demonstrate an effective resin cleaning regime. The residual protein carryover may be assessed via an integration of the UV absorbance at 280 (A_{280}) absorbance profile during the elution step of the mock elution.

2.2 Current practice: multi-product use of equipment

The cleaning of multi-product equipment is performed to ensure that potential carryover of a given drug substance into the subsequent process is controlled to an acceptable level from a patient safety perspective[10]. This is evaluated through a safety-based maximum allowable carryover assessment for the target product purity. The conventional approach assumes that the drug substance remains active after exposure to the cleaning reagents.

'Multi-product use of equipment' in the manufacture of biologics refers to the practice of utilizing the same equipment or facilities to produce multiple products. Multi-product use of equipment enables production of different biologics within the same manufacturing environment, reducing the need for separate dedicated facilities for each product. To achieve this, manufacturing processes must be carefully designed and validated to minimize the risk of cross-contamination between products. An appropriate cleaning procedure is implemented to prevent carryover of materials or contaminants that could affect product quality or safety. In the case of chromatography unit operations, the equipment utilized consists of a chromatography column and chromatography skid. The empty chromatography column is cleaned after unpacking at the end of a production campaign and again after maintenance activities, prior to packing resin for the next product. The empty column cleaning procedure typically involves flushing with caustic and acid buffers or using formulated acid and base detergents. Detailed cleaning considerations are described in the BioPhorum publication *Changeover cleaning of empty columns and column-packing equipment*[11].

Cleaning verification acceptance criteria for the empty column and chromatography skid are generally aligned with those for other equipment in the manufacturing area. Column cleaning rinsate samples are taken during the final clean-in-place (CIP) rinse phase which typically comprises total organic carbon (TOC) analyses and may include bioburden and endotoxin samples, depending on the company's approach to equipment turnover. The column rinsate samples may be taken from the column outlet line or from the outlet line of the chromatography skid used to clean the empty column. The final CIP rinse may be carried out with water for injection (WFI), equilibration buffer or storage buffer, if demonstrated that the buffer used does not interact with assays.

TOC rinsate samples demonstrate removal of residual product and the cleaning agents, if applicable. Cleaning verification acceptance criteria are aligned with typical established limits. As with other equipment in the manufacturing area, typical TOC values range from one to two parts per million (ppm)[12, 13]. The cleaning verification acceptance criteria applied for MRR must be reflective of the carryover risk and process capability, and documented accordingly.

Chromatography columns often require an additional cleaning assessment due to the potential for resin ingress in crevices near column frits and O-rings. As a result, the empty column cleaning verification may include manual cleaning, with a visual inspection to confirm resin removal and TOC swabs to confirm product removal.

Introduction of a new product into a multi-product facility includes a cleaning assessment to identify necessary cleaning and analytical requirements. This ensures that the new product, once deemed suitable for introduction, can be produced without compromising product safety, quality or facility standards. Cleaning processes are designed to clean equipment to predefined acceptance criteria to ensure that the potential for product carryover is controlled to an acceptable level and there is no impact to product quality or patient safety. Before the introduction of a new product, the product cleaning challenge and manufacturing suitability are assessed by evaluating the new product using available product data outlined in Figure 6.

Figure 6: Introduction of new product assessment

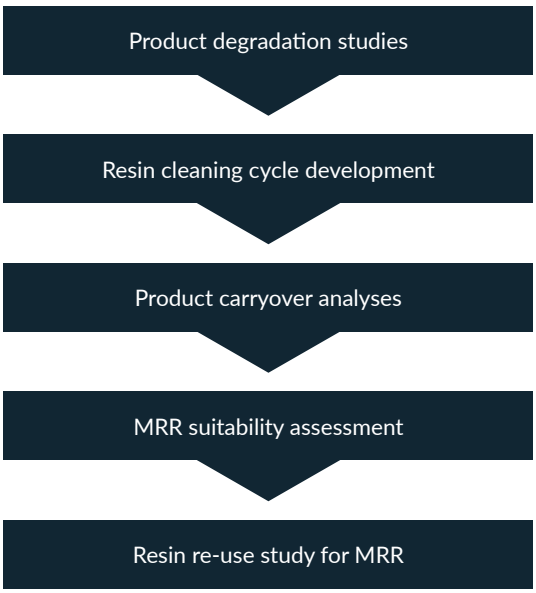
3.0

Laboratory-scale suitability assessment prior to implementing MRR

To assess the suitability of using resin across multiple products, insights can be drawn from existing practices in biopharmaceutical manufacturing, as outlined in Section 2. One major focus is understanding the product cleaning challenge, which builds on product degradation studies and equipment cleaning knowledge established for multi-product equipment use (Section 2.2). The greater challenge for cleaning resins, relative to equipment, is acknowledged and needs to be accounted for in developing robust cleaning conditions.

Understanding the product, and the strip/cleaning buffer solutions used, is key to eliminating the potential for resin fouling. Small-scale studies are performed to assess product degradation, to optimize the resin cleaning parameters and to generate product cycling study data to support the potential implementation of MRR. Under typical cleaning and sanitization conditions used for chromatography unit operations, proteins are known to degrade and denature which renders them pharmacologically inactive[10]. ProA resin presents the greatest cleaning challenge due to the strong affinity of the product for the resin and the limited stability of the ligand under denaturing conditions. Therefore, a balance between the concentration of the cleaning solution and total exposure time needs to be achieved to ensure the cleanliness of the resin and ligand stability. The laboratory-scale suitability assessment for implementing the MRR strategy is illustrated in Figure 7, outlining product degradation studies, resin cleaning studies, product carryover analyses, MRR suitability assessments and resin re-use studies. The assessment is product specific. However, prior laboratory studies may be leveraged across platform products where appropriate.

Figure 7: Small-scale data package and assessment prior to implementing MRR

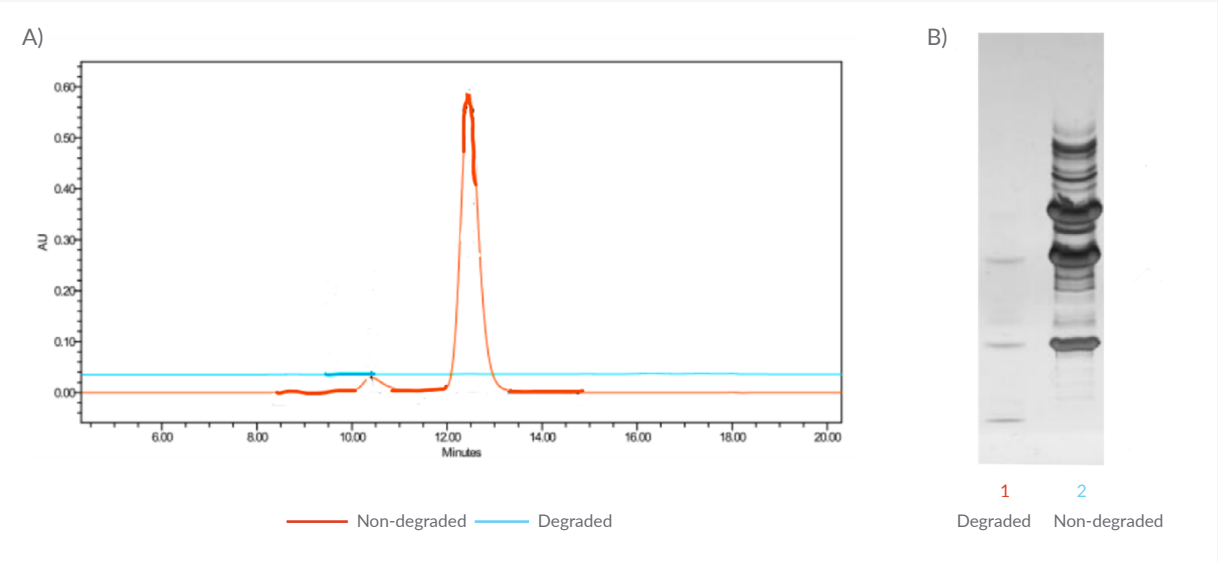


3.1 Product degradation studies

Chromatography cleaning and sanitization cycles typically expose the resin to various concentrations of acidic and basic solutions. Product inactivation studies can be performed under column cleaning conditions to ensure the drug substance is degraded, this mitigates the risk if any carryover is observed. Most proteins break down into smaller fragments at high pH and fragments tend to be more soluble at a lower pH. If the product is not degraded when exposed to the cleaning conditions, the cleaning conditions should be adjusted (e.g. by increasing concentration, exposure time) to ensure inactivation of the product. Unlike traditional product inactivation studies used to support multi-product use of equipment, product inactivation studies used to support MRR would not expose the product to elevated temperatures.

A product degradation study similar to that described by Li, H. et al., 2024[1] can be performed for MRR. In this study, the product was exposed to various concentrations of sodium hydroxide (0.1M, 0.5M and 1.0M) and incubated for at least 15 minutes and up to 60 minutes. The incubation times correlated to potential static hold times that could be used in manufacturing, based on the resin type. The samples were then analyzed using various techniques to demonstrate the degradation of the drug substance. Each company's product inactivation conditions and analytical methods to demonstrate inactivation may be different (Section 3.3). Two examples of analytical techniques displaying degraded versus non-degraded product are provided in Figure 8.

Figure 8: Degraded and non-degraded mAb samples



Analytical techniques displaying product degradation:
A) SE HPLC profile degraded mAb sample versus non-degraded sample. B) SDS-PAGE profile degraded mAb sample versus non-degraded sample

3.2 Resin cleaning cycle development

Understanding the degradation profile of the product, as outlined in Section 3.1, enables identification of optimal strip/cleaning buffer conditions to effectively break down and clear the degradants[14], while also ensuring the properties of the resin are taken into consideration. The optimal cleaning cycle should be sufficiently harsh to eliminate resin fouling and product carryover while avoiding the potential for ligand degradation. Ion exchange and hydrophobic resins may be routinely subjected to stringent 1N NaOH solutions without ligand degradation, which is often not the case for ProA chromatography resins. The emergence of next-generation ProA resins, such as those with improved resistance to caustic cleaning agents, has improved the cleanability and microbial control of ProA resins. A more stringent cleaning regime is commonly used after a column-packing activity or in response to microbial contamination of chromatography resins.

A similar approach may be taken when cleaning resins as part of MRR product changeover. Several BioPhorum Drug Substance Phorum member organizations have employed an extended cleaning regime during their laboratory-scale assessment of MRR. Multiple pH cycling steps to pulse back and forth between alkaline and acidic buffers are typically employed. Additionally, static holds provide extra residence time in a particular buffer without excessive buffer consumption.

As outlined by Yuan et al.[15], flow distribution through a packed resin column may become increasingly non-uniform as the scale of the chromatography column increases. Therefore, the strip/clean cycle proposed during laboratory-scale assessments should account for the potential worst-case conditions that may arise in large-scale resin-packed columns.

The product-specific resin lifetime monitoring program verifies the resin performance over extended use, assessing the effectiveness of cleaning and sanitization through bioburden and endotoxin monitoring of the resin equilibration effluent, as well as product carryover analyses during the elution step for a blank run. With implementation of MRR, an additional MRR lifetime monitoring program is recommended that covers the entire resin re-use process across all products, verifying effective resin cleaning between each product run.

Interestingly, for the UF/DF unit operation that is used in the purification of biological products, product carryover assessment for inter- and intra-batch use is conducted through TOC analysis of a post-clean rinse sample. Companies may consider a similar approach for the resin lifetime monitoring program with the addition of rinsate samples analogous to the UF/DF membrane cleaning procedures or general equipment cleaning procedures, as described in Section 2.2. It is important to note that TOC is not a selective assay and can have interference from any other source of carbon. Of note, additional analytical analysis would need to be performed to determine what percentage of TOC recovery would be attributed to leached ProA ligand.

3.3 Quantification and characterization of product carryover

As outlined in Section 2.1, as part of resin lifetime, a blank/mock elution is performed at a defined frequency for dedicated single-product resin re-use to assess the effectiveness of the strip/cleaning cycle. Assessment of product carryover during the blank run differs depending on the company's approach; it may involve the integration of the A_{280} profile during the elution block of the blank run to taking samples for offline analyses. Table 1 outlines some current practices for performing the product carryover assessment for dedicated single-product resin re-use.

Table 1: Current analytical methods for product carryover assessment for dedicated resin re-use

Category	Assay	Limit of quantitation (LOQ)**	Reference
Residual protein content	Integration of elution UV profile*	2- to 3-digit ppm	Cytiva AKTA Pure Chromatography Systems[16]
	UV	2- to 3-digit ppm	Pandiscia, L. (2024)[17]
	Bradford	Single-digit ppm	da Silva, M.A. and Arruda, M.A. (2006)[18]
	Cleaning ELISA	Single-digit ppb	BioGenes (2023)[19]
	SDS-PAGE	Single-digit ppm	Shi, Y. et al. (2012)[20]
	TOC	Single-digit ppm	Florescu, D. et al. (2013)[21]

* Inline analytical technique; no sampling required.
** General LOQ is given for each assay. LOQ of each assay will vary depending on each companies' assay development.

These analytical methods are also applicable for the product carryover analyses for MRR. To demonstrate cleaning effectiveness for MRR, the analytical methods must be sensitive enough to quantify product carryover concentrations, ensuring carryover remains below the maximum allowable limit. Assessment of the analytical methods (sensitivity and specificity) is outlined in Table 2. Conventional residual protein content assays are suitable for routine column cleaning verification at scale. During laboratory-scale studies, it may be advisable to adopt a more sensitive method capable of detecting trace amounts of residual proteins and/or characterizing similar biological products and their degradation products, such as liquid chromatography coupled with mass spectrometry (LC-MS). This approach strengthens the data package supporting cleaning effectiveness and resin release as part of product changeover.

To date, product carryover analyses for resin lifetime have focused on assessing the elution block of a blank run. This is because the elution buffer represents a worst-case scenario for cross-contamination, as pH changes may increase product solubility. A key consideration is any difference in elution buffer between products. If the elution buffers differ, using the subsequent product's elution buffer may give a more accurate representation of product carryover, depending on the differences between the buffers. A more practical approach is to perform the blank run immediately after completing the preceding product run, using the elution buffer from the preceding product, if the subsequent product has not yet been determined. Additionally, depending on the chromatographic step being performed, the lowest pH buffer could be used during the blank run elution step to represent the worst-case scenario.

Table 2: Potential analytical methods for product carryover assessment for MRR

Category	Assay	Specificity	LOQ	Reference
Residual protein content (non-product specific)	Bradford	Total residual proteins	Single-digit ppm	da Silva, M.A. and Arruda, M.A. (2006)[18]
	Micro bicinchoninic acid (BCA)	Total residual proteins	Single-digit ppm	Li, H. et al. (2024)[1]
	Cleaning ELISA	Total residual mAbs and their fragments	Single-digit ppb	BioGenes (2023)[19]
	TOC	Total organic carbon	Single-digit ppm	Florescu, D. et al. (2013)[20]
	Flow injection protein assay (FIPA)	Total residual proteins	Single-digit ppm	Ravi, N. et al. (2023)[22]
Residual protein characterization (non-product specific)	SDS-PAGE	Separating and quantifying residual proteins based on size	Single-digit ppm	Shi, Y. et al. (2012)[20]
	CE-LIF	Detecting residual protein based on charge and size	2-3-digit ppb	Michels, D.A. et al. (2012)[23] and Nguyen, B.T. et al. (2018)[24]
Residual protein characterization (product specific)	Binding ELISA	Evaluation of antigen binding activity and quantification of residual intact protein and its fragments of a specific product	Single-digit ppb	Li, H. et al. (2024)[1] Suárez, I. et al. (2016)[25]
	Surface plasmon resonance (SPR)	Evaluation of antigen binding activity and quantification of residual intact protein and its fragments of a specific product	3-digit ppt	Tokarzewicz, A. et al. (2023)[26] Nguyen, H.H. et al. (2015)[27]
	Intact/reduced LC-MS	Detecting degradation products of a specific product	Single-digit ppm	Li, H. et al. (2024)[1] Millet. A. et al. (2021)[28]
	LC-MRM (multiple reaction monitoring)	Quantitation of total protein through surrogate peptides	2-digit ppb	Li, H. et al. (2024)[1]
	LC-MS peptide mapping	Identification of degradation pathways of a specific product	Not available	Li, H. et al. (2024)[1]

Given the inactivation of the product during the cleaning cycle, it is appropriate to demonstrate that carryover of the inactive product between products is acceptable to ensure safety of the product[10]. As residual material is inactive after cleaning, the limit based on dose/activity may not be necessary[29]. Acknowledging that the starting point for determining suitable acceptance criteria will be company specific, it is proposed that current industry best practice targets of 1 to 2ppm applied routinely for cleaning validation of equipment may be applied for MRR[13]. Alternatively, a calculation-based approach may be used to establish a carryover limit for each product[1, 30].

3.4 MRR suitability assessment

The mechanism of action, relevant preclinical and clinical data and existing knowledge are critical factors for consideration in the risk assessment. These are essential for determining a scientifically justified limit for the target population and route of exposure[31]. Degradation of the product through the cleaning mechanism, resulting in pharmacological inactivation, may be used to scientifically justify setting carryover acceptance limits based on the inactivated product instead of the active pharmaceutical ingredient (API)[22]. Finally, a guideline for setting health-based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities is recommended for consultation[30].

The MRR suitability assessment should focus on evaluating the potential safety impact of product and impurity carryover from one product to the next. The safety impact should be evaluated on a product-by-product basis, incorporating risk assessments of each molecule and process[1]. The results of these assessments will determine whether a product can be introduced to an MRR platform.

Assessments should include evaluation of cleaning procedures, manufacturing site readiness, product inactivation studies and analytical methods used to ensure potential carryover can be accurately quantified. Most biologics are specific for their target(s) and can be quite potent, therefore any carryover poses potential risk. Heightened attention should be given to potent and toxic products with acceptable daily exposure or permitted daily exposure limits less than 10µg/day for MRR[32]. Because of the low exposure limit of highly potent or toxic products, this may pose a higher safety risk for residual carryover.

A platform process is more amenable to an MRR approach. The same cell line and similar cell culture processes can result in similar resin cleaning challenges, as well as similar cellular by-products such as HCPs and DNA. A shared, proven resin cleaning regime across products may ease concerns regarding potential differences in resin cleanability and resin degradation over the lifetime of the MRR. Process issues that may result in cleaning challenges, such as abnormally high titers or atypical aggregation are outlined in Figure 9.

Figure 9: Multi-product resin re-use risk category and assessment considerations

Viral clearance data should be generated independently for each product using new resin. Prior knowledge indicates that virus removal is either unaffected or slightly increases with used ProA affinity resin, making product-specific studies with used resin generally unnecessary[33].

3.5 Resin re-use small-scale study for MRR

Multi-product use of resin increases the number of variables to consider when designing effective small-scale studies (e.g. the product mix, cleaning cycles). Reducing variables in development/small-scale studies will reduce the effort required at scale to obtain a representative dataset which reflects the resin's lifetime. Strategies such as using similar

products and adopting a generic cleaning cycle can help achieve this. Small-scale resin lifetime studies are well established for product-dedicated resins to determine the maximum number of cycles (N_{MAX}) for which the resin can be used in commercial manufacturing. Traditional small-scale resin lifetime studies can be adapted to establish the N_{MAX} for MRR. When designing resin lifetime studies to support the implementation of multi-product resin, general considerations (Figure 10)[34] can support the design of small-scale studies. Small-scale studies performed for MRR can use worst-case conditions to leverage the result of the study for the re-use of resin for multiple molecules. Worst-case conditions can include molecules from multiple classes (e.g. mAbs and Fc fusion proteins) and molecules with diverse drawbacks for purification. Molecules with low step yield and those that require harsh cleaning conditions could also represent worst-case molecules. In addition to worst-case molecules, the cycling strategy could include molecules from multiple campaigns and cycling between all combinations of molecules studied. The small-scale column can be monitored for changes in peak and transition shape, changes in dynamic binding capacity and process data such as step yield, blank runs and product carryover. Data collected would provide critical information to determine whether MRR would be feasible for the resin and class of molecule chosen.

Figure 10: General considerations for design of resin lifetime small-scale studies

If a robust small-scale study is designed and the results support the implementation of MRR, the study can be used as a one-time proof of concept for implementation at full scale for that resin. When using this method, a risk assessment should be performed on all new products being introduced to re-used resin. If the risk assessment shows a molecule as being a risk, additional product-specific, small-scale studies should be performed to support the molecule's implementation into the MRR program, or a decision should be made not to implement MRR.

4.0

Risk-based approach to implementing MRR in GMP manufacturing

If the small-scale studies from Section 3 support the compatibility/suitability of implementing MRR, a risk-based approach is required to implement MRR. A risk-based approach utilizes principles of quality risk management (QRM) ICH Q9, to develop an MRR strategy[35]. This may be implemented initially for tox/pre-clinical material manufacturing which is common practice in the biopharmaceutical industry. The experience and risk mitigation strategies from implementing MRR for tox/pre-clinical manufacturing may be leveraged for the introduction of MRR for GMP manufacturing. The potential risks and mitigation strategies are presented in tabular format in Section 4.1, including the requirement for a robust GMP-scale cleaning procedure for adequate contact. Detection controls for implementing MRR rely on heightened resin performance monitoring that occurs for GMP resin re-use (outlined in Section 4.2). Several companies have successfully taken a risk-based approach to implementing MRR and the industry experience collected through literature review and information sharing within the BioPhorum team is outlined in Section 4.4.

4.1 Risk assessment for implementing MRR

A survey was completed by BioPhorum Drug Substance member organizations to identify the quality and regulatory risks and concerns associated with using ProA resin for the purification of multiple products. All companies were very engaged and there was a full response to the questionnaire with a total of 18 responses. The output of the survey and identified risks are outlined and addressed in Table 3.

Table 3: Risk mitigation matrix

Risk category	Risk/failure mode	Mitigation strategy	Detection/monitoring
Resin cleaning	The cleaning solution does not make contact with the fouled resin, e.g. immersion of the product solution in the resin base material, near O-ring, column screen.	An enhanced cleaning regime during small-scale studies including static hold to allow for dispersion into potential low-flow areas within the resin packed column and difficult to clean areas, pH pulsing with a change in flow direction and use of back pressure.	Samples from the blank/mock elution run and the use of assays such as those outlined in Section 3.3.
	The cleaning solution does not make contact with the fouled resin, e.g. channeling through the column, stagnant air.	Prior to use of the resin-packed column, column bed integrity evaluations (e.g. asymmetry, HETP) release the column for use. This provides assurance that there is no channeling within the column prior to use.	Column bed integrity evaluation as part of the resin monitoring program. This provides assurance that the column is operating appropriately and no channeling is present.
	Cleaning reagent does not sufficiently clean the resin between products.	Caustic-stable resins are amenable to MRR methods including IEX, HIC. Next-generation ProA resins such as MabSelect SuRe (MSS) and PrismA are also well-suited for MRR. However, traditional resins like MabSelect may be more challenging for this method.	Samples from the blank/mock elution run tested for product carryover via assays outlined in Section 3.3.
	The new product is more challenging to clean than previously demonstrated products.	Implement MRR using products derived from similar cell lines (e.g. all CHO cell lines) for two reasons: 1. It is easier to apply this approach to platform processes: same kind of molecules with very similar process 2. There is less variability, easier process control, more data available and more knowledge.	Small-scale studies to demonstrate that the new product is appropriate to introduce into the MRR program are outlined in Section 3. A product-specific, small-scale study to enable MRR for products that are more challenging to clean.
	The controls around the release of the resin for MRR are not sufficient to demonstrate that the resin was clean post campaign use.	Cleaning verification/validation approach required for implementing MRR under the MRR resin lifetime monitoring program to capture the entire usage of the resin and product changeover.	An enhanced cleaning and sampling regime to demonstrate the resin is clean for release for subsequent use as part of product changeover.
	Strip/cleaning (cycle design) is not adequate to clear the residues between products.	A blank/mock elution is performed post campaign to ensure the resin is clean and released for subsequent use.	Samples from the blank/mock elution run tested for product carryover via assays outlined in Section 3.3.
Product carryover	There is cross-contamination of the product into the subsequent product.	Small-scale studies per Section 3 to provide the supportive data and determine suitability prior to making a decision to implement MRR.	At-scale monitoring for product carryover using analytical techniques outlined in Section 3.3.
	Depending on a given product, the cleaning strategy may not be appropriate to ensure no product carryover. Product chemistry impacts the resin performance (binding, cross linking, degradation, chemical entity formed that can carry over between products).	Control which products can share the resin. Small-scale studies per Section 3 to provide supportive data and determine suitability prior to making decision to implement MRR.	Samples from the blank/mock elution run tested for product carryover via assays outlined in Section 3.3.
	There are analytical challenges for quantitative measurement of product carryover.	Current analytical techniques for determining product carryover for a dedicated resin usage may not be sufficient when implementing MRR.	Ensure the assay(s) selected are suitable to characterize the carryover, see potential assays outlined in Section 3.3.
	The product carryover is active rather than inactive degradants, which may not be detectable in the analytical assay.	Successful degradation studies are required as part of the suitability assessment as outlined in Section 3.1 to confirm that the product is degraded upon exposure to the proposed cleaning solutions. Purification capability further downstream to remove product degradants in the process stream, e.g. TFF should also be considered.	Ensure the assay(s) selected are suitable to characterize the carryover, see potential assays outlined in Section 3.3.

Table 2: Potential analytical methods for product carryover assessment for MRR (continued)

Risk category	Risk/failure mode	Mitigation strategy	Detection/monitoring
Product carryover	The product carryover into the subsequent product is not acceptable.	Application of a more stringent product changeover cleaning regime for MRR than would be applied in the case of product-dedicated resin.	Conduct a blank run at the end of a campaign, prior to product changeover. The chromatogram profile and the sample analyses from the blank/mock elution run provide assurance that the resin is clean prior to introducing the subsequent product.
	Product carryover contains degradants with immunogenic potential.	Closely monitor and characterize product carryover prior to and during the runs, as outlined in Section 3.3. Sufficient degradation of a product and its pharmacological inactivation can justify that an immunogenic evaluation is not required. Small-scale studies in advance of implementing MRR can be performed which include characterization of the carryover product and its degradants.	N/A if ruled out in small-scale studies.
Process residuals carryover	Carryover of HCP and other related impurities, such as DNA, from one product into the subsequent product.	As part of the suitability assessment, MRR most likely to be implemented from products derived from same cell line such as CHO. Development characterization studies such as clearance studies support the effectiveness of clearance.	LC-MS analytical technique can detect specific HCPs associated with a given product. Consider a more sensitive assay from Section 3.3 for the small-scale studies for a greater understanding of carryover potential.
	Differences in leached ProA observed between products (especially if different cleaning strategies/procedures are used for different products).	Easier implementation of MRR for a platform process wherein there is commonality across buffers and products, e.g. consider the potential difference in leached ProA ligand with differences in elution buffer or more stringent cleaning buffers. Leached ProA ligand needs to be understood for each product to ensure that there is no greater level that challenges the clearance capability.	Leached ProA levels are monitored routinely as part of the resin monitoring program.
	Carryover of residual raw materials to a process that does not utilize the raw material, e.g. BSA-containing versus BSA-free media.	An assessment of the potential differences in raw materials used in the cell culture process is required. In the event of differences such as the BSA example, a specific assay should be considered as part of the blank/mock elution run to demonstrate clearance prior to subsequent resin use.	Consider introducing a specific assay for residual raw material analyses for the blank run as part of the cleaning for product changeover.
Microbial contamination	Microbial contamination from one product is introduced on to resin and potentially impacts all other products (organism of concern, microbial metabolite – exotoxin/endotoxin).	Confirmation that the resin is under microbial control prior to release for subsequent use. This practice is in place for re-use product-dedicated resins, no change when implementing MRR.	In-process batch-to-batch microbial monitoring.
Viral contamination	Viral contaminants from one product are retained on the resin and introduced into next product.	For chromatography resins such as anion exchange (AEX) in flow-through mode when viruses are retained on the resin and product flows through the resin, consider the associated risks to implementing MRR. For bind and elute resins such as ProA, there are orthogonal indicators such as yield and process residual removal analyses that may be leveraged to support re-use. Develop technical justification potentially leveraging data based on clearance studies and denaturing capability of the cleaning regime.	No detection at scale.
	Reduced viral clearance capacity with used resin (note this is not unique to MRR).	Traditionally, viral clearance studies have been performed on aged resin to verify that there is no reduction in capacity with resin use. For resins operated in bind and elute mode, use orthogonal indicator of yield and process residual clearance.	None during manufacturing, because ICH Q5A(R2) guidelines[36] suggest that cycled resin has equivalent or better viral clearance capability than fresh resin and cycled resin at scale viral clearance study is not required.

Table 2: Potential analytical methods for product carryover assessment for MRR (continued)

Risk category	Risk/failure mode	Mitigation strategy	Detection/monitoring
Resin re-use/ lifetime	Cleaning agent required to degrade the product and clean the resin has a negative impact on the resin performance such as binding capacity.	Limit use of higher strength caustic solutions to cleaning for product changeover rather than for each cleaning cycle. This is often done as part of resin packing at a time when microbial ingress is higher risk. Next-generation ProA resins are amenable to more stringent cleaning solutions. Small-scale lifetime studies would establish limits.	Routine yield monitoring/resin monitoring program will indicate any loss of binding capacity.
	A specific small-scale study to support the actual at-scale use of the resin may not be performed, e.g. number of representative cycles.	A robust small-scale study to support implementation across products in a given platform could be leveraged to implement MRR for other molecules once an assessment per Section 3.4 is completed and deemed appropriate.	Batch to batch lifetime sampling until lifetime program in place supported by small-scale studies. Yield and chromatography profiles are key indicators of the resin performance.
	The resin performance deteriorates with continued use or there is a trend in the resin performance for one product and not for other product(s).	Each product-specific monitoring program determines whether the resin is suitable for continued use. The selective selection of products to be paired for MRR will help mitigate.	The monitoring program outlined in Section 4.2 will provide detection of a decrease in resin performance.
	Resin lifetime tracking including resin dating/ expiry is complex for MRR.	The MRR resin lifetime program captures the entire usage of the resin and product changeover. A generic materials management unique identifier can be assigned to a column. Currently, product-specific identifiers may be in place for dedicated resins.	The materials management system will have detectability on the usage of the resin.
Regulatory acceptance of MRR	There is no global regulatory acceptance of implementing MRR which impacts supply chain.	There are no specific regulatory stipulations preventing MRR implementation. Until the practice is commonplace, a discussion with regulatory authorities may be required. To date, implementation of MRR for GMP clinical material has relied on a case-by-case example (Section 4.4). A broader discussion is required to avoid implementation by exception. Implementing MRR for early-phase clinical material generation initially, as this may be more acceptable than late phase. Although considerations outlined in this paper are also applicable for commercial use, there may be greater hurdles to implementing for commercial use until widely accepted.	Published papers such as this one and external forums provide an understanding of the regulatory acceptance of MRR.
	Information on product changeover and cleaning validation is not generally discussed in detail as part of the investigational new drug application (IND) submission. Therefore, when MRR is an option, it may be prudent to include consideration on how to present management of multi-use in the investigational medicinal product dossier (IMPD)/IND.	Need to communicate that the resin will be used in multiple clinical programs in the IND and define how the resin will be used (which products, risks from differing cell lines, operating parameters, MRR controls etc.) and consider how a new product would be added to list of products using the shared resin.	Published papers and industry/health authorities collaborative discussions to understand how to present adoption of MRR.

4.2 MRR resin lifetime monitoring program

The expectations of at-scale monitoring of resin performance over its lifetime for multi-product use is largely akin to dedicated product resin lifetime monitoring as outlined in Section 2.1. General guidance is that evaluation of resin lifetime will be performed on at least one lot of packed resin at manufacturing scale by monitoring resin performance based on in-process control (IPC) specifications and by periodically sampling the eluate process intermediates from the chromatography process. Resin at manufacturing scale should be evaluated until lifetime criteria are met and the resin is removed from service. The study may continue over multiple lots of packed resin until each resin expiration criterion has been verified at manufacturing scale.

Periodic testing throughout the lifetime of the resin should be scheduled to achieve evenly spaced sampling based on the first expiration criterion most likely to be achieved for the resin. Clearance of impurities is acceptable if it consistently meets predetermined criteria throughout the lifetime of the resin. In general, clinical products may lack sufficient data to establish limits. However, for commercial products, predefined acceptance criteria should be based on historical data generated at manufacturing scale or the DSP impurity clearance capabilities, as applicable.

A decrease in binding capacity is the most likely failure mode to occur as a chromatography resin is used in production, therefore yield and chromatography profiles are key indicators of performance of resin. Also, clearance of impurities that bind to the resin will be evaluated during at-scale studies to ensure that any decrease in binding capacity does not impact product quality or process performance. Typically, viral clearance requires spiking studies so is generally performed at small scale only. Finally, in an example assessment of a mixed-mode anion exchange (MM-AEX) chromatography stage (Table 4), fragments are present in quantifiable amounts. However, since this stage is not intended to remove fragments, it is not relevant to include them in the at-scale monitoring program.

Table 4: Example assessment for including quality attribute test in lifetime verification panel

Quality attribute	Controlled/impacted by stage	Quantifiable amounts in load material	Included in reduced-scale resin lifetime validation	Include test in at-scale resin lifetime verification
Aggregate	Yes	Yes	Yes	Yes
Fragment	No	Yes	No	No
DNA	Yes	No	Yes (required DNA spike in load)	No
HCP	Yes	Yes	Yes	Yes

4.3 Microbial considerations for multi-product resin performance monitoring

The microbial monitoring regime is generally unaffected by multi-product use of resin. As part of the resin lifetime program, microbial samples are taken at defined intervals after the column clean over the lifetime of the resin. Process knowledge of the product/buffer matrices with respect to microbial proliferation should be considered as part of the selection of products to share a resin. Routine in-process microbial testing adds another layer of confidence.

4.4 Industry experience of implementing MRR

MRR strategies are being adopted increasingly in the biopharmaceutical industry, particularly for the production of non-clinical material used in toxicology studies. This section explores the practical implementation of MRR methodologies, drawing on examples from seven non-clinical (see Section 4.4.1) and several clinical applications (see Section 4.4.2). These examples highlight key trends, challenges and best practices in MRR implementation, as summarized in Figure 11.

Figure 11: Overview of MRR applications in the biopharmaceutical industry

Non-clinical (tox) supply application

- ✓ Proof-of-concept methodologies for extending resin re-use to multiple products have been described in a series of papers by Sharnez et al.[3, 5, 6]
- Benchmarking data within the BioPhorum team indicates that MRR is routinely adopted for tox/preclinical material supply at pilot-plant scale across the biopharmaceutical industry
- Variations between the approaches shared within the BioPhorum team can be observed for the following points:
  - Monitoring and control of product carryover: analytical assays used and carryover limits applied
  - Resin cleaning regimen: varying protocols include pH cycling or specific cleaning solutions and conditions
  - Supportive small-scale studies and the extent of toxicological considerations.

Case-specific clinical trial supply application

- ✓ Proof-of-concept papers have been published for the implementation of MRR for product-specific scenarios[1, 22]
- Several companies have implemented MRR for early clinical-phase GMP manufacturing, driven by chromatography resin material shortages during the COVID-19 pandemic
  - One such example was shared by a member within the BioPhorum MRR team for the use of MabSelect PrismA™ resin to purify similar Fe-fusion proteins (Product A and B) in the same manufacturing facility
  - Merck & Co., Inc., Rahway, NJ, USA have recently published on the use of MRR for AEX and CEX resins for phase I GMP manufacturing[1].

4.4.1 Case studies of MRR strategies for tox/ preclinical manufacturing

MRR methodology has been adopted by several members in BioPhorum Drug Substance, primarily for the generation of preclinical material for toxicology studies. A total of seven preclinical and one clinical MRR case study have been reviewed as part of this publication, and many trends have been identified. A significant amount of commonality observed in these examples can be attributed to the foundational concepts laid out by Sharnez et al.[3, 5, 6].

Monitoring and control of product carryover is an essential element in product changeover control of all MRR concepts provided by the authoring team. Cleaning effectiveness and the presence of product carryover are commonly studied at small scale and/or pilot scale. Blank/mock elution runs are conducted after resin cleaning and analyzed for residual product by analytical assays such as BCA, and silver stained SDS-PAGE. Different member organizations employ diverse approaches to establish acceptance criteria for residual product. These approaches may involve using assay LOQ (e.g. 1ppm or 1.5ppm), equipment cleaning limits (e.g. 10ppm), literature references and toxicological considerations review.

The design of resin cleaning protocols is such that they significantly minimize product carryover, degrade and inactivate any remaining product. For most case studies shared within the team, MRR concepts are based on preceding studies demonstrating product degradation (e.g. characterized by SDS-PAGE or capillary gel electrophoresis (CGE)) and product inactivation (tested by activity assays such as Ig-ELISA) by resin cleaning regimes. These typically involve multiple pH cycling steps or resin-specific stripping, basic and neutralization solutions as well as consideration of incubation time. Several BioPhorum members follow stringent CIP strategies. Others have also mentioned storage conditions as a prerequisite for resin re-use. Over a decade ago, Genentech published a case study for implementing MRR for MabSelect SuRe™ columns for multiple CHO products at pilot scale for manufacturing material for preclinical toxicology studies[37]. This case study outlined a cleaning procedure involving multiple pH cycling and static hold steps utilizing various assays to demonstrate product carryover of less than 1ppm.

Besides product carryover, several companies have described additional considerations for resin re-use for a new product. As column performance is of concern, the following precautions were outlined as possible safety measures: monitoring of product yield and binding capacity, assessment of column integrity parameters, such as general peak shape, overall product quality and clearance of impurities or leachables, chromatogram comparability to a reference in terms of UV, pH, conductivity, pressure and flow rate. To confirm column cleaning effectiveness, the column effluent is tested for endotoxin levels in some case studies. The factors described above are often studied in proof-of-concept studies and/or implemented as acceptance criteria during product changeover at pilot scale. Two strategies were outlined with regard to resin lifetime. It can either be limited to a predefined number of cycles evaluated in small-scale studies, or it can be monitored concurrently at pilot scale, for instance by tracking yield reductions due to cleaning and extended utilization.

Generally, ProA resins seem to be the primary focus for MRR implementation due to significant financial benefit. Yet, some member organizations have broadened its application to polishing resins. Most companies have captured the risk associated with MRR in internal risk assessments, either before implementation or prior to the introduction of new products. Two organizations report taking toxicological considerations into account, particularly for non-clinical runs. Experience of companies that have implemented the MRR strategy for products used in clinical studies is limited (see Section 4.4.2) and to date this is not a widely adopted practice. The confined adoption could be attributed to the scarcity of literature, as well as the significant efforts, risk assessments and preliminary small-scale studies required.

4.4.2 Success stories and insights of MRR implementation for clinical manufacturing

A proof-of-concept study published by AstraZeneca[22] may facilitate the next steps required for implementation. This study outlined the potential of MabSelect PrismA™ resin re-use with three distinct IgG1 subtype mAbs for up to 90 cycles (30 cycles per mAb). All product carryover levels detected were well below the established maximum allowed carryover limit of 0.1%, and no decline of performance in terms of yield, product quality or impurity clearance were observed. Increased leached ProA levels were shown for one mAb only, suggesting that resin responses may also depend on the feed itself. The AstraZeneca study highlights how, besides a reduction in costs, an MRR approach in GMP facilities can help minimize waste and save time during product changeover. It further outlines considerations for a risk assessment, which combined with the data of the proof-of-concept study, provide valuable guidance toward the utilization of MRR in clinical GMP facilities.

To date there have been two reports of the application of MRR in the GMP manufacturing of early-stage clinical material. These include an unpublished case study shared within the BioPhorum MRR team, as well as publication by Merck & Co., Inc., Rahway, NJ, USA[1]. The material shortage induced by the COVID-19 pandemic was a key factor that led both companies to consider re-using resins in their clinical manufacturing processes. In addition, enabling clinical regulatory filing timelines and preventing any delays to clinical studies was stated as a motivation by the BioPhorum member organization that shared the case study.

Specifically, the BioPhorum member organization utilized MRR for the MabSelect PrismA™ resin to purify a Fc-fusion protein (Protein B). The resin was previously used for another cGMP campaign of a similar but unique Fc-fusion protein (Product A) in the same manufacturing facility. The two Fc-fusion proteins share the same general processing solutions and operating conditions for the chromatography unit operation. The strategy was based on developing a methodology for resin re-use that leverages protein inactivation during cleaning to prevent cross-contamination and demonstrate acceptable carryover from the previous product from a predictive safety standpoint. Laboratory-scale inactivation studies were conducted to establish column cleaning parameters. Qualification of a BCA method was completed and the LOQ established as below the MACO for each product. During product changeover, column cleaning effectiveness was confirmed by bioburden, endotoxin and BCA analysis of the column effluent and column performance was ensured mainly by visual confirmation of the chromatogram before releasing the column for Product B. Drug substance product quality and safety were evaluated through release testing. No impact to stability of Product A or B was observed. Viral clearance testing was completed for Product B and the downstream process was shown to be suitable for manufacture with an acceptable overall safety margin. Viral clearance testing of used resin was comparable to previously reported values with new resin from Product A. The company was able to successfully complete the clinical cGMP campaign of Product B in a timely manner with no impact on patient supply. Regulatory filing for Product B was approved by health authorities (HAs) on schedule which allowed the phase I clinical trial to start as planned.

In the publication by Merck & Co., Inc., Rahway, NJ, USA[1], a MRR strategy for AEX and CEX resins at 2,000L scale is presented and the successful purification of two products for clinical supply is reported: a mAb (Product A) and an antibody-based therapeutic (Product B)[1]. The manufacturing runs were preceded by laboratory-scale studies to generate an efficient resin cleaning protocol using NaOH. The experiments comprised an extensive inactivation study including the characterization of resulting product degradants and their post-translational/chemical modifications by several analytical methods including LC-MS. Clearance and inactivation of the product were further confirmed in blank/mock elution studies by micro BCA and residual binding ELISA. Before GMP manufacturing, a risk assessment was conducted to evaluate the safety impact of Product A carryover to Product B. The risk assessment encompasses three categories. First, a product safety assessment in which the safety profile of the previous product is rated and highly potent molecules are excluded. Second, a resin re-use compatibility assessment, in which product characteristics (Isoelectric point (pI), modality, mechanism

of action (MOA)) and compatibility of the manufacturing processes are assessed. Third, an operational risk assessment which takes into account cleaning procedures, timelines and manufacturing site readiness, among other considerations. The authors suggest that to ensure safety, the risk assessment should be conducted on a product-by-product basis before execution of GMP manufacturing. Consequently, the analytical strategy may need to be adapted based on the availability and readiness of appropriate methods, and risk controls may need to be implemented prior to the GMP campaign. The general strategy shared in the Merck & Co., Inc., Rahway, NJ, USA[1] publication can provide guidance to determine which products can share resins. The publication provides a comprehensive summary of considerations for the implementation of MRR in clinical manufacturing sites.

Generally, there is consensus that adopting MRR to produce non-clinical material is technically feasible and beneficial from a financial perspective. Effective cleaning procedures and sensitive analytical methods to control product carryover must be in place to ensure the safety and efficacy of products purified by MRR. Despite broad implementation for the generation of material for non-GMP toxicological studies, there has been limited adoption in GMP clinical manufacturing. For atypical processing scenarios, such as those arising during the COVID-19 pandemic when there was limited supply of critical reagents, interactions with regulatory authorities indicated that they could enable a MRR path under discussed and agreed conditions. Given such circumstances, several companies have successfully adopted MRR in the production of clinical material.

5.0

Registration of MRR for clinical or commercial use

As outlined above, MRR for non-clinical material supply has been widely employed across the industry. There are several instances where MRR has also been adopted for clinical material supply. One such company in the BioPhorum MRR team shared their experience driven by a restricted supply of ProA chromatography resin during the COVID-19 pandemic. Another example recently published by Merck & Co., Inc., Rahway, NJ, USA[1] is for MRR re-use for AEX and CEX chromatography resins for early-phase clinical manufacturing Section 4.4.2. The COVID-19 pandemic also played a role in accelerating the implementation of MRR for clinical manufacturing in the Merck & Co., Inc., Rahway, NJ, USA[1] example. For both companies, a specific Product A/Product B process scenario was presented as the specific business case to ensure clinical material supply.

From a regulatory perspective, considerations involve interactions with health authorities regarding the implementation of a MRR strategy, which is dependent on a thorough risk assessment. While the quality of material and equipment, including the re-use of resin, should adhere to GMPs, there may be additional aspects that require discussion or need to be described in the regulatory dossier. These aspects may include evaluating any remnants from previous products on the resin, discussing cleaning dependent on the type of resins to be used in the MRR strategy, and considering factors such as the extent of resin sharing between multiple products.

For companies who have already implemented MRR for clinical GMP use, a discussion with the appropriate regulatory authorities often occurred in advance of implementing MRR for clinical material supply. This is driven primarily from uncertainty on the acceptance of MRR by global HAs. From discussions in the BioPhorum MRR team, the implementation of MRR was accepted by multiple regulatory authorities on the strength of the data package provided in the IND/IMP regulatory dossier.

When submitting a regulatory dossier for clinical trials or commercial products, companies need to consider how and where to present the MRR strategy to the authorities. Typically, information regarding the MRR can be provided for the purpose of comparing the processes between batches, sharing raw material information and outlining measures to prevent cross-contamination. While depending on the phase of development, the amount of information submitted varies.

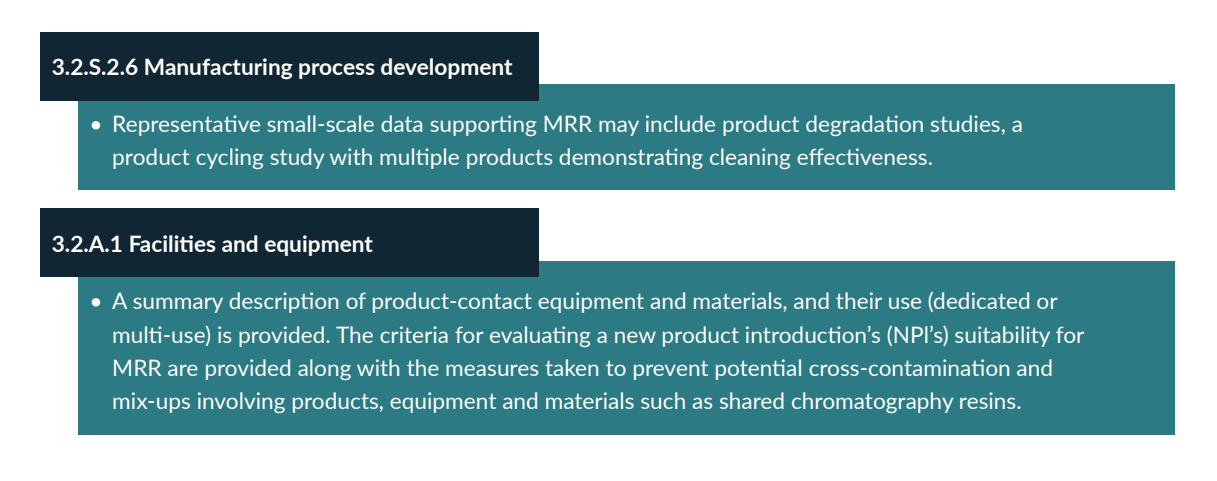
Initially, the BioPhorum MRR team proposed implementation of MRR for clinical material supply. In the following, considerations regarding MRR-related information are outlined together with a suggested placement in the registration dossier. It is important to note that the ultimate decision rests with the company, which needs to determine the most appropriate approach.

A key consideration for the implementation of MRR is the proposed extent of resin sharing between multiple products. The dataset to support the implementation of MRR might be primarily located within 3.2.S.2.6 Manufacturing Process Development.

The BioPhorum MRR team intends to provide guidance on regulatory considerations for implementing MRR for clinical use across multiple products, beyond a specific case for a Product A/Product B scenario. The principles of multi-product equipment use can be applied to MRR. This involves confirming product degradation, evaluating cleaning effectiveness and assessing product carryover. An additional assessment should be completed to determine whether the new product is suitable for introduction into the multi-product facility, as outlined in Section 3.4.

For commercial products, the 3.2.A.1 section of the common technical document (CTD) requires a summary of product-contact equipment and its use (dedicated or multi-use) (Figure 12). Information about the cleaning of specified equipment and materials should also be provided as appropriate to ensure prevention of contamination or cross-contamination during product manufacturing. Although this information is not required for dossiers submitted for clinical studies, it might be considered necessary to include information related to MRR in Section 3.2.A.1. A similar assessment on whether a new product is suitable for MRR could also be provided in 3.2.A.1 even if an A.1 section is not usually in the I(MPD).

Figure 12: Dossier sections and their content according to the CTD guidance



In consideration of the potential future implementation of MRR for commercial manufacturing, additional regulatory content outlines the conditions for re-use of chromatography resins, validation studies and required facility controls in 3.2.S.2.2, S.2.S.2.5 and 3.2.A.1, respectively (Figure 13). It is assumed that the dataset provided in 3.2.S.2.6 remains the same for both clinical and commercial material supply (Figure 12).

Figure 13: Other dossier sections and their content to be considered according to CTD guidance

3.2.S.2.2 Description of the manufacturing process and process controls

- Information for conditions of use and re-use of the chromatography resins might be provided. Typically, the number of re-use cycles for the chromatography resins, as supported by representative lifetime studies, is provided for commercial registration.

3.2.S.2.3 Control of materials

- The raw materials that are used in the cell culture and purification unit operations are provided, including the chromatography resins. It is not expected that the implementation of MRR will be captured in 3.2.S.2.3 as the control and release of the resins will be the same for dedicated product use and MRR.

3.2.S.2.5 Process validation and/or evaluation

- No process validation is required for early-stage development and, therefore, no content is provided in this section in the IND/IMPD. For commercial registration, information on validation studies for the re-use and cleaning of chromatography resins is provided. This will include small-scale resin lifetime study data, a product-specific concurrent validation resin lifetime program which captures cleaning effectiveness, microbiological monitoring, product carryover, resin and column performance criteria at commercial scale.

3.2.R Comparability protocol (regional)

- Similar to a comparability protocol used for introducing an NPI into an existing facility, a common strategy in commercial registration dossiers, a comparability protocol may be considered for implementing MRR for clinical material. This would involve a comprehensive, prospectively written plan with predefined criteria for MRR implementation. The submission and approval of the comparability protocol will facilitate the implementation of MRR once the predefined criteria are met.

6.0

Conclusion

Re-use of chromatography resins (MRR) in the purification of biopharmaceutical products presents a promising opportunity to enhance efficiency and cost-effectiveness in production processes. Given the potential risks associated with product carryover, the implementation of MRR requires rigorous validation and adherence to regulatory guidelines.

A well-structured comparability protocol, as commonly used in commercial registration dossiers, can be instrumental in demonstrating the efficacy and safety of MRR. Such a protocol should include a comprehensive, prospectively written plan with predefined criteria, facilitating regulatory submission and approval once met. For clinical applications spanning multiple products, it is essential to conduct thorough product cycling studies. These studies should assess cleaning effectiveness, establish robust analytical methods and set stringent product carryover limits.

There are potential sustainability benefits around MRR however a full lifecycle assessment is needed to understand the potential positive impact of reuse when offset against the increased use of cleaning chemicals, water and energy.

This publication creates a framework of considerations that extends beyond single-product scenarios, ensuring that the principles associated with multi-product equipment use and a risk-based approach is applied effectively to MRR. The successful implementation of MRR hinges on meticulous planning, comprehensive validation and ongoing collaboration with regulatory bodies. By addressing these factors, the biopharmaceutical industry can leverage MRR to achieve significant advancements in both operational efficiency and regulatory compliance.

Glossary

Term	Definition
AEX	Anion exchange chromatography
API	Active pharmaceutical ingredient
BCA	Bicinchoninic acid
BSA	Bovine serum albumin
CEX	Cation exchange chromatography
CGE	Capillary gel electrophoresis
cGMP	Current good manufacturing practice
CHO	Chinese hamster ovary
CIP	Cleaning-in-place
CTD	Common technical document
DBC	Dynamic binding capacity
DSP	Downstream processing
FiH	First in human
GMP	Good manufacturing practice
HAs	Health authorities
HCP	Host cell protein
HETP	Height equivalent theoretical plate
HIC	Hydrophobic interaction chromatography
IEX	Ion exchange
IMPD	Investigational medicinal product dossier
IND	Investigational new drug application

Term	Definition
IPC	In-process control
LC-MS	Liquid chromatography mass spectrometry
LOQ	Limit of quantification
mAbs	Monoclonal antibodies
MACO	Maximum allowable carryover
MM-AEX	Mixed mode anion exchange
MOA	Mechanism of action
MRR	Multi-resin re-use
MSS	MabSelect SuRe™
NPI	New product introductions
pI	Isoelectric point
ppb	Parts per billion
ppm	Parts per million
QRM	Quality risk management
SDS-PAGE	Sodium dodecyl-sulfate polyacrylamide gel electrophoresis
SPR	Surface plasmon resonance
TFF	Tangential flow filtration
TOC	Total organic carbon
UF/DF	Ultrafiltration/diafiltration
WFI	Water for injection

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