

Designing Downstream Processes for Successful Tech Transfer from Development to Manufacturing

Applying Quality by Design principles to achieve reliable scale-up and seamless GMP execution.

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Abstract

Transferring a downstream bioprocess from development into manufacturing is one of the most critical, and risk prone phases of biopharmaceutical Process Development (PD). Many late-stage challenges do not arise from product quality, but from mismatch between development assumptions and manufacturing reality.

This e-book provides practical guidance on how to design downstream processes in PD so they are ready for successful transfer into GMP manufacturing. Drawing on industrial tech transfer experience, scale-up best practices, facility fit and economic modeling, it highlights the key decisions that determine whether a process transfers smoothly, or becomes a bottleneck at scale.

Why Tech Transfer Fails —and How to Avoid it

Processes that perform well at laboratory or pilot scale can fail during GMP execution due to:

- Buffer volumes that exceed preparation or storage capacity
- Column formats, pressure ratings or flow rates that are incompatible with site equipment
- Cycle times that do not fit shift patterns or campaign windows
- Elution or viral inactivation volumes that exceed tank limits
- Hold time assumptions that do not survive real GMP delays

Successful tech transfer starts early, with PD designing processes that are not only robust and high performing, but also manufacturable within real facility constraints.

A Shared Responsibility

Effective transfer is not a document hand-off, it is a shared design exercise between PD and Manufacturing.

TABLE 1 **Roles and Responsibilities Across the Technology Transfer Lifecycle**

Phase	Development Focus	Manufacturing Focus
Early development	Process understanding, risk identification	Facility capabilities and constraints
Late development	Robust, scale relevant data	Fit for purpose review
Tech transfer	Clear intent and scientific justification	Translation into GMP execution
GMP manufacture	Scientific support	Compliance, execution and control

Step 1 – Define the Quality and Control Strategy

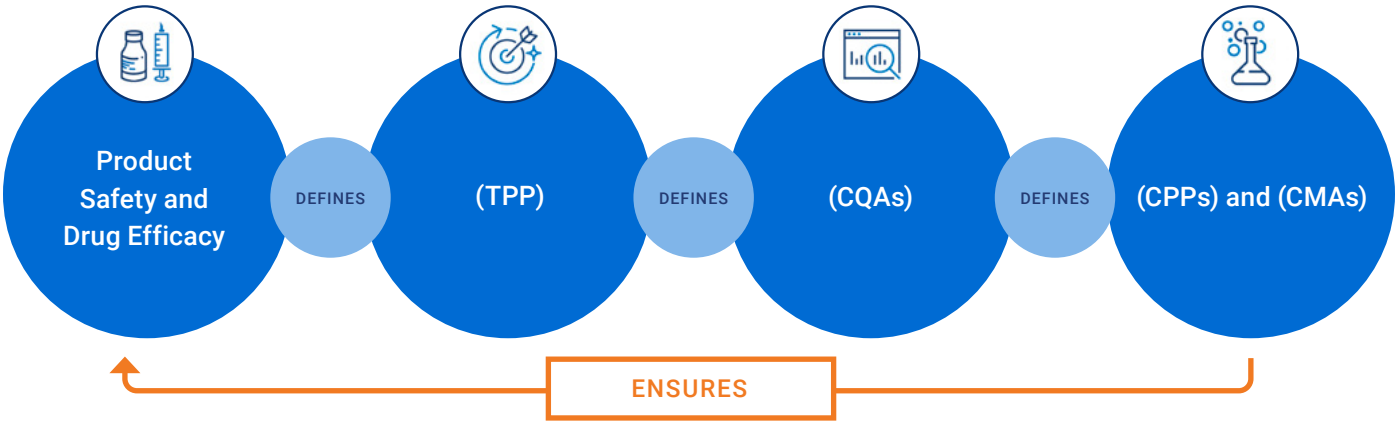
A successful Tech transfer is built on a Quality by Design (QbD) approach. QbD is a systematic framework that ensures process performance and product quality are designed in from the outset, rather than tested in at the end. Instead of defining a single optimal set of conditions, QbD uses process understanding and Design of Experiments (DoE) to establish a robust window of operation - a multidimensional space in which the process consistently delivers acceptable product quality despite normal process variability.

This approach is essential for manufacturing readiness, as it clearly defines where flexibility is acceptable and where tight control is required. By linking process parameters to product quality and understanding their interactions, QbD enables predictable scale up, supports deviation management, and provides the scientific justification required for confident GMP execution.

Development Considerations

During process development, the focus is on building the scientific foundation of the process:

- Define the Target Product Profile (TPP) and Critical Quality Attributes (CQAs)
- Identify Critical Process Parameters (CPPs) across each downstream unit operation
- Establish targets and acceptable operating ranges, supported by experimental data
- Assign criticality to each parameter to indicate its impact on product quality and process performance



(QbD) is a systematic, science-based approach that links product safety and efficacy to predefined quality targets and critical quality attributes (CQAs). These CQAs are achieved by controlling critical process parameters (CPPs) and critical material attributes (CMAs), ensuring consistent product quality throughout manufacturing.

A clear definition of flexibility versus control is essential, as GMP deviations are assessed against development defined criticality.

Manufacturing Considerations

During scale-up and GMP implementation, the focus shifts to feasibility and control within the real facility:

- Confirm that defined CPP ranges are achievable with site equipment and control systems
- Verify sensor accuracy, skid capability and operational tolerances
- Identify parameters that may require tighter control, additional monitoring, or process redesign

Alignment between development intent and manufacturing capability ensures that the defined design space can be reliably executed at scale.

Step 2 – Design for Facility Fit

Processes developed in PD are typically designed on flexible, well monitored systems with small working volumes, rapid buffer preparation, and minimal logistical constraints. In contrast, manufacturing operates within fixed facility limits, where buffer preparation, storage, water availability, tank sizes, and scheduling often dictate what is practically achievable. As processes scale, assumptions that are benign in PD - such as buffer volume, preparation time, or sequencing - can quickly become limiting factors in GMP. Designing for facility fit therefore requires PD to anticipate manufacturing constraints early, and for manufacturing to confirm that proposed strategies can be reliably executed at scale without introducing operational risk. A well-designed process can be thought of as a scaled-down version of a process at its manufacturing scale.

Buffer Preparation and Storage

At manufacturing scale, buffer strategy becomes a critical design decision, with two primary options: preparing buffers at their final working concentration, or preparing concentrated buffers that are diluted inline on the chromatography system. Preparing buffers at working concentration is operationally simple and robust, requiring minimal system integration and qualification, but can demand large preparation and storage volumes. Concentrated buffers with inline dilution can reduce tank volume requirements and increase operational flexibility; however, they introduce additional complexity, requiring well qualified dilution systems, accurate flow control, and robust mixing to ensure consistent pH and conductivity. Importantly, the benefits of buffer concentrates are highly facility dependent. If sufficient water for injection (WFI) is not available on demand, facilities may require large water storage tanks or delivered water totes, often negating any space or volume advantage gained through the use of concentrates. As a result, buffer strategy must be selected based on overall facility capability, not theoretical volume reduction alone. In all cases, buffer preparation at scale must account for appropriate safety factors to ensure uninterrupted operation. Buffers are typically prepared in excess of calculated demand, commonly 20% higher than the required volume for large scale buffers (>100 L), with higher safety factors (up to 50%) often applied for small volume buffers (≤50 L), depending on facility practice and risk tolerance.

These safety margins must be applied consistently whether buffers are prepared at working concentration or as concentrates. In addition, effective mixing is essential at multiple stages: during buffer preparation, during inline dilution (where applicable), and mixing of the feed prior to column loading. Manufacturing facilities typically perform mixing studies as part of equipment validation to confirm homogeneity. Insufficient mixing will result in a process that is not robust. Inadequate mixing of buffers can lead to concentration gradients. Insufficiently mixed feed can result in uneven column loading, overloading when drawing from the bottom of a tank or under loading when drawing from the top. Intermediate mixing prior to loading is therefore critical to ensure a homogeneous solution and reproducible chromatography performance at scale.

Key Development Actions:

- Calculate true buffer volumes at manufacturing scale, including safety factors and system priming
- Consider tank minimum and maximum working volumes
- Account for hold times, preparation rates and sequencing
- Propose buffer concentrates or inline dilution only where qualified

Manufacturing Alignment:

- Confirm WFI availability and buffer prep capacity
- Assess whether proposed strategies reduce, or simply shift, operational burden

Step 3 – Column Sizing, Cycles and Productivity

Scaling chromatography from development to manufacturing is based on preserving the separation performance observed at small scale, while increasing throughput to meet manufacturing demand. In practice, this is most commonly achieved by scaling width wise, increasing column diameter while maintaining a constant bed height. This approach preserves the hydrodynamic and mass transfer conditions that govern binding and elution, making scale-up more predictable and robust. Bed height is therefore defined in process development, based on a balance between Dynamic Binding Capacity (DBC), residence time, and process productivity. Shorter residence times can increase throughput but may reduce capacity, while longer residence times maximise capacity at the expense of cycle time. PD must define a bed height and operating window that balance speed and capacity, while manufacturing applies this design within the constraints of available column diameters, flow rates and facility scheduling.

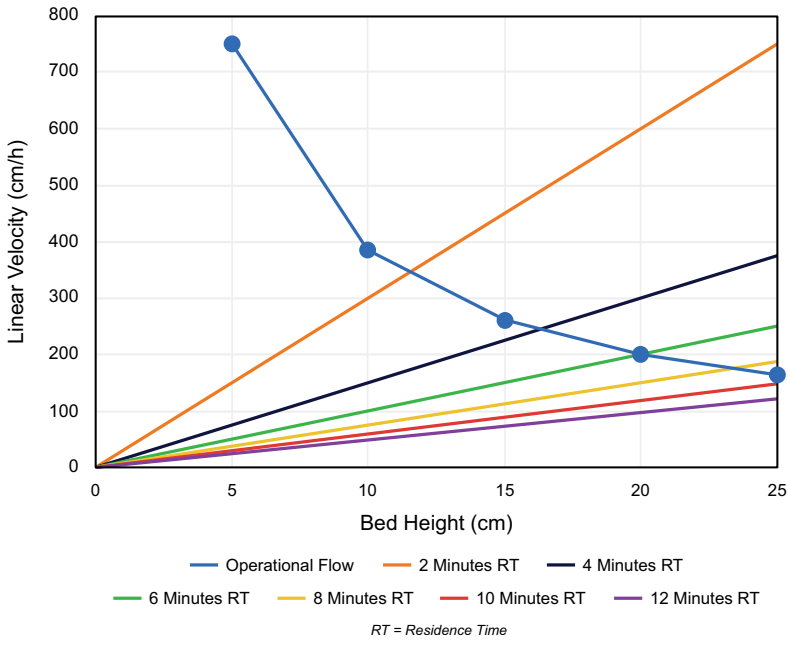


DBC study underway to establish the best bed height for the process.

Column wall effects are an important consideration when scaling chromatography, as they influence local packing structure and flow distribution. At small scale, the wall-affected region represents a significant proportion of the column cross-section, leading to differences in packing density, interstitial void volumes, and flow velocity near the column wall. This can result in non-uniform flow, altered pressure – flow behavior, and reduced separation efficiency, meaning that small-scale performance may not fully represent true packed-bed behaviour. As column diameter increases, the relative contribution of these wall effects decreases, and flow becomes more uniform and representative of the bulk resin bed. However, because small-scale systems may under- or mis-represent hydrodynamic limitations, scale-up should be based on the most limiting observed behaviour rather than the most favourable performance. Explicitly accounting for wall effects ensures that column sizing and predicted productivity remain robust and transferable to manufacturing scale.

FIGURE 1

Expected operational flow window for DurA Cycle™ A50 generated at 30 cm inner diameter.



At manufacturing scale, column diameter is selected to balance throughput, cycle count, and facility operating constraints. Wider columns process more material per cycle, reducing the total number of cycles required, but operate at higher flow rates and generate larger individual elution pools. Narrower columns reduce instantaneous flow and pool size, but require more cycles to process the same batch, increasing pooling, hold times, and operational complexity. The optimal choice therefore depends strongly on how many cycles can realistically be executed within the available manufacturing window. For example, in a non-24-hour facility with a two-day Protein A operation and a 12-hour shift pattern, only two cycles per day may be achievable, limiting the process to four cycles in a week, which is the common time available for the capture step. In this case, column diameter must be increased to ensure the full batch can be processed within that constraint. By contrast, a 24-hour operation can accommodate a higher number of cycles, allowing the use of smaller column diameters if desired. Aligning column diameter with facility operating hours and campaign length is therefore essential to ensure that development-defined performance can be delivered reliably in manufacturing.

Development Considerations

- Define bed height, residence time and scale relevant DBC
- Model number of cycles per batch and elution volume per cycle
- Anticipate increases in elution volume due to system hold up at scale

Manufacturing Considerations

- Confirm available column diameters and maximum flow rates
- Assess realistic cycle numbers within facility operating hours
- Align process design with campaign length and scheduling constraints

Processes that require excessive cycles may meet performance targets but fail operationally.

Step 4 – Elution Pools and Viral Inactivation

Elution optimization is a critical step in downstream process design, as it directly determines product concentration, pool volume, and downstream operability. In development, elution conditions are optimized to achieve complete product recovery while maintaining acceptable purity, typically by balancing elution strength, Column Volume (CV), and peak shape. At manufacturing scale, however, elution performance must be considered beyond chromatography alone. Larger elution pools increase demands on tank capacity, extend processing and hold times, complicate viral inactivation, and reduce overall process flexibility. A smaller, more concentrated elution pool is therefore highly desirable, as it improves facility fit, simplifies viral inactivation and pooling strategies, and reduces scheduling and documentation burden. Effective elution optimization ensures that recovery targets are met while delivering pool volumes that are practical, controllable, and compatible with GMP manufacturing realities.

At manufacturing scale, each chromatography elution cycle typically generates a discrete product pool that must be collected, stored, and then combined to form a final batch pool prior to viral inactivation. This pooled volume must be accommodated within a suitable tank that can hold not only the combined elution material, but also the additional volume required for pH adjustment. Viral inactivation is normally performed by titrating the pooled material to a defined low pH and holding for a validated time. To minimize processing time, documentation burden, and risk of over or under titration, this adjustment is ideally performed as a single addition. For this reason, PD teams commonly generate viral inactivation titration curves during development, allowing precise calculation of the titrant volume required at scale. Accurate prediction of pool volume and titrant requirements is therefore essential to ensure tank fit, enable single step pH adjustment, and support efficient, reproducible GMP execution.

Worked Example: Impact of Column Diameter on Cycle Number and Operability

Consider a capture step processing a harvest at 11 g/L, with 95% recovery and a maximum loading of 53 g/L resin. This corresponds to a total harvest volume of approximately **2,000 L** (~20,900 g post harvest).

Using a 20 cm bed height, a 45 cm internal diameter (ID) column has a CV of 31.8 L, corresponding to a binding capacity of approximately 1,685 g per cycle. At this scale, the batch requires 13 cycles to process the full load. While technically feasible, this cycle count is incompatible with most manufacturing schedules, particularly in non-24-hour facilities, due to extended processing time and the need to pool multiple elution fractions.

Increasing column diameter reduces the required number of cycles. For example, a 60 cm ID column operating at the same bed height reduces the cycle count to eight cycles. However, in a 12-hour manufacturing facility capable of running only two cycles per day, this would still require four days to complete the capture step, exceeding a typical two-day capture window. In this scenario, further scale out is required.

Using an 80 cm ID column (CV ≈ 100.5 L) increases per-cycle capacity to approximately 5,326 g, reducing the process to four cycles, which can be completed within two days at two cycles per day. While this configuration fits the operational window, it introduces new considerations: significantly higher flow rates (up to 1,300 L/h compared with ~400 L/h), substantially larger buffer volumes, and increased elution pool sizes (for example, ~201 L per cycle for a large column compared with ~64 L per cycle at smaller diameters).

This example illustrates the trade-off manufacturing must manage: wider columns reduce cycle count and fit shorter manufacturing windows, but increase instantaneous flow rates, buffer consumption, and pooling volumes. The optimal column diameter is therefore determined not by capacity alone, but by a combination of facility operating hours, allowable cycle count, system flow capability, and downstream tank and buffer constraints.

Development Considerations

- Predict elution pool volumes at scale
- Define pooling strategies across cycles
- Generate viral inactivation titration data to enable single addition pH adjustment

Manufacturing Considerations

- Confirm tank availability and working volume limits
- Verify feasibility of viral inactivation, holds and any post VI filtration

Reducing pool volume simplifies GMP execution and documentation.

Step 5 – Processing Time, Hold Times and Stability

Even in well-run facilities, delays are common: buffers may need to be remade, filters or consumables may be unavailable, columns may fail bioburden testing and require replacement and requalification, or documentation and release steps may take longer than anticipated. In non-continuous, day shift facilities, processes often start later than scheduled, further compressing available processing time. As a result, downstream operations are frequently extended over one or more days, and intermediate pools must remain stable throughout these unplanned holds. Experience from GMP manufacturing shows that achieving zero downstream deviations is exceptionally rare; therefore, intermediate stability data provides essential operational insurance, enabling manufacturing teams to recover from issues without compromising product quality or batch success.

Development Considerations

- Perform intermediate stability studies under realistic worst case conditions
- Define maximum allowable hold times and temperature requirements
- Include scenarios such as overnight holds or reprocessing delays

Manufacturing Considerations

- Map true process duration, including documentation and verification steps
- Identify where holds are unavoidable and ensure they are supported by data

Stability data provides the operational flexibility needed for robust GMP execution.

Step 6 – Feed Conditioning and Cold Loading

The temperature of the capture feed can have a significant impact on manufacturing efficiency. Harvest material is often stored at 2–8 °C to preserve product quality, and at large scale it can take many hours to equilibrate this volume to room temperature prior to column loading. If manufacturing is able to load the column at cold temperature, this equilibration step can be eliminated, saving valuable processing time and reducing overall cycle duration. However, cold loading can affect binding kinetics, DBC, pressure drop, and filter performance, and therefore must be evaluated during PD. A dedicated small scale cold loading study is required to demonstrate acceptable performance before this strategy can be implemented in GMP. Early assessment of cold loading provides manufacturing with additional flexibility while avoiding unvalidated operational changes at scale.

Filter sizing is another critical consideration at this stage, particularly early in downstream processing when feed streams are typically dirtier and filters are more prone to fouling. For post harvest and capture feeds, PD should determine filter capacity in terms of loading per unit area (L/m²), especially for guard and depth filters used to protect chromatography columns. As material progresses through polishing steps and becomes cleaner, filter fouling is generally reduced and sizing becomes less critical; however, early stage filtration often defines operational robustness. In addition, depth filtration steps require careful consideration of chase volumes and any titrant additions, all of which contribute to the total process volume. These combined volumes must fit within available tank capacity, while a facility may nominally have large tanks (e.g. 2,000 L), availability and scheduling constraints can be limiting. Early evaluation of filter capacity, chase volumes, and total tank fit ensures that feed conditioning strategies remain practical at scale and do not introduce avoidable bottlenecks during GMP execution.

Development Considerations

- Evaluate cold loading early, including impacts on binding capacity and filterability
- Size guard filters using scale relevant loading data

Manufacturing Considerations

- Confirm available filter formats and installation constraints
- Ensure conditioning, titration and chase volumes fit within tank limits

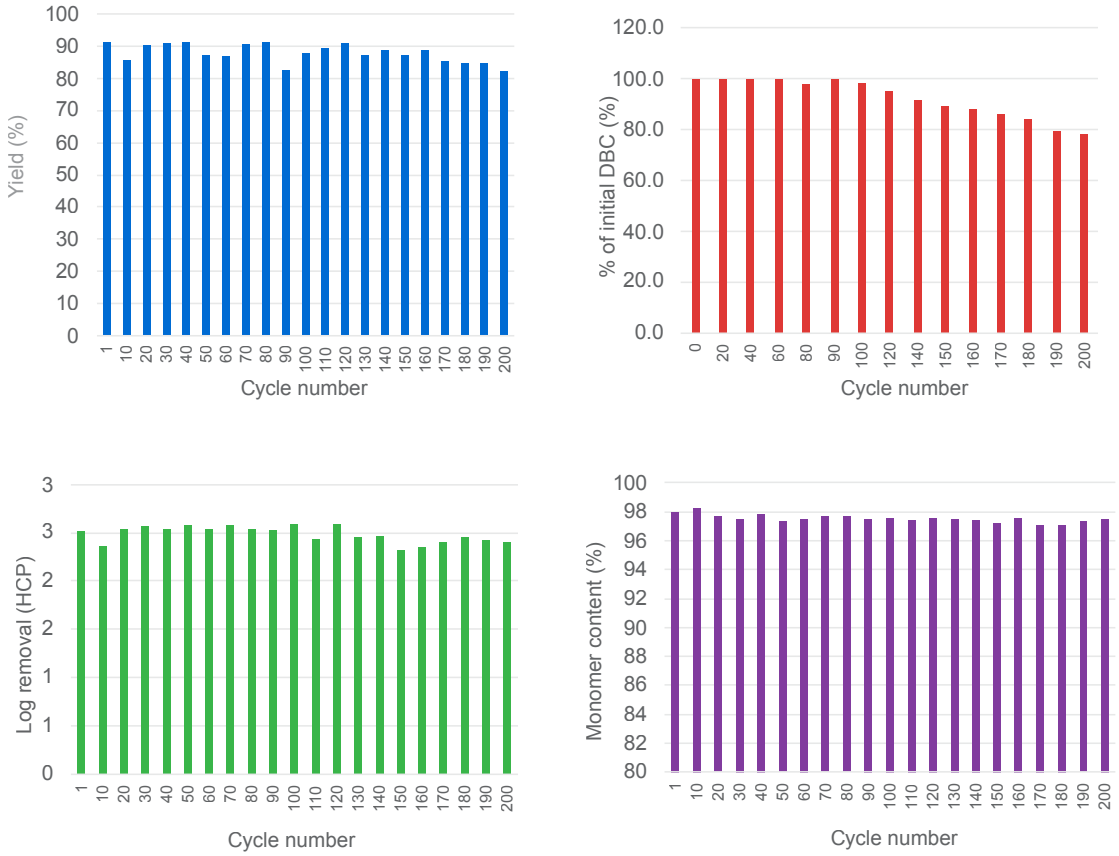
Operational strategies not tested in development cannot be introduced in GMP.

Step 7 – Cleaning, Sanitization and Resin Lifetime

Cleaning, sanitization, and resin lifetime are critical determinants of both product safety and process economics in downstream manufacturing. Effective cleaning ensures consistent performance, prevents cross contamination, and protects product quality, while resin lifetime directly influences cost of goods, campaign planning, and supply reliability. Overly aggressive cleaning conditions can unnecessarily shorten resin lifetime and increase operating costs, while insufficient cleaning increases risk of fouling, bioburden, or carryover. Process development must therefore establish cleaning strategies that are robust enough to ensure product safety, yet balanced to preserve resin performance over repeated cycles. Defining and validating this balance early enables manufacturing to operate efficiently, predict resin usage, and avoid unplanned resin replacement or revalidation during GMP campaigns.

FIGURE 2

Long-term resin performance was tested during repeated purification cycles.



Long-term resin performance was tested during repeated purification cycles. A total of 200 purification cycles were performed using a CHO cell culture containing 3.3 g/L IgG1 monoclonal antibody, with a constant resin loading of 46.1 g/L (73% of the initial DBC at 10% breakthrough) and a residence time of 4 minutes. Product recovery, HCP removal, and monomer content remained largely unchanged throughout the study, indicating consistent purification performance. While a gradual reduction in DBC was observed, the resin retained approximately 78% of its initial capacity after 200 cycles, demonstrating excellent lifetime stability under routine NaOH cleaning conditions.

Development Considerations

- Define cleaning and sanitization conditions under process relevant stresses
- Generate resin lifetime data using representative CIP conditions
- Justify cleaning agent concentration and contact times

Manufacturing Considerations

- Align strategies with site SOPs and validation requirements
- Confirm mixing, contact time and rinse capability at scale

Step 8 – Cost, Sustainability and Facility Efficiency

Design choices made during process development have a lasting impact on manufacturing cost, facility utilization, and environmental footprint. In downstream processing, these choices determine not only whether a process can be executed, but how efficiently it can be run over repeated campaigns. Column sizing, buffer volumes, cycle numbers, and pool sizes all directly influence cost of goods, throughput, and waste generation. Processes that are over-designed for flexibility or under designed for scale often result in excessive buffer usage, long processing times, and inefficient use of manufacturing assets. By considering cost, sustainability, and facility efficiency early, and selecting technologies and operating conditions that maximize productivity, development teams can deliver processes that are not only technically robust, but also economically viable and scalable for long-term GMP manufacture.

High-capacity, Robust Chromatography Resins Can:

- Reduce column and skid size
- Reduce buffer preparation and storage volumes
- Decrease elution pool volumes
- Shorten batch and campaign durations
- Improve facility utilization and sustainability metrics

Economic modelling demonstrates that such benefits are only realised when processes are designed to exploit capacity and robustness, rather than simply optimized for small-scale performance.

The 8 Principles of Manufacturing Ready Downstream Design

Designing Processes That Transfer First Time Into GMP

If a process cannot be run within facility, time, and volume constraints, it is not ready for transfer, regardless of performance.

1 **Quality & Control Strategy**

Design with QbD

CQAs, CPPs, and operating ranges defined using DoE and scale relevant data

2 **Facility Fit**

Design for real constraints

Buffers, tank volumes, WFI availability, and sequencing must fit the manufacturing site

3 **Column Sizing & Cycles**

Design for schedule

Column size and cycle count must align with operating hours, instrument capability and campaign windows

4 **Elution Pools & Viral Inactivation**

Design for tank fit

Minimize pool volumes and enable single step viral inactivation

5 **Processing Time & Stability**

Design for delays

Stability must cover real GMP hold times, overnight steps, and process interruptions

6 **Feed Conditioning & Cold Loading**

Design for feed reality

Validate cold loading and size filters using scale relevant loading data

7 **Cleaning & Resin Lifetime**

Design for repeat use

Balance CIP effectiveness with resin lifetime to support consistent performance and cost

8 **Cost, Sustainability & Efficiency**

Design for lifecycle performance

Reduce buffer demand, cycle count, waste, and overall cost of goods

In summary, downstream processes that are simple, well-understood, designed around real facility constraints, supported by scale-relevant data, and built with operational flexibility are consistently easier to transfer, easier to validate, and more robust in GMP manufacturing. When manufacturing considerations are integrated from the earliest stages of process development, technology transfer becomes a confirmation of readiness rather than a recovery exercise, reducing risk, improving efficiency, and enabling reliable long term production.

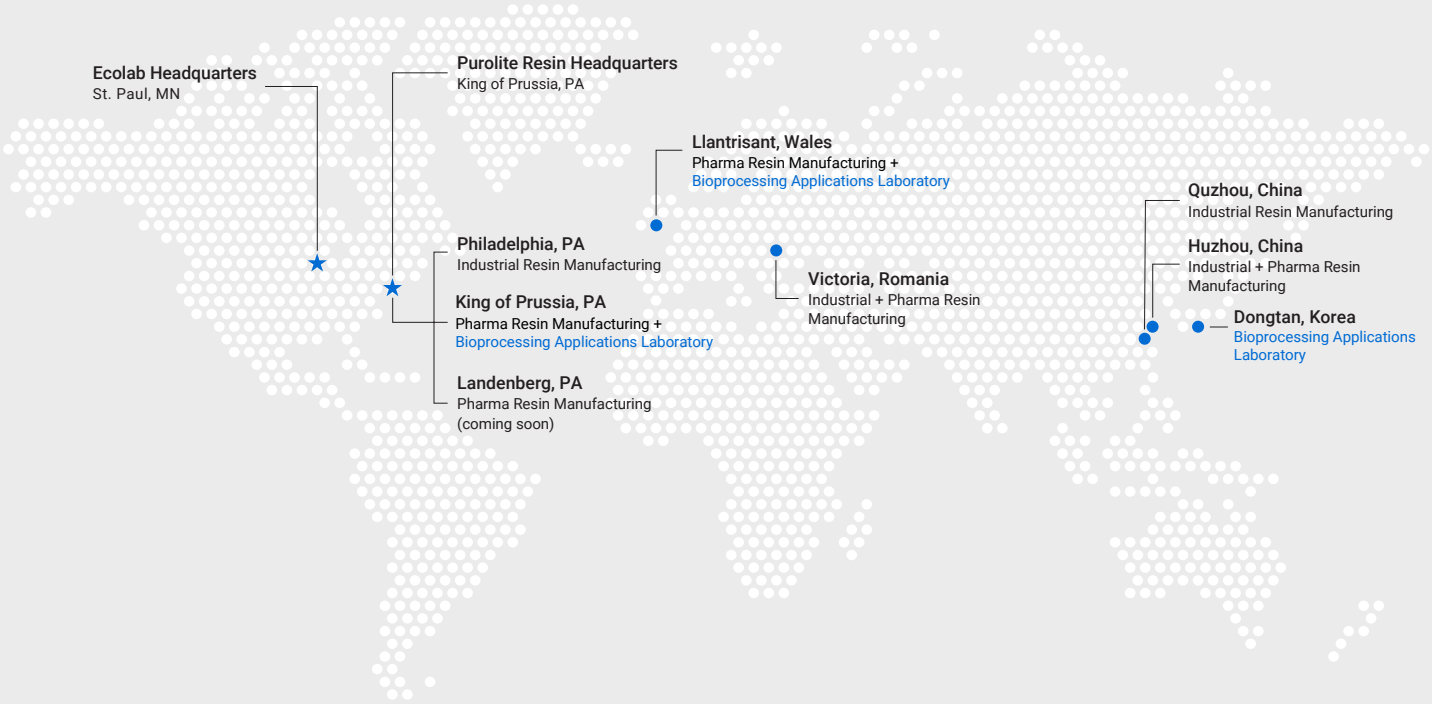


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