Integrated Downstream Processing

An Enabling Manufacturing Approach

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1. Abstract

Over the last decades, the pharmaceutical industry has invested a tremendous amount of resources and capital into the development of continuous processes to improve process efficiency and robustness. Increasing expression levels in modern cell culture and implementing continuous upstream processes has caused the downstream purification to become the “bottleneck” in the manufacturing of biopharmaceuticals, especially of monoclonal antibodies. New downstream approaches are required in time and cost effective ways to purify biomolecule’s while retaining the protein’s characteristics. Approaches such as integrated downstream processes with multi-column continuous chromatography show promising results with increased throughput and reduced capital and operational expenses. Recently, the first integrated continuous downstream process at the production scale was reported by Amgen [1]. This White Paper highlights the major advantages and remaining barriers when implementing these process approaches into the downstream purification scheme. In the first part of this paper, the focus is on the process development aspects. Guidelines for the development of robust integrated continuous processes are discussed. Examples for multi-column continuous chromatography and inline buffer adjustment approaches are introduced. Next, guidelines are presented on how overcome technical barriers in the regulated environment of the pharmaceutical industry. The appropriate equipment designs, applicable automation and analytical tools suitable for multi-column chromatography, as well as their proper risk assessments are described.

Although, when implementing these approaches the initial research and capital investment costs are significant, the manufacturing costs decrease and risks are mitigated due to smaller equipment. Ultimately, this leads to a more robust, yet flexible processes. By minimizing complexity of the integrated continuous downstream processes, additional benefits are obtained.
2. Downstream Processing

Since introducing for the manufacturing of recombinant insulin in the 1980’s, a tremendous amount of resources have been investigated in the development, scale-up and optimization of bio-pharmaceutical processes, in particular, in the downstream purification processes (DSP). These processes are an essential part of the manufacturing of polypeptides, proteins, enzymes, and monoclonal antibodies (mAb). A typical DSP scheme, as shown in Figure 1 for mAb purification, includes capture, purification and polishing steps. Different chromatographic modes are applied such as affinity, ion exchange, size exclusion and hydrophobic interaction chromatography to purify complex cell culture mixtures containing very closely related but also very different molecules.

The chromatographic steps process usually the complete batch in one or two injections onto large LPLC columns requiring large tank systems. Between chromatographic steps, there are filters and membranes for viral clearance or buffer exchange, as well as large hold-up tanks that are also used for viral inactivation. Membranes and filters are operated continuously by installing parallel units.

Approximately 15 years ago, research started on implementing continuous chromatography into the DSP to improve the process efficiency and reduce equipment sizes [3-19]. At that time, multi-column continuous (MCC) chromatography such as the simulated moving bed (SMB) technology became an established separation tool for synthetic molecules [20-24]. Some of the early research in the field of continuous DSP were conducted at the ETH Zurich, University of Magdeburg and Purdue University [10-13, 15, 17]. Due to technical and assumed regulatory barriers, MCC processes were not adapted into the bio-manufacturing and only picked up again 5 years ago [25 - 43].

Initially, upstream processes were the “bottleneck” when titers were less than 1 g/L of mAb. Over the last decade, the upstream expression levels rose above 10 g/L. Downstream became
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the “bottleneck”, especially first capture step. Resins such as Protein A are expensive and have limited lifetime. Another important driver is the introduction of bio-similar and bio-better to the market, in particular, with the first approval of Remsima in 2012 by Celltrion [44].

New downstream approaches are now required that are time and cost effective and retain physical, chemical and biological integrity of molecules. Industrial and academic research teams are re-examining approaches such MCC chromatography integrated into the continuous DSP as shown in Figure 2.

This integrated platform is now a closed system with limited or no hold points. Not only the missing tanks reduce the footprint but also the smaller equipment scale due to the continuous operation. The smaller sizes enable also the implementation of single-use technology [37, 38, 42, 45, 46]. All these efforts together simplify the cleaning procedures and process validations; and, therefore, shorten the turn-around time between batches. This is especially important for CMO’s.

Replacing batch chromatography with MCC chromatography as shown in Figure 3 [18] improves the process efficiency and robustness, reduces the buffer consumption and decreases the equipment size used for the chromatographic step. Increased throughput and packing utilization have been demonstrated at the bench-top scale, which reduce equipment and manufacturing costs; however, the full potential of the integrated continuous DSP platform is reached when both the capture and IEX chromatographic steps (see Figure 2) are operated continuously [30-36].

As shown on the left of Figure 3, columns operate in a parallel flow direction. During one switch, each column fulfills a particular task of the separation recipe. This is in contrast to the sequential execution of the recipe on a large column as explained in Figure 4. After switching the column in the flow direction, tasks are changed based on the recipe. Due to the switching,
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the process can be continuously fed, one column at a time. This process has no internal buffer recycling. Significant buffer reduction can be obtained in a true counter-current processes. Such a process is shown on the right of Figure 3. A regeneration section for cleaning and re-equilibration is added to the conventional SMB process.

Figure 3 MCC chromatography: left – parallel operation, and right – partial counter-current operation [18]

To guarantee the success of the integrated operation, each DSP step must be scaled and scheduled accordingly to avoid any hold-points or idle times. Some single process units can easily operate continuously such as filtration and buffer-inline adjustment steps (see Section: Inline-Buffer-Adjustment). Traditionally, chromatographic processes are run in the batch mode. If they are transferred into the continuous mode, products eluting of the column have no uniform characteristics but a cyclic one which changes composition with time. These behaviors can be observed in the cyclic characteristic of capture processes from GE HealthCare [31], NovaSep, Inc. [25] and ChromaCon [43].

Multi-column continuous chromatography applications and the technical challenges [2, 40- 42] are in the design of the chromatographic skid, the valves and the chromatographic columns, as well as in the implementation of process analytical tools (PAT). These challenges are weighted with the high initial capital investment for the skid, multiple pumps and columns, as well as more of a complex process design working in a regulated environment. For each of the chromatographic steps, comprehensive risk assessment and control as well as for the entire DSP are required. Some of the inherent risks of the traditional batch DSP are reduced due to the continuous operation. For instance, the entire batch is not lost in the event of a failure, as happens during single one-time injections into large column. Other risks are enhanced but can

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be mitigated by implementing control strategies [30, 47, 48] using PAT such as a guarantee of the stability of the bio-molecules during long-term operation.

When connecting process units to an integrated continuous DSP scheme, process automation systems control not only the single processes but also the complete DSP scheme. Based on the critical process parameters (CPPs) and critical quality attributes (CQAs) of the processes, sensors and detectors are selected to monitor the process parameters and quality attributes in the required ranges during continuous operation.

The process parameters for each downstream process (DSP) step are defined during the process development phase. Parameters such as flow rates depend on the process throughput requirements, upstream operations and batch sizes. Based on these parameters and pressure limitations of the resins and membranes, the size of the pumps, valves, pipes, and columns can be determined. In case of an integrated continuous DSP process (see Figure 1), the scale of sequential process units depends on their previous process steps.

The major chromatographic processes are connected using inline-buffer adjustment systems that are described in the section below. Surge tanks are installed as a risk mitigation measures to avoid issues arising from the cyclic collections of the previous product streams and/or unexpected delays.

Until the recent announcement of Amgen [1] there has not been a reported case of continuous DSP at the production scale. Barriers remain by implementing these innovative approaches into the downstream processing. With its high degree of complexity, a number of technical and regulatory/QA questions as well as risk assessment have to be answered during the process development phase and manufacturing [1, 39-41]. However, the benefits of integrated DSP will be substantial when executed as a full manufacturing platform.
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3. Process Development for Capture using MCC Technology

Implementing MCC chromatography into the DSP scheme is straightforward for the capture step. In affinity chromatography, the molecules of interest are captured by Bind-Elute or Flow-Through mode. Figure 4 shows a typical recipe and chromatogram of a batch chromatographic process [2] that includes regeneration, equilibration, load, wash, and elution steps. Columns are typically loaded up to 10% breakthrough (DBT) of their dynamic binding capacity of the resin (see Figure 5). Thus, only parts of the loading capacity are used but the yield losses of the capture step are minimal.

![Figure 4 Batch chromatogram: left – typical receipt and right – chromatogram with corresponding regeneration/equilibration, load, wash and elution steps. During elution, linear gradient applied [2]](image)

During elution, the buffer compositions are changed by step or linear gradients. Their adsorption behaviors are modified from the on- to the off-mechanisms. Depending on the CIP strategy, the column is cleaned and re-equilibrated. Due to the limited load onto the column, the buffer consumption is relatively high in a batch process. Additionally, the exposure of the column to the CIP solutions is high which has significant impact on the lifetime of the Protein A.

![Figure 5 Breakthrough Curves at three different linear velocities: ul1 > ul2 > ul3. Grey area 10% DBC](image)
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To improve the loading onto the column, residence times of biomolecules are increased to overcome the slower mass transfer. The breakthrough curve of the slower loading velocity (blue line) is steeper and later than for faster loading velocities; thus, more CV feed are loaded onto the column. The processing time increases significantly due to the slower feed rate.

High resolutions and high yields are generally obtained due to the specific binding behavior in affinity chromatography. Process optimization now becomes a question between column capacity and throughput and, therefore, buffer consumption as illustrated in Figure 6.

Due to the high cost of the resin (i.e. Protein A), the focus has been on the optimal utilization of the packing. One simple approach is to divide one long batch column into multiple shorter columns (see Figure 3) which can either be operated in parallel or/and sequential. One column is loaded to complete saturation while the breakthrough is captured on the next connected columns (see Figure 7). The saturated column is segregated, eluted and regenerated while the other columns are continuously fed. The first column returns then to the back of the sequential connected column. The recovery step repeats after the next column is completely loaded. In the ideal case with a sharp breakthrough curve, one additional column is sufficient. If the breakthrough curve is broader as may be seen for some bio-molecules, more columns are required to load completely the initial column.

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The other optimization parameter is the throughput or better production rate of the step:

\[ PR = \frac{m_{\text{reb}}}{V_{\text{resin}} \ast t} \]

which is the amount purified per total resin volume per time [kg/L_{\text{resin}}/d]. The total resin volume refers to the resin volume of all columns and not only the one, which is in the recovery phase.

The production rate is directly correlated to the feed flow rate. If the feed is put into the column faster, the bind-elute cycles can be repeated more frequently, and, therefore, more product per time can be recovered. The elution is generally less dependent on the flow rate during capture, and therefore, it can be performed at the highest possible flow rate. The wash, regeneration and equilibration steps are usually defined by column volumes, and, therefore, can be performed at the highest possible flow rate.

In traditional batch chromatography, the highest possible flow rate is defined by the pressure limits of the column. The pressure drop \( \Delta p \) across the column is calculated for instance by the Carman-Kozeny equation as a function of column length, linear velocity and resin porosity. In the MCC processes, multiple shorter columns not only operate in parallel but are also sequentially connected at times (see Figure 8). Thus, the pressure drop depends now on the number of connected columns during the loading. If more columns are connected the feed flowrate needs to be reduced. Accordingly, the load time and processing time increase, and, therefore, the production rate reduces. During the recovery, only one column is usually segregated, thus, higher flow rates are applied.

The optimal loading time is determined from the dynamic breakthrough curves on a bench-top system using different linear velocities (see Figure 5). Of course, when determining the loading time for the sequential connected column, the pre-load has to be taken into account. Otherwise, breakthrough will occur earlier resulting in the loss of valuable product.

On the left side of Figure 8, a 3-column parallel process is displayed. In this 1-2 setup there are always two columns in the loading phase. The third column is in the recovery phase. During loading the breakthrough of the column in the first position binds onto the second column.

Switch time is defined by the recovery phase (time for washes, elution and regeneration) as well as by the loading to full capacity of the first column in the loading phase. Optimally, both are completed before the next switch. After the switch, the loaded column is segregated for product recovery. The clean column is now connected to the outlet of the partially loaded column. These process steps are repeated until the batch (lot) is completed.
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On the right side of Figure 8, the CaptureSMB process with 2 columns is shown [36]. This process includes also an interconnected step in addition to the parallel loading and recovery. While the sequential connected columns are loaded, the breakthrough of the first column binds onto the second column. After the re-equilibrated column is re-connected to the end of the column train, all columns are continuously loaded and neither of the columns are in the elution step. The flow rates are reduced to such a degree, that the process has a low productivity even though the columns are loaded to the maximal capacity.

Figure 8  Capture step using MCC technology in parallel and sequential mode: One or 2 columns are loaded while product is removed from one column [42]
4. Example: Theoretical comparison of different column arrangements

Using the mass balances of the MCC process, the production rate and buffer consumption can be calculated based on the feed flow rate for different column arrangements of a sample system (see Table 1) [40]. The batch process is laid out for one affinity column. The feed concentration is 2.5 g/L protein. Before loading of 15 CV starts (see Figure 4), the column is equilibrated with 5 CVs. After the loading is completed, the column is washed with 5 CV low salt and then 5 CV high salt. The product is eluted with 5 CV. If necessary the batch process is repeated until the entire batch is purified. The estimated production rate and buffer consumption of this process are 0.45 kg/Lresin/d and 0.67 L/gprod, respectively (see Table 1). Using two columns in the CaptureSMB process (see Figure 8) allows an increase in loading of 5 CV while interconnected. The production rate rises to the highest value in this comparison, to 0.6 kg/Lresin/d with some reduction in the buffer consumption.

The lowest buffer consumption of 0.23 L/gprod was reached using 4 columns. Although, the highest load per column (cycle) was obtained; this arrangement has the lowest production rate due to the total number of 4 columns. Furthermore, due to pressure limitation, feed flow rates need to be reduced to avoid use of more costly high-pressure columns when the columns are switched sequentially. The linear velocity is reduced to 150 cm/h, which reduces the production rate even further. The results of the comparison need to be verified for other chromatographic separation.

Concluding, systems with less columns can generally run faster which improves the production rate. The lowest buffer consumption is obtained with more columns. Faster processing is generally more favorable due to longer loading period and, therefore, fewer cycles for regeneration and elution.

Table 1 Theoretical comparison of different column arrangements [41]

<table>
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<th># of col</th>
<th>L sin CV</th>
<th>L con CV</th>
<th>uL sing [cm/h]</th>
<th>uL con [cm/h]</th>
<th>Cycle [min]</th>
<th>load per cycle [g]</th>
<th>L per col [kg/Lres]</th>
<th>L per h [g/h]</th>
<th>prod [kg/Lres/d]</th>
<th>buffer [L/gprod]</th>
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</thead>
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</table>

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5. Inline-Buffer-Adjustment

To connect consecutive chromatographic steps in a DSP scheme (see Figure 2), the product compositions of the first chromatographic step have to be adjusted before entering the next step. In Figure 9 a flow chart for the inline-buffer adjustment is displayed where either pH or conductivity are modified. Although, the first step is operated continuously, its product stream changes its composition periodically as described above. The critical quality attributes such as concentration and composition changes in pre-define ranges. In this particular case, the product stream is concentrated during the adjustment. Thus, a robust control strategy is implemented. Critical process parameters are continuously monitored by online PAT [35, 39-41].

Sensors and instrumentation should have the required mechanical and chemical strength and durability for continuous operation. They can be calibrated while online or while segregated briefly. The control systems have either open or close feedback loops. These control strategies of each step are incorporated in the overall control strategy of the integrated DSP scheme; thus, the variability in the prior chromatographic step can be controlled in the subsequent chromatographic step. This requires rigorous sensitivity analyses of all critical process parameters and definition of their limits during the process development phase.

Assuming conductivity is adjusted between the two steps; three major points have to be examined: (1) variability in the conductivity value leaving the first step, (2) allowable variability of the feed entering the second step, and (3) sensitivity of the separation processes to these variability’s, particularly in the second step.

Figure 9 Schematic of an Inline Buffer Adjustment between two chromatographic steps [41]
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The buffer adjustments need to be timed correctly. They need to be synchronized to allow the integration of the continuous DSP platform.

6. **Systems for Multi-Column Continuous Chromatography**

   The process steps of multi-column continuous chromatographic separation are equivalent to batch process in the DSP. As described in Figure 3, Figure 4 and Figure 8, the time-sequential process steps are transferred into process steps running parallel on multiple columns allowing the continuous loading of the systems. Hence, multi-column continuous chromatographic processes generally use the similar skid design as batch processes (see Figure 3, Figure 4 and Figure 8). Only in a few cases, like in MCSGP processes [19], process steps are modified in such a way that allows internal buffer recycling within the chromatographic skid.

   Nevertheless, already due to the parallel column processing as described for the PCC system from GEHC [30, 31], the SMBC system from NovaSep [25] and the CaptureSMB system from ChromaCon [43], additional skid hardware is needed e.g. valves, columns, flowmeters, pH probes, pressure gauges, control hardware and possibly pumps. These additional components translate to higher capital investment costs. The required modifications in the system design introduce complexity in the skid (see Figure 10 and Figure 11) and in the process automation and control strategies. These complexities increase the failure risk of processes and their equipment designs. These risks can be mitigated by conducting risk assessments and implementing the appropriate control strategies (see Section: **Risk Assessment**).

   Due to the improved productivities of continuous processes, smaller columns are used for the parallel and sequential operation schemes. Smaller columns lead to reduced sizes of pumps, valves and piping. The capital investment of complete chromatographic systems (for both skids and columns) are reduced. Smaller equipment scales improve the process robustness and, consequently, lower the process risks. Smaller scale also reduces the footprint of the chromatographic skid and entire DSP. Using modular design allows parallel operation of multiple chromatographic skids or entire manufacturing schemes without any additional scale-up efforts. Modular design provides more flexibility when demands change without adjusting the equipment scale. For instance, one of the CaptureSMB [43] unit can be added or removed if batch sizes change due to schedule modification.

   As shown by the complex tubing arrangement of an 8-column system on the left of Figure 10, there is an obvious benefit to simplify a MCC system to the minimum number of columns. Currently, systems are being proposed with three or more columns [25, 30, 31]. Only one
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system uses an innovative approach altering between parallel and interconnected column operation that operates with high productivities using just two columns, the CaptureSMB [43] and MCSGP [19] technology from ChromaCon. The ChromaCon technologies have, therefore, simpler hardware design due to fewer components, (far less complex valve arrangements). The streamlined design further reduces the complexity of the process, and, thus, the potential for minimizing related failure risks. A bench-top unit is displayed on the right in Figure 10.

The flow chart in Figure 11 shows in more detail the twin column skid for the continuous capture process. Unique pre- and post-column valve blocks allow operating two columns and, the equipment design is similar to a batch system design. The dashed lines show the connections between the columns when operating both columns sequentially. To assure proper operation the piping design between the valve blocks must be symmetrical.

Figure 10 Picture of 8-Column (left) and 2-Column (right) bench-top units [43, 49]
To reduce dead volumes that may cause deviations to the ideal design parameters the piping of the entire skid must be minimized. Because external volumes cannot be entirely avoided, the ratio between these external volumes to the column volumes should remain constant while scaling up. This simple twin column design enables robust operation by reaching comparable throughputs and high productivities as described above in aforementioned Example.

The product materials of construction (MoC) for the skid must be compliant with FDA-requirements. Characteristics such as inertness (no impact on the mechanical and chemical stability and the bio-comparability of the bio-molecules) and cleanability are important. This is in particular important for valve and pump design. In the past, only high-grade stainless steels were implemented. Recently, polymers such as polystyrene, polysulfone, polyethylene, polyaminde and ethylene vinyl acetate have gained popularity [37, 38, 45-46]. This SU technology is applied either for piping, bags, and sensors, or for entire systems and DSP schemes. Their advantages are low costs and flexibility. The cost for equipment cleaning and their validation are minimized. However, SU components might not have the same chemical and mechanical stability as steel components. SU components are more affected by their operational environment e.g. temperature, light, oxygen levels, pressure and sterilization irradiation. Their lifetime is limited. Stricter monitoring of extractables are also required [37, 50].

To secure accurate liquid flow through the skids without any cavitation, the skid piping must be to be designed with a great deal of thoughtfulness and components such as sensors, filters and valves should be chosen accordingly. Pressure regulators can be installed to adjust the pressure contribution. Computational fluid dynamic (CFD) tools are helpful to estimate not only
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the pressure contributions within the skid, its piping and components but also to determine the correct fluid and cleaning flow design.

An innovative pump inlet and outlet design is shown in Figure 12 that is based on CFD calculations. The symmetric design allows the proper operation of the pump with multiple pump heads and proprietary fluid handling on the outlet. The LEWA ecodos® triplex pump (Figure 12) is a three-headed diaphragm-metering pump that very precisely, but more importantly, reproducibly delivers buffers. The reproducible delivery of buffers is important for continuous, steady state operation. The advanced fluid control with LEWA intelligent drive technology via servomotor delivers extraordinary reproducibility across a large flowrate range (pump turndown ratio 1:150) with a high accuracy (below 0.5%). This performance allows a linear gradient specification better than the 1 to 2% that is common in conventional chromatography systems.

In the system design dead volumes should be avoided especially in critical components such as pumps and valves. Any dead volume may result in stagnant liquids allowing cross-contamination. It is best to source pumps with hygienic designs.

CIP options during and after the purification batches can be integrated into this skid design. Additional hardware is required (valves, piping and tanks). The CIP step can be a direct part of the process step sequence or it can be taken offline (decoupling of the column from the process). Ensure that the feed streams are segregated from the CIP lines and that no CIP solution remains in hidden dead legs (see in Figure 13). The valve arrangement is therefore important. In the case shown, the CIP buffer is not in direct contact with the feed and product streams. Due to this arrangement, the CIP buffer is flushed out by the re-generation and elution buffer.
SIP options can also be implemented. The systems must be fully drainable to avoid any accumulation of condensate in the system. Using air-blow-down enhances the removal of condensate from the system.

As previously mentioned, valves are one of the most important components. In particular, when using multi-column continuous chromatography, choice and positioning of the valves are important (see Figure 13). The repeating valve arrangement on each column are closely evaluated. Are arrangements containing simple two-way valves preferred over complex multiport valves, even if a very large number is needed? Or, is this a matter of scale? At the bench-top scale, there might be other valve types available than at the pilot or large manufacturing scale. Additionally, FDA-requirements are different when working in PRD or GMP manufacturing environments.

At the bench-top scale, pre-manufactured valves are implemented. Cleanability requirements are not as stringent as at the GMP scale. Here, one can use on/off valves with a simpler design or custom-made block valves. Choosing the first option leads to very large number of valves for the multi-column skids, which increases the failure probability significantly. Furthermore, using the single valves requires the proper positioning of inlet and outlet ports (see Figure 13) and minimization of the dead volume in between ports. Because these are generally all-pneumatic valves and all actuators need space, and space consumption can be especially critical at the larger scale.
Choosing the custom-made block valve option requires additional testing to mitigate failure risks (see Figure 14). Long-term endurance and internal leakage tests must also be conducted. For instance, the valve block above was switched 500,000 times at high-pressure conditions without any observation of leakage during and after the test.

Valve blocks are either designed to handle the complete process or just one of the columns. Figure 14 shows a particular design with low internal dead volumes that can be installed on the inlet and outlet of each column. To maintain the advantage of the block valves, their manufacturing becomes very cost intensive, especially if one valve is handling the entire process at the larger scale. At the manufacturing scale, such single multi-port valves as shown in Figure 15 are generally only implemented in the food and commodity industry. Single on/off valves are re-considered at the manufacturing scale in the pharmaceutical industry due to high risk of internal leakage in a multiple-port design.
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7. Chromatographic columns are smaller

MCC processes use smaller columns which has multiple advantages such as more efficient column packing and, therefore, more effective processing, and reduced capital investments (lower equipment costs and less packing material), and lower operational cost (faster processing time). Columns for DSP are typically packed with low and medium pressure media. Due to the nature of the soft media, differences in the packing characteristics, and, therefore, column performance, occur depending on the column scale. Column efficiencies are lower at larger scales. The homogeneity of the packing is not always a given. Variables that influence the column packing at different scales are:

- Wall effects which disappear at column sizes larger than 2” and their impact on the packing stability.
- Pressure rating of the column hardware is lower at larger scales.
- Differences in the frit design at the column inlet and outlet affects the flow distribution across the packed bed significantly. Frits used in analytical (small-scale) columns provide higher column efficiencies that translate into sharper peaks and breakthrough curves and, therefore, better separation performance.
- The scale-up of the packing procedure is not straightforward due to mechanical limitations. Even if the large ID columns are slurry packed, the slurry preparation might be done in steps.

Having reproducible packing characteristics (i.e. efficiency and homogeneity) is particularly important if multiple columns are implemented in the MCC process. Any variability in the column characteristics affects the performance of the process. By implementing the control strategies, like setting tight efficiency limits, column variability can be controlled but not avoided. Knowing the challenge to pack “identical” columns, one should include variability during the process design phase. As required in the QbD directive of the FDA, this will allow more robust yet flexible processing.

Due the scale down of the columns in a MCC process, pre-packed single-use columns can be implemented into manufacturing processes. These columns are factory packed and might already be qualified, therefore performing more accurately and reproducibly. This is particularly attractive for CMOs due to reduced demands on cleaning and pre-campaign qualification, leading to shorter turn-around times between campaigns.

During the continuous operation of the columns, the mechanical and chemical stability of packing material and characteristics thereof must be guaranteed. Switching valves changes not the flow directions in the MCC process, and also influences the pressure in the system and columns. The packed bed should not shrink or expand when going through the process steps, as this negatively affects the column performance and lifetime.
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Additionally, the packing material must maintain its integrity while increasing the column load during the MCC process and the cleaning cycles. Some of questions to be considered during the process design phase are:

- Is the packing lifetime limited by load or cleaning cycles?
- What cleaning requirements, like frequency, have to be investigated?
- Are cleaning cycles defined by exposure time or load?
- How will cleaning be implemented if running 24/7?
- Are columns cleaned as part of the purification steps, by decoupling the columns from the process, or just at the end of the campaign.
- What are the appropriate control strategies to mitigate the risks of batch failure or cross-contamination between batches and campaigns?

If SU columns and other components are implemented, strategies of monitoring leachables and extractables over time have to be implemented [37, 38, 45-46, 50].

8. PAT implemented into the Control Strategy

To ensure the physical, chemical and biological integrity of the molecules, the critical process parameters (CPPs) and critical quality attributes need to be determine during the DSP scale-up [35, 39]. CPPs and CQAs are monitored by online and/or offline by process analytical tools (PAT). This monitoring allows the implementation of comprehensive control strategies for the continuous operations during the different scale of process development as required by the quality of design (QbD) initiative of the FDA [39]

The premise of continuous manufacturing is that operating under steady state conditions ensures consistent process parameters and quality attributes of the products. When steady state conditions are reached, the control strategies become more robust when compared to batch operations. Of course, such stringent definitions cannot be applied to integrated continuous DSP. Assuming a coherent feed stream, (i.e. no variability in the concentration and composition), is continuously loaded into the first continuous unit operation of the DSP, the CaptureSMB step; products are taken cyclically. The basic process within the CaptureSMB remains as in batch mode; however, multiple columns are run parallel but offset. Due to this “flip-flop” operation (Figure 16), the process becomes continuous. The product streams maintain their batch characteristics like changing concentrations and compositions.

Feed variability is caused by batch-to-batch variability of the upstream bioreactor, by parallel operating bioreactors, or during continuous operation of the bioreactor. This variability in quality
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and process parameters do not automatically cause the failure of the batch. Using QbD process design approaches, [52], and appropriate control strategies the implementation of integrated continuous DSP is enabled.

Control strategies developed in the batch mode on the benchtop scale can be implemented into the continuous operation of the process. The base line data sets of CPP and CQA are generated on the bench. The impact of any process modifications can be compared back to the batch parameters. This includes scale-up in general but also the transition of batch to continuous chromatography. Knowing that the process steps and parameters remain unmodified, the same concentration and composition of the product stream should be obtained. Changes observed in the quality attributes are generally caused by the increased load, loading time and modified cleaning regiment. The effects of increased load on the elution and process variability can be investigated on the benchtop systems during process development. If needed the control strategies can then be adjusted and tested.

Controlling integrated continuous processing requires enhanced control strategies of both the steps and the transitions between the steps. There are times without any product leaving the column and entering the next operational step (i.e. like viral clearance (see Figure 2)). Control strategies should guarantee that the product identity and purity remains within design limits and that during processing no additional fragments and aggregates are formed [53]. With the help of PAT tools like HPLC/SEC analyses, peptide mapping and SDS-page, the CQAs and CPPs are monitored.

As an example, the following analytical tools are applied to monitor off-line the biomolecule during the processing:

- **Protein determination**: Bradford protein assay, UV-spec at 280 nm
- **Identity**: Peptide mapping, HPLC C18, SEC, SDS-Page with Western Blot
- **DNA determination**: UV spec at 260 nm
- **Yield**: ELISA, HPLC and SEC
- **Purity**: HPLC C18, SDS-Page
- **Aggregate and Fragment**: SEC
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PAT uses either inline/online or offline approaches. UV, conductivity and pH-values are monitored with inline sensors. At production scale, analytical HPLC systems are implemented online with automatic sample taking allowing close-system operation. At the benchtop and pilot scale, the samples are manually taken. Due to the time and work intensive nature of the biophysical tool, they are mostly offline tools. This requires special sampling ports at the production scale.

For example, process development and monitoring tools were introduced for the capture chromatographic step that are based on UV monitoring. The first strategy monitors the absolute UV signal of the dynamic breakthrough curves on the column outlets [30]. This method allows the direct comparison with feed signal. Other strategies evaluate the elution profile by either correlating the peak area to the load [47] or comparing multiple wavelengths [48]. The latter strategies using the UV response of the purified product that is not as affected by variability in the impurity profile than the absolute UV response of the feed. Furthermore, UV responses are easier to keep in the linear range of the UV detector. Due to use of the area, any drifting of the UV signal during operation does not influence the response of the control strategy as long the detector remains in its linear range.

Based on the GMP requirements, all monitored CPPs and CQAs of the production process are stored in data historians and reported in the batch records. Inline/online PAT allow the implementation of the real-time release assays which enable the integrated continuous DSP. Waiting periods for test results are minimized. Decisions on proceeding with the operation can be made as soon as the test data are available.

In the framework of QbD [52], these data can also be used during processing to adjust process parameters. For instance if feed concentrations vary in defined limits, loading times are adjusted. Direct feedback control is implemented such as flow rate adjustments of pumps or the pH-adjustment for continuous inline-buffer adjustment. In latter case, the pH-value of the incoming feed stream is depending on the protein concentration in some cases. Any pH-changes affects when proteins elutes during the chromatographic step (see Section: Inline-Buffer Adjustment). In the coming years, there will be tremendous development in the field of process automation and control strategies using real-time release assays, which should further mitigate process risks.
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9. Risk Assessment

During the previous sections, the need for risk assessments was addressed. Detail risk assessments of equipment components and process aspects of the integrated continuous DSP should be conducted prior to designing and building the equipment, and implementing such processes [54-56]. In each phase, a group of subject matter experts with backgrounds in quality control, regulatory affairs, automation, skid design, pharmaceutical PRD and manufacturing come together. Using formal risk assessment tools, they are able to provide more quantitative evaluation of the process or equipment [54]. Parts of a simple, generic assessment and analysis is shown for the capture step in Table 2.

In addition to the evaluation of throughput and capacity during process design of the capture process, (see Figure 6), a cost-risk assessment has to be conducted which has two pumps: feed and buffer pump. The latter pump delivers buffers for the washes, elution gradient, CIP, regeneration and equilibration. The assessment should also include performance improvements of small columns with higher efficiency and, therefore, better separation performance. Less complicated systems with fewer valves, pumps and columns will have lower performance risks. More details are in the following sections and elsewhere [40-42].

General risks as well as of the skid components of the CaptureSMB are listed in in Table 2. The probability and severity of a failure or risk are evaluated under the consideration of patient safety. Additional comments evaluate the impact on GMP and GAMP5 directions, and the complexity and novelty of the risk and if it is detectable. Within the scope of the product life-cycle management, these assessments are revised, as new knowledge about the process and skid becomes available.

Each of the subject matter experts has different sets of experiences, and, thus, different understanding of the risks and the requisite mitigation. For instance, the research scientists have data about the long-term chemical and mechanical stability of the molecules, conduct the required experiments to characterize the molecules, and know how to monitor these characteristics. The design engineer implements the recommendation for risk control and mitigation into a revised PI&D and functional specifications.
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### Table 2 Parts of Generic Risk Assessment for EcoPrime Twin Process

<table>
<thead>
<tr>
<th>Description</th>
<th>Probability</th>
<th>Severity</th>
<th>Impact (GMP, GAMP5 ...)</th>
<th>Detectable</th>
<th>Comments Complex, Novelty ... Detectable</th>
<th>Risk Control Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Risks CaptureSMB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Same process steps only feed continuously using multiple column, possible longterm operation (24 h to 6 weeks), perception that different process</td>
<td>Monitoring using PAT, process and cleanability verification on benchtop scale, adjusted automation</td>
</tr>
<tr>
<td>Process: batch vs continuous</td>
<td>medium</td>
<td>medium</td>
<td>medium</td>
<td>yes</td>
<td>Shear stress, temperature of the fluid in the column</td>
<td></td>
</tr>
<tr>
<td>Skid: batch vs continuous</td>
<td>medium</td>
<td>medium</td>
<td>medium</td>
<td>yes</td>
<td>Very similar design that is capable to run two column parallel or sequential</td>
<td>Verification of design (see below) no dead legs or back mixing</td>
</tr>
<tr>
<td>Mechanical and chemical stability of bio-molecules</td>
<td>medium</td>
<td>medium</td>
<td>high</td>
<td>yes</td>
<td>Novel continuous process, longterm stability data needed under this operating conditions</td>
<td>Longterm feasibility studies, control strategies, PAT implementation, equipment cleanability studies</td>
</tr>
<tr>
<td>Mechanical and chemical stability of resin</td>
<td>low</td>
<td>medium</td>
<td>medium</td>
<td>yes</td>
<td>Novel continuous process, longterm stability data needed under this operating conditions</td>
<td>Longterm feasibility studies, control strategies, PAT implementation, equipment cleanability studies</td>
</tr>
<tr>
<td>Skid Design</td>
<td>high</td>
<td>medium</td>
<td>medium</td>
<td>yes</td>
<td>More complex design with additional parts, need for more complex automation and control strategie</td>
<td>Rigorous design to avoid any dead volumes, monitoring CPP, implementing cleaning procedure,</td>
</tr>
<tr>
<td>Valves</td>
<td>medium</td>
<td>high</td>
<td>high</td>
<td>yes</td>
<td>When one fails more potential negative effects</td>
<td>Double valves, feedback from valves</td>
</tr>
<tr>
<td>Multiple port valves</td>
<td>medium</td>
<td>high</td>
<td>high</td>
<td>yes</td>
<td>Large number of valves but the effect of one failing is not as</td>
<td>Double valves on important points, valve feedback</td>
</tr>
<tr>
<td>Single on-off valves</td>
<td>high</td>
<td>medium</td>
<td>high</td>
<td>yes</td>
<td>Large number of valves but the effect of one failing is not as</td>
<td>Double valves on important points, valve feedback</td>
</tr>
<tr>
<td>Columns</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Two column but smaller design, more robust and efficient</td>
<td>Testing of columns, pressure monitoring, cleaning of skid and column according to strategie</td>
</tr>
<tr>
<td>Twin</td>
<td>medium</td>
<td>medium</td>
<td>medium</td>
<td>yes</td>
<td>Two column but smaller design, more robust and efficient</td>
<td>Testing of columns, pressure monitoring, cleaning of skid and column according to strategie</td>
</tr>
</tbody>
</table>

As shown above for the continuous capture process and its equipment implementation, similar assessments have to be executed for each of the process units and for the entire integrated DSP. Of course when assessing the entire scheme, one needs to be aware of the complexity and interconnections of each step and potential risk mitigation. A process change in the upstream bioreactor will affect the performance of the DSP units. As previously mentioned, variability in the concentration of feed stream can be designed into the capture process like by adjusting the loading time. Appropriate control strategies can be implemented while monitoring the concentration online. Inaccurate or non-reproducible buffer delivery during elution causes variability in the composition of the product stream. Changes in the feed composition has to be investigated more thoroughly to ensure that subsequent process units handle higher impurity without negatively affecting the CQAs of the drug product.
10. Regulatory Aspects

In May of 2014, Dr. Janet Woodcock stated at the International Symposium on Continuous Manufacturing of Pharmaceuticals at MIT [57] that the “FDA supports continuous processing for pharmaceutical manufacturing.” and “There are no regulatory hurdles for implementing continuous manufacturing, but there is lack of experience”. These clear statements support not only the technical drivers but also regulatory aspects that continuous manufacturing “offers potential quality advantages in both development and manufacturing”. Based on the 21th century quality initiative of the FDA [39], continuous manufacturing will lead to agile, flexible and geographically independent manufacturing processes that deliver at high product quality and low production costs [57].

Over the last decade, the regulatory agencies have laid out the framework with a number of guidelines [39, 52 -59] that should enable us now to implement continuous manufacturing processes into the pharmaceutical industry. Their focus was on Pharmaceutical Quality Systems (PQS) [55, 56], QbD [52], PAT [53], and real time release testing [58]. It is now our task to show that we have the expertise and experience to overcome existing and perceived hurdles. As shown in the previous sections, innovative process approaches and technology together with analytical and control tools are developed that should enable us to transfer batch into continuous processes.

Based on the engineering principles, continuous processes operate at steady state conditions where process parameters and quality attributes of pharmaceuticals are more consistent. By implementing the appropriate control strategies and risk mitigations, it will be demonstrated that the processes are under control. Now this “Demonstrably under-control processes can lead to decreased regulatory oversight.” [57].

Initially, additional efforts are required to prove that control strategies and analytical method are transferrable, and that all critical process parameters and quality attributes are determined correctly. Using PAT will provide in-process monitoring and also real-time release assays [58]. Development procedures for the DSP have to be proven on the benchtop or pilot scale, even if they have been proven for synthetic molecules for years.

Downstream processes are generally purifying products that were cultured upstream. In contrast, the API is synthesized step-by-step in the synthetic process route; thus, the risks of continuous manufacturing may only affect an intermediate process step, not the final API. Scale-down models with extensive monitoring capabilities will verify that the extended exposure of the molecules to the process conditions and cleaning do not affect the quality of the
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molecules and do not cause denaturation or aggregation of the molecules. These scale-down models provide supportive data for process and cleaning validation strategies. Risk assessment of the products, processes and equipment are based on ICH Q9 [55]. Their results will also support the process and equipment qualifications.

Providing sufficient technical evidence of process and equipment understanding and control strategies will support the implementation of continuous multi-column chromatography and integrated DSP. Answering questions such as:

- How to design equipment for continuous, long-term operation?
- How to implement parallel operations (for filtration steps), and continuous buffer exchanges?
- How to eliminate/reduce hold points?

will provide the confidence in the process understanding.

During any discussion about implementing continuous manufacturing the question of batch definition is raised, in particular when organizations are first exposed the concept of continuous processing. The FDA has clear definition of “lot” and “batch” in 21 CFR 210.3: “Lot - a batch, or a specific identified portion of a batch, having uniform character and quality within specified limits; or, in the case of a drug product produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits.” The word “batch” refers to a quantity of material and not to the mode of operation. The definition is therefore applicable to continuous processes.

And it has for simulated moving bed chromatography (SMB) in synthetic routes. Multiple synthetic molecules are on the market for years that use SMB technology [18].

Close collaboration between the regulatory agencies, pharma and equipment vendors are needed to overcome perceived regulatory hurdles. CDER has formed an Emerging Technology Team (ETT). Its “Initial focus is innovative or novel products, manufacturing processes, or testing technology processes” [57]. The ETT will also identify hurdles in the existing guidelines and review current inspection practices. These initiatives and collaborations are established as evidenced by the current approval of production scale facilities.
11. Conclusion

Implementing integrated continuous downstream processes is not only driven by the pharmaceutical industry to improve the process efficiency and robustness but also by the regulatory agencies. During the last two years, there was a tremendous increase of activities in this area. All major biopharm companies and equipment manufacturers have invested significant resources. New research results are presented constantly to the community. Initial investigations are scaled up into the GMP environment of manufacturing facilities. Biochemists have access to new evaluation tools [43] and closely work with engineers to make the transition from the bench-top to the manufacturing scale possible.

With this combined White Paper, the drivers and barriers of this transition were highlighted. Guidelines on how to overcome the barriers, in particular in process development, were provided. The implementation of multi-column chromatography and inline-buffer adjustments were explained as essential parts of integrated continuous downstream processes. The latter operational step enables the connection of sequential purification steps without the need of large hold-up tanks. Proper process analytical (PAT) tools and controls are crucial.

In the first part, the focus was on the transition from batch to continuous operation, in particular for the capture step. Due to the multi-column chromatography technology, integrated continuous processes become most cost effective. This technology not only further reduces the footprint of manufacturing facilities but also improves the process performance and robustness.

The design and optimization for the multi-column continuous chromatographic separation of the capture step was described in details. The effects of the number of columns on the production rate (amount purified per time per total packing amount) and buffer consumption were evaluated. The highest production rate was obtained for a two-column system. The lowest amount of buffer was consumed on a four-column system. Savings in the resin costs, especially Protein A resins, have significant impact on the capital cost of the production costs of monoclonal antibodies. The two-column system is therefore especially attractive for the early development phase. Its fast turn-around times based on the higher production rates are desirable. Buffer consumption is not as critical due to the small scale in this development phase.

Even at the manufacturing scale, less complexity in the chromatographic equipment and other related DSP equipment is preferred based on the risk assessments.

The latter portion of this White Paper focuses more on the technical and regulatory aspects of the integrated continuous DSP. Due to the significance of the chromatographic steps in the DSP, the equipment requirements and challenges for multi-column continuous chromatography,
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as well as their risk assessments were discussed. The design of the chromatographic skids with their piping, valve and pump was evaluated, in particular for the twin column design. Requirements for design and packing of chromatographic columns were reviewed. Answers to all open questions cannot be given in this White Paper; however, guidelines were provided how to overcome some of them in the GMP environment when designing a new integrated continuous DSP w/o MCC technology or transferring an existing batch process to an integrated continuous process. This integrated continuous DSP enables us to implement SU technology due to size reduction of the DSP equipment. It also allows modular design of a process train that can be easily multiplied during process scale-up and that provides the flexibility in multi-product facilities with different batch sizes (i.e. when producing personalized medicine, higher titre products, orphan drugs…). Therefore, fast turn-around time are not only important for CMOs but for all bio-pharmaceutical companies.

Time is of the essence in addition to the better utilization of the Protein A resin, reduced capital and operation costs, reduced risks and more robust processing; thus, the DSP will not remain the “bottleneck” in the manufacturing of biopharmaceuticals. Integrated continuous DSP in combination with the continuous upstream processing is becoming a manufacturing platform.
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Dr. Mihlbachler has worked for almost 20 years in area of process chromatography. Prior to joining LPT she was an Independent Consultant for the Clean Markets at LEWA-NIKKISO for more than two years. During this time, she supported the technical transfer of process chromatographic technology from Bayer Technology Services and consulted in customer projects. Dr. Mihlbachler worked at different levels Sr. Researcher in the pharmaceutical industry at BMS, Eli Lilly and Pfizer. She was involved in the development, scale-up and manufacturing of purification/separation processes for chiral and non-chiral compounds, peptides and proteins, in particular to implement continuous processes.

From 2011 to 2013, Dr. Mihlbachler taught undergraduate courses for chemical and biomedical students as a Sr. University Lecturer in the Department of Chemical, Biological and Pharmaceutical Engineering at New Jersey Institute of Technology. She also holds a Director position at the AIChE’s Separation Division, Programming Chair of the Area 2G BioSeparations and she is also a member of the Industrial Advisory Committee of the International Symposium on Preparative Chromatography, chairing workshops on "Preparative chromatography of pharmaceutical intermediate and API" at this annual symposium.
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About LEWA

LEWA provides advanced purification and fluid management systems and engineering services that are shaping a new age in Life Sciences manufacturing. Our broad expertise in process innovation and our open source software help our customers to deliver exceptional quality and cost effective engineered solutions for the purification and blending of critical fluids. We are aligned with LEWA GmbH, and Nikkiso, Corporation to leverage the global sales and service and fluid dynamic innovations of these multi-national leaders in fluid management and precision pumps. LEWA Process Technologies is the only company that combines deep expertise in fluid dynamics with proven pump technology to engineer advanced systems that move fluids with unmatched precision, reproducibility, flexibility and efficiency. Headquartered in Devens, MA, USA, LEWA Process Technologies is a unit of LEWA GmbH and its parent NIKKISO Co., Ltd.

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Of Note:
LEWA has licensed the ChromaCon™ AG technology for CaptureSMB™.

The Capture SMB process principle allows faster capture step processing, preserves protein integrity, increases economic use of Protein A resins and uses less space on the manufacturing floor. In addition, the commercial collaboration also includes the future development of novel continuous processing employing LEWA’s downstream suite of custom purification technologies and multi-unit control software expertise with certain ChromaCon technologies. This will allow the use of multiple process principles such as batch chromatography, sequential multi-column chromatography, Capture SMB, and MCSGP process principle confined to the same platform.

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