Simplifying Progress

# Process Intensification and Connected Processing For Robust, Cost Effective, and Fast Manufacturing of Monoclonal Antibodies

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## Introduction

In a fast-growing biopharmaceutical world, accelerated, flexible, and cost-effective manufacturing has become an inherent requirement for industries to cater to the demand of new therapeutics for complex diseases. This has made process intensification one of the key approaches for developing processes. Process intensification (PI) is a holistic framework to maximize the overall productivity of the unit operation(s), the manufacturing process and|or the facility output for biomanufacturing. PI enables faster drug development, increases the efficiency and productivity of manufacturing processes. Savings of time due to higher productivity can be translated into efficient utilisation of facilities or even smaller footprints to achieve target capacities. Implementation of different PI approaches involves change of consumables or equipment which can lead to considerable reduction in the facility footprint. More importantly PI potentially make the processes more cost effective and sustainable. Current work presents a proof of concept of how a batch process for mAbs purification can be converted into an intensified process and then to a connected process in a stepwise and strategic manner.

## 1. Strategic PI Approach

At Sartorius, significant emphasis is given to process intensification while working on developing new equipment, improving the existing equipment, or even while helping the customers build their processes with Sartorius equipment and consumables. Internally at Sartorius, we have defined 4 different levels of PI strategies as shown in Figure 1. Starting from a basic batch process (Level 0) to a continuous process (Level 3), time taken for the DSP to complete is reduced from 75 hours to <30 hours.

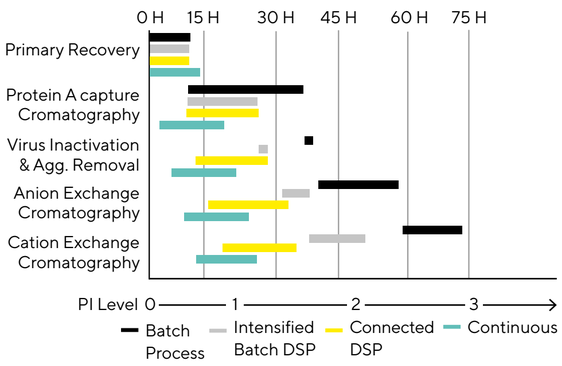


**Figure 1:** *Schematic Showing the Comparison of Different PI Approaches for DSP Chromatography Steps and Difference in Benefits of time that can be Achieved .*

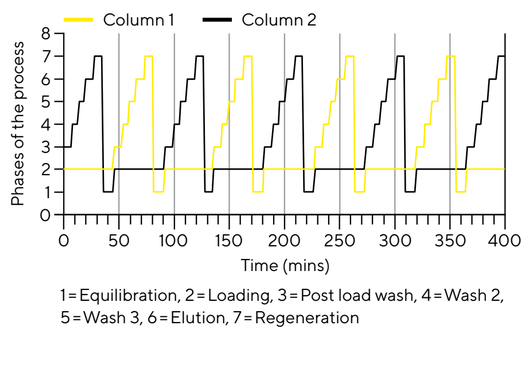


**Figure 2:** *Capture Step was Carried out in Twin Column Chromatography Mode for Making the Process Semi-Continuous (Credits: Enzene-H. Londhe, A. Bhori , Sartorius- B. Raut, B. Chauhan,G. Kumar, S. Lahiri, S. Jadhav)*

In this work, Level 0 (basic batch resin platform) is converted into level 1 (Intensified Platfrom 2) in a stepwise manner as shown in Figure 3C. Further the level 1 was then converted to a level 2 process (connected process) as shown in Figure 6B. The capture step was performed with protein A on a single column but then was further converted into a twin column chromatography (Figure 2) process to enable the conversion to a connected process. Choice of consumables was the key for polishing steps to make it possible to connect the processes without much adjustments|compromise on the productivity. For the first polishing step, a sensible switch was done from resins to single use Sartobind membrane to attain higher productivity (10–30× higher). The flowthrough process also allowed higher loading capacity for mAbs (>50×). Furthermore, CMM Hypercel was chosen as a resin for the 2nd polishing step as it gives considerably higher binding capacity at basic pH as opposed to normal cation exchange resins. This allows loading of flowthrough from the Sartobind Q directly on to CMM Hypercel without any intermediate holding step or buffer adjustment step. On the larger scale this eliminates the need of intermediate storing vessels|bags and saves the floor space.

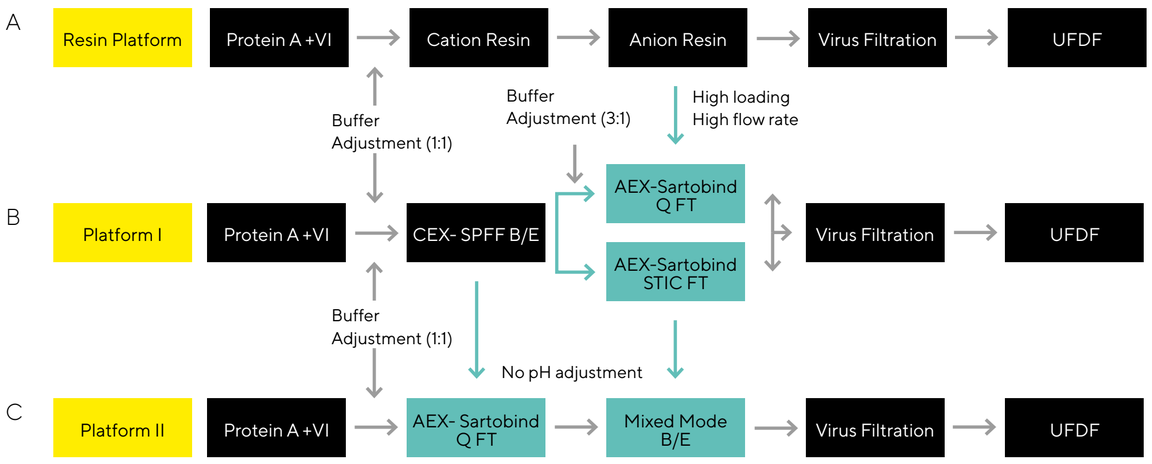


**Figure 3:** *Strategy of Platform Intensification Showing Elimination of Intermediate Steps A) Resin Based Platform (Level 0) B) Incorporation of Sartobind in Place of Resin for Increasing Productivity. C) Final Intensified Platform Showing Sartobind Q in 2nd and CMM Hypercel in 3rd Chrom Steps.*

## 2. Results: Platform Development – Sartobind

Sartobind Q was tested for both 2nd and 3rd polishing steps, where 5 kg/L and 8 kg/L loading was obtained, respectively. It was decided to place the Sartobind Q in the second step even with 5 kg/L capacity as the choice of orthogonal step on the 2nd polishing step becomes easier

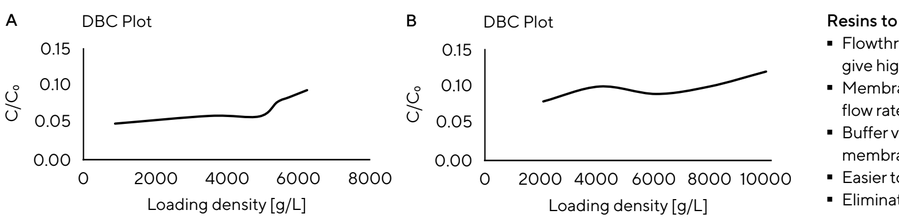


**Figure 4:** *Dynamic Binding Capacity of Sartobind Q at 2nd (5 kg/L) and 3rd (8 kg/L) Chromatography Steps. (Credits: Enzene-H. Londhe, A. Bhori , Sartorius- B. Raut, B. Chauhan, V. Patil, G. Kumar, S. Lahiri, S. Jadhav)*

## 3. Results: Platform Development – CMM Hypercel

Design of experiments using MODDE® (a Sartorius tool) was performed for buffer volume (BV) and elution volume (EV) optimization. It was found that the buffer consumption and elution volume is a function of pH (Higher pH -> lower elution volume). It was also found that recovery is a function of pH and conductivity. Sweet spot analysis gave the optimum window of operation. The optimization helped reduce the BV by 33% and EV by 35%. Validation experiments showed similar results as predicted by the model (Purity: >98%, Recovery: >91%, and HMW: <1%)

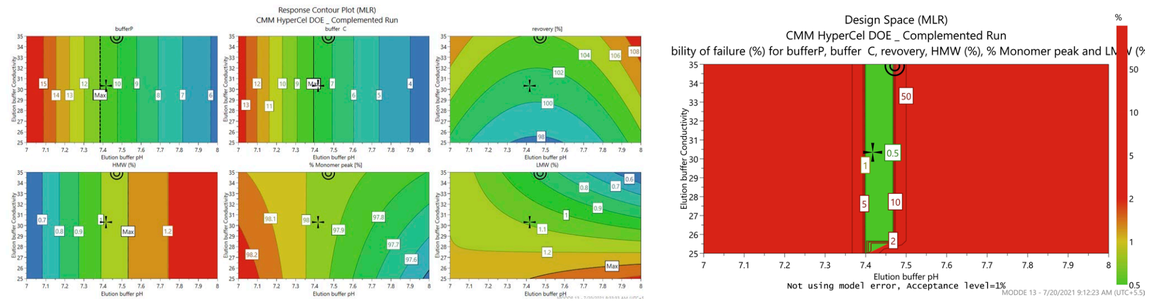


**Figure 5:** *DoE Results from MODDE® for Optimization of CMM Hypercel Step A) Contour Plots for Relational Analysis Between CPPs and CQAs B)Sweet Spot Analysis for Finalizing the Optimum Process Window. (Credits: Enzene-H. Londhe, A. Bhori , Sartorius- B. Raut, B. Chauhan, V. Patil, G. Kumar, S. Lahiri, S.Jadhav)*

## 4. Connected Processes

Platform 2 was further run in a connected format by running all the operations in parallel. While transition from a batch to connected process, loading capacity for both protein A and Sartobind was adjusted to meet the time requirements for CMM and making the connected process possible. Results showed consistency with the batch process. (Purity : >98%, Recovery >91%, and HMW: <1%). It was seen that the connected process took 17 hours to finish as compared to 29.2 hours for the platform 2 (Time savings of >40% for DSP).

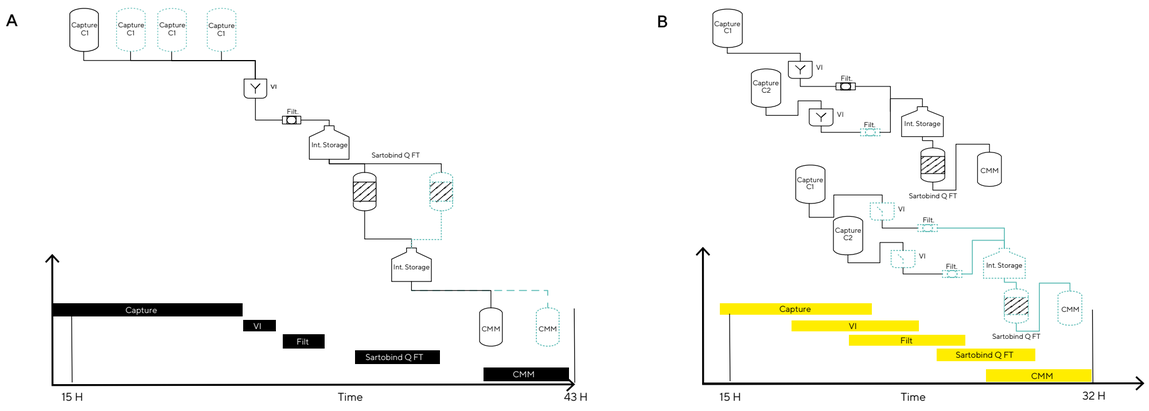


**Figure 6:** *Schematic for Comparison of Batch Process to Connected Process Demonstrating Savings of Time of Processing A) Platform 2 Batch Process B) Platform 2 Connected Process*

## 5. Cost Modelling

Cost modelling was performed in BioSolve for comparison of a conventional batch process (resin platform|PI level 0) to the connected process with platform 2 (PI level 2). Assumptions set for both the processes were same (4 × 2000 L fed batch bioreactor process with 6 g/L mAb titer, 70% facility utilization, 500 kg/year plant capacity, 71 batches per year). Only difference for the connected process was that the seed was prepared in (N–1) perfusion process to shorten the seed train. This is reflected in the media costs for the connected process. Despite this the CoGs for both the processes is almost same. Significant reduction can be seen in the buffer consumption, and DSP costs for the connected DSP. Due to time savings in the connected process, campaign length can be shortened by 8 weeks as compared to batch process as shown in Figure 7B and 7C. Connected process also proved more sustainable as it showed significant reduction in $CO^2$ consumption and electricity usage.

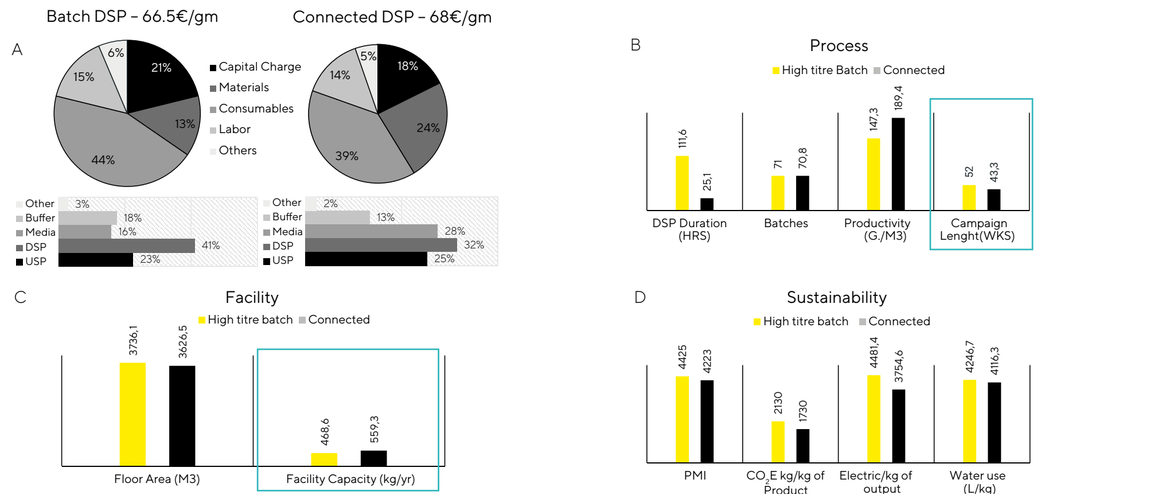


**Figure 7:** *Comparison of Batch and Connected Process Based on Cost Modelling Performed in Biosolve (A) Comparison of Costs from the Manufacturing Plant B) Process Parameter Comparison C) Facility Parameter Comparison D) Sustainability Related Comparison (Credits: Sartorius- G. Patel, G. Kumar, S. Jadhav)*

## 6. Conclusion

The work presented here serves as a blueprint to effectively intensify the mAb production processes to reduce the time of operation while sustaining the quality and consistency of the process. Strategic choice of consumables, efficient analytics, use of modelling tools for better process and cost optimization, and efficient decision making based on the process knowhow were found to be the key enablers. Cost modelling showed that the connected processes proved more cost effective, reduced facility footprint, enhanced effective resource utilization, and made the manufacturing more sustainable.