BIOTECH

Technical Regulatory Topic

USTR 3491

Quality by Design in Continuous Bioprocesses

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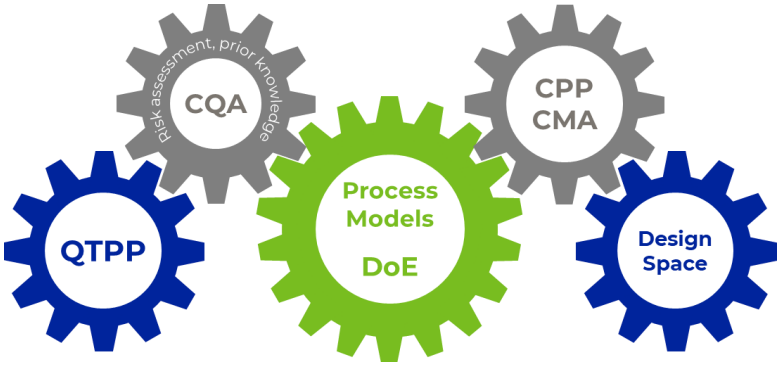
1 Quality by Design

For well over a decade, the Federal Drug Administration (FDA) has advocated for Quality by Design (QbD) in pharmaceutical processes, and for new approvals QbD approaches are requested by regulatory authorities. QbD follows the rationale of quality being achieved by design and planned into the process rather than confirmed through final testing. It is a science-based approach that bridges product knowledge and process knowledge to define the target quality attributes, critical quality attributes, and critical process parameters that impact drug quality. Evaluating the design space of process parameters enables creation of a process control strategy that assures product quality throughout the manufacture process as conceptually shown in **Figure 1**.

Figure 1

The principle of quality by design starts with defining the quality target product profile (QTPP) and deriving critical quality attributes thereof. Through process models and design of experiment testing, critical process parameters or critical material attributes and their design space can be evaluated. Manufacturing a drug within the characterized defined ranges therefore assures that the product quality specified in the QTPP is met.



QTPP	Quality Target Product Profile
CQA	Critical Quality Attribute
CPP	Critical Process Parameter
CMA	Critical Material Attribute
DoE	Design of Experiments

In continuous processing, there has been the perception that the cyclic and interconnected nature of the process comes with higher efforts in process characterization. However, both batch and continuous processes use the same process steps which greatly rely on the same fundamental parameters: there is typically no change in the chromatography chemistry since the same chromatography sorbent and buffers are used. As another example, the same filtration membrane material is implemented in nano- or microfiltration and thus, the material properties remain unchanged. Consequently, it would be possible to obtain characterization data from small-scale batch experiments and translate the results to a continuous process. Strategies and concepts to support this approach have been presented and bring savings in time, material, and cost in the process characterization stage.

According to the FDA, bridging Design of Experiments (DoE) data from batch to a continuous process requires a good process understanding and an assessment early-on in the process to assure that the continuous manufacturing principle does not impact product aspects [1]. For a monoclonal antibody (mAb) downstream process, it has been evaluated at what stages a direct translation from batch to continuous is possible, and where the continuous manufacturing principle impacts the product aspect and thus requires a verification run in continuous mode, see **Figure 2**.

2 QbD for Continuous Bioprocessing

Figure 2 shows that several critical process parameters (CPPs) of a continuous downstream platform are identical to the ones of batch processing. For others, processing differences between batch and continuous operation would still justify evaluating the parameter under batch conditions but would require a verification in continuous processing.

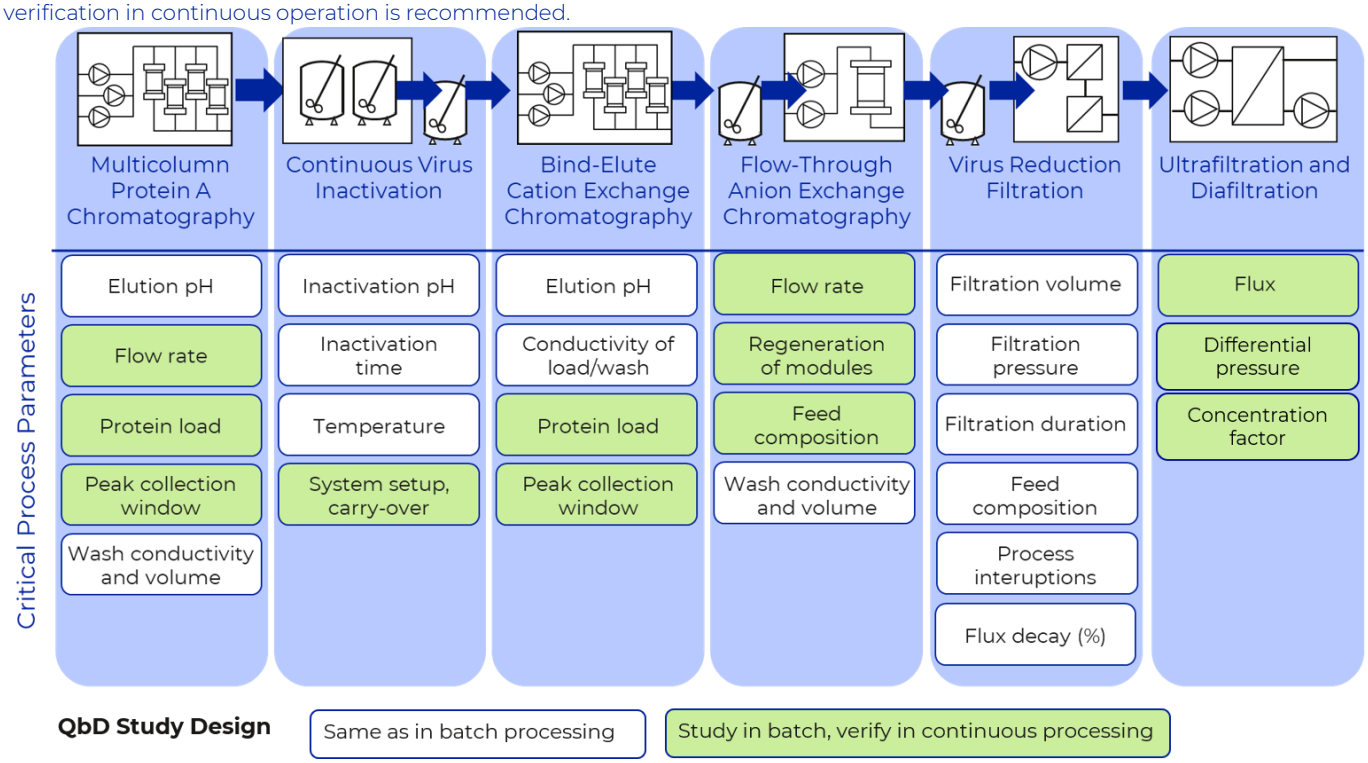
What needs to be considered, is that the connection of the individual unit operations can impact the process conditions and should therefore be included in the design space characterization. Due to the cyclic nature of continuous unit operations, the fluid composition can vary: this variation can originate from a perfusion upstream process with differences in product titer or impurity profile, and also from chromatography elutions where product is eluted in a peak rather than in a constant flow with uniform concentration. Another aspect of the cyclic nature is that the fluid flow from certain unit operations is not constant but rather intermittent, as is the case for bind-elute chromatography or for some techniques of low-pH virus inactivation. To harmonize fluid flow and fluid composition in between unit operations, a suitable surge container strategy is required. Surge containers can be placed in between unit operations to:

- Balance flow variations of different unit operations;
- Transform intermittent flow from previous unit operation to constant flow;
- Dampen or homogenize fluctuations in fluid composition.

A scientific rationale can be the basis of a surge container strategy and should be defined to evaluate the impact of feed composition and flow on the different unit operations within the QbD framework.

Figure 2

CPPs of typical downstream unit operations for mAb processing. Since the processing fundamentals for batch and continuous are similar, several of the CPPs can be validated in small scale batch studies. The remaining CPPs can be studied in batch but a verification in continuous operation is recommended.



3 QbD in Multicolumn Chromatography

For capture and bind-elute polishing chromatography, multicolumn chromatography processes are implemented in continuous operation. In such settings, a primary load column is overloaded, and break-through protein gets captured on a secondary load column. This is to achieve higher binding capacities at short contact times.
For protein load and load flow rate, operating ranges can be directly translatable from batch experiments: break-through data based on single-column experiments for evaluation of mass transfer kinetics and static binding capacity have been verified to be a solid basis for operating ranges in continuous operation [2, 3]. Impurity removal and yield have been described as equivalent when moving from single-column to multi-column chromatography, despite the higher binding capacity and lower contact times [2, 4].

This solid data basis published over the past years suggests performing a DoE characterization on one single column in batch mode. The protein load, load flow rate, and peak collection window can be verified in continuous operation to catch influences that come from the column overload or the different system architecture. The non-load sequence which includes wash, elution, and regeneration steps remains unchanged and critical parameters linked to these steps can therefore be assessed under batch conditions.

4 QbD in Continuous Virus Inactivation

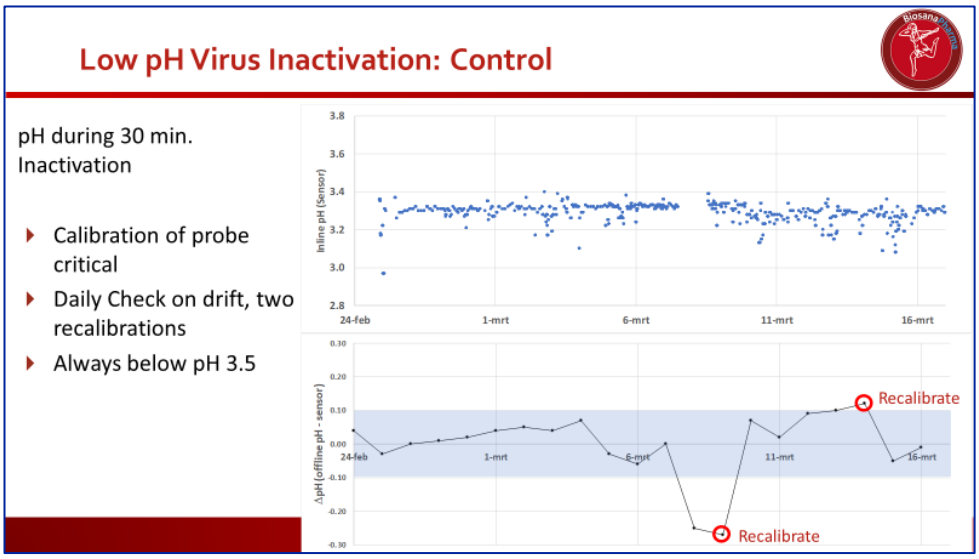
Continuous virus inactivation at Pall Corporation implements the Cadence® virus inactivation system: a single-use system with two alternating mixers that relies on repetitive batch inactivation. The mixers repeatedly fill, inactivate, and empty neutralized material. The process is scheduled for one mixer to steadily fill with eluted material from the Protein A chromatography, allowing time for the second mixer to move through the inactivation and neutralization steps before it is emptied. At that point, the emptied container starts collecting chromatography elutions which allows time for the already filled mixer to start the inactivation procedure.

The process sequence is identical to virus inactivation in batch, and it is expected that the critical process parameters: pH, time and temperature, and their design space are identical. As the inactivation is performed repetitively, the same mixers go through multiple rounds of inactivation. To mitigate the risks of carry-over from cycle to cycle and stop the product undergoing two inactivation cycles, adequate system design is critical. A virus inactivation system needs to be designed for 1) optimum mixing to assure harmonized inactivation conditions within the mixer, 2) minimal hold-up volume and optimized drainability to minimize carry-over of already inactivated material, and 3) product and buffer inlets to avoid splashing and a design that assures that not only product in the mixer, but also the feeding lines is inactivated. Such a design has shown to be an effective way to mitigate the risk of dead volume and carry-over [5].

An additional challenge in long-term virus inactivation is related to the pH probe accuracy: pH probes are known to drift over time and may require one or several recalibrations within the manufacture process. As the single-use system is maintained in a closed state throughout the operation, a two-point recalibration of the reusable pH probe is not an option. Alternatively, a design space and a narrower control space can be defined for the process. In regular sampling with an offline and calibrated pH probe, the accuracy of the inline pH sensor can be monitored. A one-point recalibration can be performed if the sensor drifts outside of the control space which allows the pH sensor to be kept within the design space at all times and pH drift can be addressed early on. An example for such a control strategy was presented by Maarten Pennings from BiosanaPharma at the ICB Conference in Brewster, MA in 2019, see Figure 3.

Figure 3.

An example of how the concept of control and design space is implemented in low-pH virus inactivation. The picture is printed with permission from Maarten Pennings and has been presented at ICB Conference in Brewster, MA in 2019. Courtesy of BiosanaPharma.



Concluding, for continuous virus inactivation the design space can be assessed through batch DoE given that the system is adequately designed for continuous or repetitive inactivation.

5 QbD in Continuous Filtration

In continuous filtration, the operating space typically shifts towards longer filtration times and lower flow rates that need to be reflected in the DoE. For sterile filtration, the FDA has issued various Question based Review (QbR) documents [6, 7] for different product types. All mentioned questions can be applied to batch and to continuous processing.

In virus filtration, batch operation typically runs with constant pressure over a defined time and defined volume and/or flux decay while a continuous viral filtration is operated under reduced constant flow. That shifts the operating space towards what is commonly regarded as higher risk conditions: low pressure, flow, and potential process interruptions caused by other unit operations. In batch operation, pressure, duration, flux decay, and volume throughput have been identified as critical process parameters [8]. For continuous applications, the low flow, extended filtration times, and possible process interruptions must be considered in addition as part of the QbD approach [9]. Thereby, prior knowledge is available that can support identifying the design space for example related to virus filters specifically designed for continuous applications such as the Pegasus™ Prime virus filters (Pall Corporation) [9].

6 References

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