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Technical Regulatory Topic

Process Characterization Approach for Continuous Downstream Bioprocessing

Document Number:	USTR 3640
Revision Number:	2.1
Date:	March 14, 2022
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Contents

1 Introduction

Continuous downstream processing systems are specially developed to deliver a high specific productivity to enhance manufacturing efficiency. The immediate consequence of this is that even at laboratory scale, these technologies exhibit quite significant throughputs and hence process characterization may consume significant amounts of material.

Another aspect of continuous downstream processing that sets it apart from traditional (batch) downstream processing is that it may take some time to reach steady state and hence, experimentation on such systems – even at laboratory scale – during process development may be a time-consuming exercise.

Nowadays, most companies use the philosophy of Quality by Design (QbD) in characterizing their manufacturing process and defining an adequate control strategy. Considering the high specific productivities and the time-consuming experimentation, a smart approach towards process characterization is essential.

Once the desired operating conditions have been defined, either in terms of a design space, or in terms of proven acceptable ranges (PAR) and normal operating ranges (NOR), this has to be translated into a control strategy for the automated continuous downstream processing platform.

2 Process Characterization

Continuous downstream processing technologies essentially rely on the same fundamentals as the equivalent batch downstream processing steps. Continuous downstream processing does not require any different materials, filters, adsorbents and/or buffer compositions compared to traditional batch process steps. On top of that, the purification mechanisms rely on the same fundamentals such as mass transfer kinetics, fluid dynamics, thermodynamics, etc.

The consequence therefore is that the vast majority of design conditions can be defined in batch processes. Good examples of this have been published for various chromatography steps in a continuous downstream processing platform [1 - 5].

Following this rationale, a Quality by Design review of a fully integrated downstream processing platform has been reviewed to explore to what extent the proven acceptable ranges and normal operating ranges for the critical process parameters (CPPs) can be identified using batch processes[6]. This study suggested that nearly all CPPs can be defined using small-scale batch experiments following traditional Design of Experiments (DoE) strategies. The translation to continuous bioprocessing conditions is straightforward and has been proven many times.

3 Control Strategy

In order to run multiple unit operations in a connected way, some adequate process control is required. This also provides an opportunity for implementing the control strategy that connects from the actual operations to the results process characterization (or QbD) results.

With this, adequate process characterization translates into a process control strategy with statistical or model-based control algorithms. This will result in a more consistent process performance and hence in more consistent product quality.

4 Conclusion

Process characterization and Quality by Design for continuous downstream processing rely on the same fundamentals as batch processing and hence the proven acceptable ranges (PAR) and normal operating ranges (NOR) for the critical process parameters (CPPs) can be defined based on miniature batch experiments. This reduces the complexity of process development for continuous downstream processes dramatically.

The results can be translated into advanced control strategies, allowing the continuous downstream processing platform to operate under more consistent conditions, generating more consistent product quality.

5 Reference

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