

Expert Panel – Q&A

			
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Questions & Answers from the webinar,

“Pioneering an Approach to Integrated Continuous Bio-manufacturing”

Click on any question below to be taken to the answer.

- Q. How long can the filter be used in ATF process before it has to be changed/cleaned?
- Q. How do you adjust cycle time (load and all the steps) when the concentration in perfusion is changing?
- Q. What are the optimal column criteria when implementing continuous processing for proteins other than monoclonal antibodies, *i.e.* methods that do not use Protein A resin?
- Q. How we can maintain required time for viral inactivation (low pH)?
- Q. When utilizing a continuous process system for GMP manufacturing, how would you address viral clearance studies in a scaled down model. Additionally have you worked with any of the regulatory bodies on or around viral clearance modeling and proof of concept?
- Q. Where do you think Continuous Biopharm Manufacturing will first take hold at a commercial level? What combination of regulatory philosophy, economic conditions, and leadership vision is required and where might it exist?
- Q. What about productivity increase for a chromatography step in which residence time does not play such a huge role like for Protein A?
- Q. Did you experience fouling of the filters at perfusion?
- Q. Are you aware of any perfusion system that can be used for < 1L working volume in bioreactor
- Q. What type of technical issues did you have in linking continuous systems? (e.g. What if there is a hold up?)
- Q. Do you think Protein A resin that offer shaper breakthrough will be advantageous in CaptureSMB system?
- Q. Did you evaluate data on bioburden?
- Q. What is the efficiency difference between 2c-pcc and 3c-pcc or 4c-pcc?
- Q. What was the bed height used in the columns?
- Q. How long would it take to set up a pilot multi—column capture system?
- Q. Can I just run 12 or 24 hours instead of weeks?

Q. How long can the filter be used in ATF process before it has to be changed/cleaned?

A. Filter capacity is process dependent and is characterized during your Process Development. Most XCell ATF operations run for 20-30 days without the need for filter change out. Please contact Repligen for additional information. (answered by GebSKI)

Q. How do you adjust cycle time (load and all the steps) when the concentration in perfusion is changing?

A. Either you design the process with safety margin covering the range of titer that you expect or - better - you use dynamic process control based on UV. The Contichrom CUBE has a software tool, AutoMAB that does dynamic process control based on the UV signal. (answered by Müller-Späth)

Q. What are the optimal column criteria when implementing continuous processing for proteins other than monoclonal antibodies, *i.e.* methods that do not use Protein A resin?

A. Continuous Capture is most attractive if you have LOW utilization, *i.e.* a shallow breakthrough curve, of an EXPENSIVE affinity material. For non-affinity methods, MCSGP is an option. (answered by Müller-Späth and Muhlbachler)

Q. How we can maintain required time for viral inactivation (low pH)?

A. The eluate is kept at low pH for the required time as in batch chromatography. You may need to use two alternating VI tanks or an extended spiral flow path. (answered by Müller-Späth and Muhlbachler)

Q. When utilizing a continuous process system for GMP manufacturing, how would you address viral clearance studies in a scaled down model. Additionally have you worked with any of the regulatory bodies on or around viral clearance modeling and proof of concept?

A. You can use a Contichrom lab scale system for scale down studies. We have developed a concept with 2 different spike houses. Contact ChromaCon for additional information. (answered by Müller-Späth)

Q. Where do you think Continuous Biopharm Manufacturing will first take hold at a commercial level? What combination of regulatory philosophy, economic conditions, and leadership vision is required and where might it exist?

A. Continuous Biopharm manufacturing (perfusion) is already being used in a number of commercial biopharm processes. In downstream processing, continuous affinity capture will be applied first where there is a need to increase productivity and reduce cost. FDA has publically stated that it supports continuous biomanufacturing. (answered by Müller-Späth and Muhlbachler)

Q. What about productivity increase for a chromatography step in which residence time does not play such a huge role like for Protein A?

A. During continuous operation, the capture process is less dependent on residence time and loading can be executed more quickly as compared to batch operation. Breakthroughs are captured on the second column. Regardless of residence time, productivity improvements are still realized during continuous operation. (answered by Muhlbachler)

Q. Did you experience fouling of the filters at perfusion?

A. In our system we had fouling with TFF but not with ATF. In general, I do not believe that ATF is prone to fouling but may foul under more extreme conditions when compared to TFF. (answered by Morbidelli)

Q. Was antifoam used in any of the runs that data was shown for here? If so, did you experience any problems with antifoam and ATF fouling?

Repligen has demonstrated that anti-foam does not contribute to hollow fiber filter fouling in ATF applications. Fouling is most correlated with LDH which is an indicator of cell viability. (answered by Gebski)

Q. Are you aware of any perfusion system that can be used for < 1L working volume in bioreactor

A. The XCell ATF 2 system could be considered for perfusion at this scale, but bridging studies would be required to understand appropriate scale-up as the ATF 2 filter area is oversized for this specified working volume. (answered by Gebski)

Q. What type of technical issues did you have in linking continuous systems? (e.g. What if there is a hold up?)

A. The Contichrom systems can communicate with other Contichrom systems so if one pauses, the other one will pause too. To get even more safety you can add small surge tanks. In addition, any hold up would facilitate synchronization. In general, dilution in-line requires attention. But, at least at our scale there is nothing that modest engineering cannot solve. (answered by Müller-Späth and Morbidelli)

Q. Do you think Protein A resin that offer sharper breakthrough will be advantageous in CaptureSMB system?

A. Generally, sharper breakthrough curves will be more advantages. For the continuous operation, sharper breakthrough may allow for shorter cycle times. (answered by Mihlbachler)

Q. Did you evaluate data on bioburden?

A. No. (answered by Morbidelli)

Q. What is the efficiency difference between 2c-pcc and 3c-pcc or 4c-pcc?

A. The processes have similar performances as shown during the presentation, however the 2 column process and system are less complex. For higher titers, the 2C-PCC is more favorable because it has an independent interconnected loading phase that can be shortened as the titer increases. (answered by Mihlbachler and Müller-Späth)

Reference: DOI: 10.1002/biot.201500481, Baur et al. Comparison of batch and continuous multi-column protein A capture processes by optimal design. 2016. Biotechnology Journal

Q. My plant will only use single use equipment – is the perfusion cell culture device available in a single use format?

A. Yes. (answered by Gebski)

Q. Is the multi-column instrument that was used in the ETH study capable of both capture and polish chromatography?

A. Yes. (answered by Müller-Späth)

Q. What was the bed height used in the columns?

A. While multiple column bed heights were used at various times during the study, the standard height is 10 cm. (answered by Morbidelli and Müller-Späth)

Q. How long would it take to set up a pilot multi-column capture system?

A. Generally, as long as all utilities are available, an EcoPrime Twin 100 is up and running in a day. (answered by Mihlbachler)

Q. Can I just run 12 or 24 hours instead of weeks?

A. Yes, you can use the 2C-PCC capture in conjunction with a fed-batch fermenter and run it instead of batch chromatography (answered by Müller-Späth)

More questions? Ask us! ecoprime@lewapt.com

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