BIOTECH

Technical Regulatory Topic

Equipment Design for Continuous Bioprocessing

Document Number:	USTR3445
Revision Number:	1.0
Date:	24-Mar-21
Author:	Britta Manser

Fully closed systems are key for successful and bioburden-controlled implementation of continuous bioprocessing platforms. Full containment or closure of systems can be achieved through adopting single-use systems, which provide flexibility and facilitate sterile connections. However, they can also introduce risks linked to equipment robustness or extractables and leachables control.

With regards to equipment durability, an exchange of some consumables might be necessary during the process. Chromatography columns can decline in separation performance, dead end filters can create a high back pressure due to blocking or fouling, or parts of the single-use fluid pathway can reach the end of their validated lifetime. There may also be a higher risk of sensor failures or general outtakes in comparison to batch processes because of the longer processing times. Therefore, special effort should be put in to develop strategies to:

a) Minimize the probability of equipment failures.

b) Detect failures or abnormal equipment performance.

c) Enable an easy and safe exchange of the affected components[1].

A simple concept to allow the exchange of components without process interruptions is implementing redundant devices in a switch-in/-out setting. Preconfigured equipment assemblies can be used to replace faulty equipment; they can be connected to the process stream by using sterile connectors and disconnectors or by simple tube welding. Such a concept applies to a variety of process steps, including:

a) Filtration devices.

b) Chromatography columns.

c) Single-pass tangential flow filtration (SP-TFF) modules.

With the appropriate auxiliary equipment, a parallel switch-in/-out assembly can enable online sanitization, conditioning, or integrity testing.

The extended operating times can also cause potential difficulties for sensors. Sensor readings can shift or drift over time. Glass surfaces from ultraviolet (UV) sensors can foul due to proteins or chemical components from the product stream, or pH electrodes can move out of calibration[2,3,4]. In continuous processes with strict bioburden control, exchanging or removing a sensor for calibration may be impossible. Instead, means to detect the shift, verify readings and apply corrective actions in closed systems are required. A verification of a sensor reading is, for example, possible through an independent monitoring system with a separate sensor for feedback control. This secondary sensor monitors and verifies proper operation of the system independently and detects potential drift early[5].

Another method is to pass process buffers checked with calibrated off-line equipment through the in-line sensors at certain time intervals to verify the sensor readings and allow for one-point recalibration if needed.

It is essential to characterize leachables and understand possible interactions between a drug product and leachables when performing a patient safety toxicology risk assessment. According to the FDA, qualification of equipment is expected to be performed both on separate unit operations and the integrated system to demonstrate equipment suitability for its intended purpose[1]. The qualification protocols should thereby reflect the operating conditions such as flow rates, pressures, and contact time of the product. Industry guidance on risk-based extractables and leachables profiling is provided in the BPOG protocol, which uses a quality by design (QbD) approach to identify compounds[6]. The equipment qualification and risk assessment can be simplified by adopting a QbD approach based on a combination of well characterized materials and prior knowledge on the potential origin of the leachables and the process capability of clearing them.

It is expected that a continuous platform provides a better understanding of where leachables arise and get removed. Assessments of the impact of extended processing times of various continuous bioprocessing steps on the leachables profile suggest only little risk[7,8]. The high throughput of liquid in continuous operation has even indicated to lower the risk of equipment related leachables compared to batch operation[8]. To establish a leachables and clearance profile, the simulation runs for continuous platforms could be performed as described by Song *et al*[7].

References

1. FDA. *Quality Considerations for Continuous Manufacturing*. U.S. Food & Drug Administration Website. [accessed 22 March 2021] (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/quality-considerations-continuous-manufacturing).

2. Undey, C. *PAT applied in biopharmaceutical process development and manufacturing : an enabling tool for quality-by-design*. Boca Raton, Fla.: CRC Press, 2012.

3. Eibl, R., Eibl, D. *Single-use technology in biopharmaceutical manufacture*. Oxford: Wiley-Blackwell, 2011.

4. Teixeira, A. P., Oliveira, R., Alves, P. M., Carrondo, M. J. T. *Advances in on-line monitoring and control of mammalian cell cultures: Supporting the PAT initiative*. Biotechnology Advances 2009; 27(6):726-732. DOI: 10.1016/j.biotechadv.2009.05.003.

5. Bull, K. *A Simple Solution for Sensor Drift*. PharmTech.com. [accessed 22 March 2021] (https://www.pharmtech.com/view/simple-solution-sensor-drift).

6. BioPhorum Operations Group (BPOG). *Best Practices Guide for Evaluating Leachables Risk From Polymeric Single-Use Systems Used in Biopharmaceutical Manufacturing*. BioPhorum.com. [accessed 22 March 2021] (https://www.biophorum.com/download/best-practices-guide-for-evaluating-leachables-risk-from-polymeric-single-use-systems/).

7. Song, B., Liu, L., Ren, J., Gjoka, X. "*Extractables and Leachables in a Continuous Processing System*" (Poster Content, [accessed 22 March 2021]. https://www.pall.co.uk/uk/en/biotech/posters-presentations/extractables-leachables-continuous-bioprocessing.html

8. Hauck, A. *The Prediction of extractables and leachables and the fate of leachables in intensified and/or continuous biopharmaceutical manufacturing*. Wädenswil. [accessed 22 March 2021].

PALL CORPORATION

Visit us on the Web at www.pall.com/biotech
Contact us at www.pall.com/contact

Corporate Headquarters
Port Washington, NY, USA
+1-800-717-7255 toll free (USA)
+1-516-484-5400 phone

European Headquarters
Fribourg, Switzerland
+41 (0)26 350 53 00 phone

Asia-Pacific Headquarters
Singapore
+65 6389 6500 phone

USTR3445 / March 2021