

Biopharmaceutical quality optimisation

Stuart Tindal and Nick Hutchinson of **Sartorius Stedim Biotech** discuss some of the challenges the industry faces in implementing continuous bioprocesses and how they can be addressed with process analytical technologies.

Continuous bioprocessing is attracting intense focus within the industry. It has the potential to increase efficiency for manufacturing biopharmaceuticals, while simultaneously delivering consistent product, with the desired critical quality attributes. The extent to which firms are implementing continuous processing varies. The industry has been operating perfusion cell cultures since its inception, even though fed-batch culture recently became the dominant format. Biomanufacturers have seen continuous downstream processing as a powerful antidote to rising purification costs. Leaders in the field have described the integration of continuous upstream and downstream processing as necessary, in order to realise the technique's full potential.

Technological obstacles

A number of barriers stand in the way of a conservative industry. Some of the challenges companies face are technological. Sanofi Genzyme, for example, has cited having the appropriate process analytical tools (PAT) as a key requirement to promote the adoption of continuous processing. PAT technologies include real-time process analysers such as univariate sensors and multivariate analytics, process control and multivariate tools that are necessary to maintain continuous bioprocesses within a known operational state over the whole process stream.

Upstream variation

In continuous bioprocessing, achieving this operational state is important so that downstream operations receive a consistent feed stream from those further upstream. Variation in the amount of host cell protein and product generated by cells in a perfusion bioreactor could lead to the overloading of downstream chromatography operations and a detrimental impact on intermediate product quality. Engineers can use a feed-forward control approach to increase the throughput of downstream operations according to increases in upstream protein production. However, controlling the process by this method alone is not possible once the upper limit of downstream throughput reaches maximum capacity.

The alternative approach is to minimise variations in the output of the perfusion culture. Cell culture scientists should monitor the viable biomass in the bioreactor. The BioPAT ViaMass is one such sensor capable of doing this in a single-use vessel. Continuous bioprocess practitioners can maintain the viable biomass concentration within a steady state, by integrating the BioPAT ViaMass with the perfusion and bleed pumps, via the bioreactor



The BioPAT ViaMass sensor.

DCU. By exercising control over the biomass concentration and bioreactor output, more minor adjustments are all that should be required in the throughput capacity of the downstream process.

BioPAT-SIMCA-online

The manufacturer's ability to sustain control over a perfusion bioreactor for prolonged periods can be increased, using real-time multivariate statistical process control. Software tools like BioPAT SIMCA-online allow operators to visualise a multitude of bioreactor data that might include pH, metabolites, temperature, gravimetrics and viable biomass. Operators can easily compare the batch trajectory to that of the "golden batch", and detect deviations that could impact product quality at an early stage. This provides operators with a chance to use the software to diagnose system faults and make an appropriate intervention. In the future, multivariate analytical tools will be essential in allowing the real-time release of biopharmaceuticals from continuous bioprocesses.

Bioprocess evolution

Continuous upstream and downstream processing continues to evolve. The technology platform companies install must be sufficiently adaptable to incorporate future innovations. Biomanufacturers should consider the management of interfaces between the various elements necessary for the advanced real-time control of continuous processes. All of these interfaces need to be tested and qualified to ensure they will function correctly. Sartorius Stedim Biotech manages the life cycle of its upstream processing platform on behalf of its customers to ensure that new developments can be integrated as the field progresses. ■

Further information

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