BIOTECH

Technical Regulatory Topic

USTR 3456

Quality and Regulatory Considerations for Continuous Bioprocessing Overview

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1 Intensified and Continuous Bioprocessing

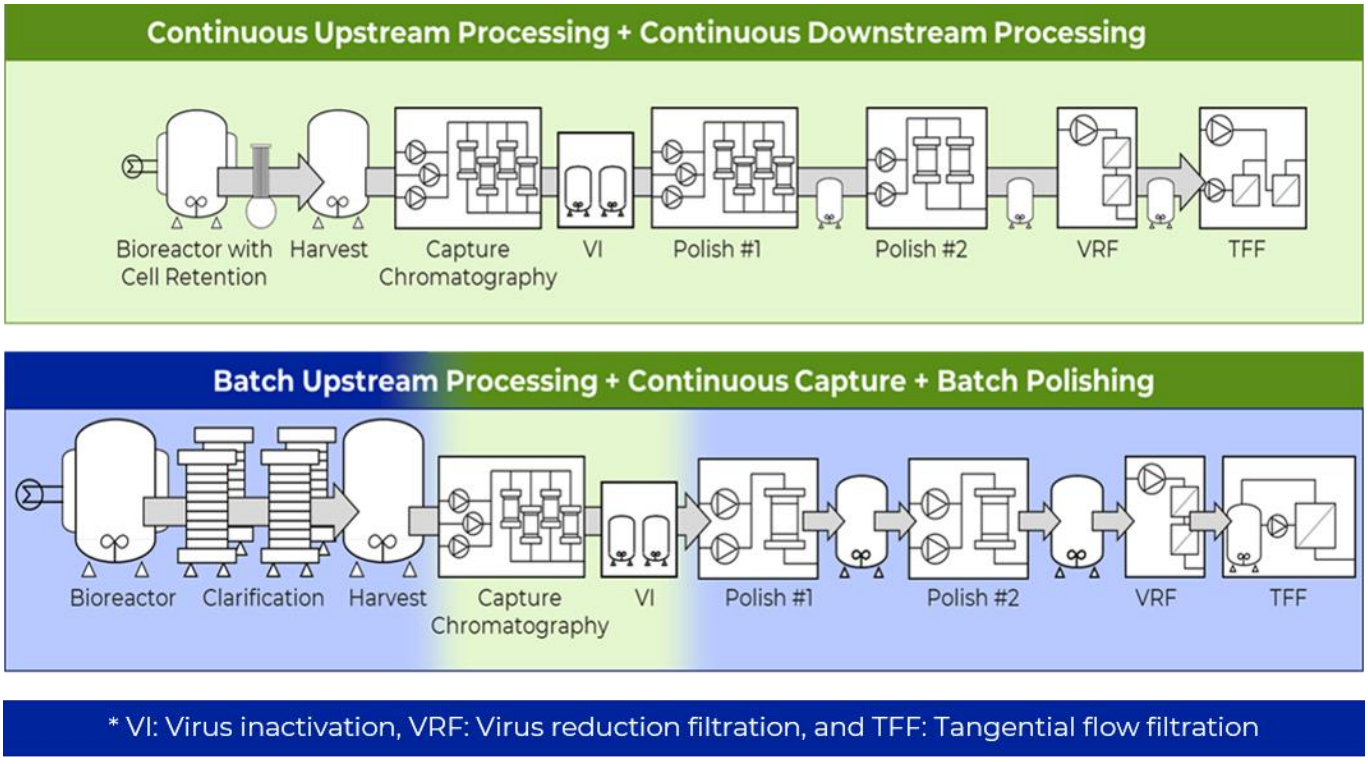
For over 30 years biopharmaceutical manufacturers have successfully produced valuable therapies such as antibodies or recombinant proteins using batch or fed-batch manufacturing concepts. Over the past decade, cell lines for expressing the proteins of interest have been advanced and have increased the titer of the target protein in upstream processing significantly. To match these increases in productivity upstream, advances in downstream processing have been developed which have led to an optimization of auxiliary materials such as chromatography adsorbents with higher binding capacity, and high-flux membranes. However, these efforts downstream have not been significant enough to reach the productivity needed. An additional technology driver comes from the increasing number of biosimilars on the market, and the availability of multiple drugs targeting the same indication. These have shifted the industry needs towards smaller and more flexible multi-product facilities.

To meet the needs for intensified and flexible processing, single-use technologies have become state-of-the-art and several manufacturers have explored means of process intensification through continuous bioprocessing. Continuous manufacturing steps when applied to both upstream and downstream processing, and when connected, have enabled the fully integrated manufacture of drug substances. Instead of processing drug substances in one unit operation after another and keeping the product in hold containers between steps, continuous processing operates through an interconnected cascade of unit operations. The operations are connected and operate simultaneously whilst product runs seamlessly from one step to another.

Through this form of step integration, unit operations tend to be smaller as flow rates decrease, which reduces the facility footprint and the risk of scale-up. The platform approach using mostly single-use equipment provides the agility and flexibility to respond to market dynamics rapidly and minimizes the risk of product shortage. The highly automated and controlled platform provides opportunities for advanced data management to improve product quality, and faster product release [1]. Continuous or integrated technologies bring the potential to react to manufacturing variability, provide flexibility, and increase productivity whilst reducing manufacturing costs [2, 3].

Figure 1.

Conceptual process of a fully integrated end-to-end continuous process (top), and a hybrid manufacturing platform using both technologies from batch and continuous processing (bottom).



A few companies have started implementing fully integrated end-to-end continuous platforms such as Bayer♦, Merck♦ [4, 5], BiosanaPharma [6] and Genzyme♦ [7]. The first of these processes has led to a successful clinical phase I study using a biosimilar monoclonal antibody (mAb) (omalizumab) in a fully integrated continuous downstream process [8]. Hybrid processing approaches are investigated by a larger industry field. Hybrid describes a combination of technologies from today's well-known batch processing with more novel techniques for process intensification. The work horse for process intensification or continuous processing is multicolumn chromatography. It therefore doesn't surprise that most hybrid downstream platforms include a multicolumn chromatography step. Different types of such hybrid platforms have been published for monoclonal antibodies by a variety of end-users including, for example, Sanofi♦ [9].

2 Position of Regulatory Authorities

Regulatory authorities have recognized and repeatedly articulated the advantages of continuous manufacture, in a slideshow presented by the U.S Food and Drug Administration (USFDA) [1], they identified the advantages of continuous manufacture as:

- Efficient use of space, resulting in lower costs for companies, increased safety, and the potential for modular units to be used;
- Integrated processing with less steps, meaning greater efficiency in manufacturing and simplified scale-up;
- Operational flexibility, giving production the capability to adapt to demand, emergencies etc;
- It provides benefits to both patients and industry.

The USFDA has identified continuous manufacture as an emerging technology, which enables the pharmaceutical industry to engage with the Emerging Technologies Team (ETT) to seek early guidance on the application of continuous manufacturing in pharmaceutical production. Similarly, the European Medical Agency (EMA) recognizes the benefits of continuous manufacturing. The EMA has launched the Innovation Task Force (ITF) to promote and support innovations in therapeutic and technological areas, including continuous manufacturing. These programs allow end user quality assessment teams to engage with the authorities early on in submission reviews.

3 Regulatory and Quality Considerations for Continuous Processes

The main responsibility of regulatory authorities revolves around public health and thus assuring that medicinal products are both safe and effective. The regulatory expectations involve different patient safety aspects such as bioburden, virus, and impurity control. Especially in these areas some uncertainty has been present in the past years: how to meet the regulatory expectations in continuous processing?

While at first it may seem that continuous processing could require novel regulatory concepts, the difference between continuous and batch processes is much smaller than expected. From a regulatory perspective, continuous processing is not inherently different from batch processing. Both processes rely on the same fundamental concepts and operations. Multicolumn chromatography, for example, still utilizes the same chromatography resin and identical buffer compositions, and a filtration step still employs the same filter membranes and materials. As a result, many concepts for patient safety, quality assurance, and process consistency can be based on the current best practices applied to batch processing. An additional assessment is needed where continuous processing can introduce additional risks that originate from, for example, interconnection of unit operations, the cyclic nature of operation, or extended operating times. An official guideline that covers these unique aspects of continuous bioprocessing is not available to date but possible approaches and strategies have been shared by Pall Corporation [10].

From proactive interactions with regulatory bodies, Pall Corporation has taken the opportunity of presenting developed strategies to the authorities and receiving their feedback. These insights together with lessons learned and best practices from early manufacturers of continuous drug substances have been summarized in different documents available on this page.

The main regulatory questions relate to the following topics:

- Batch Definition and Process Traceability (USTR 3490 Batch Definition and Traceability in Continuous Bioprocessing)
- Quality by Design (USTR 3491 Quality by Design in Continuous Bioprocesses)
- Process Control and Automation (USTR 3492 Automation and Control in Continuous Bioprocesses)
- Equipment Design (USTR 3445 Equipment Design for Continuous Bioprocessing)
- Virus and Bioburden Control

All above listed documents can be located on the SME Corner of the Accelerator℠ Documentation Center.

4 Conclusion

Continuous or integrated bioprocessing has been recognized as a powerful tool to intensify bioprocesses and meet patients' need for fast, widely available, safe, and effective biopharmaceuticals. When it comes to current good manufacturing practice (cGMP) implementation of continuous concepts there are regulatory questions and uncertainties. However, the regulatory challenges existing today are currently being addressed: strategies and solutions to the most prominent questions have been developed and first experiences have been undertaken by the industry. Regulatory and quality aspects of continuous processing are manageable and remaining hurdles are being overcome through close collaboration between manufacturers, suppliers, and regulatory authorities.

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