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Ganapathy Subramanian

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Innovative Technologies and Methods

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Part One

Overview of State-of-the-Art Technologies and Challenges

1

Continuous Bioprocess Development: Methods for Control and Characterization of the Biological System

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1.1 Proposed Advantages of Continuous Bioprocessing

1.1.1 Introduction

The change from batch to continuous processing has led to the intensification of processes in a number of industries, including steel casting, automobile and other devices, petrochemicals, food, and pharmaceuticals. Advantages include, aside from a significant increase in volumetric productivity, reduced equipment size, steady-state operation, low cycle times, streamed process flows, and reduced capital cost.

In bioengineering, continuous processing is the standard in wastewater treatment, composting, and some bioenergy processes such as biogas and bioethanol fermentations. In contrast, most production processes run as batch type operations or more specifically fed-batch processes, which is the major production technology today.

Konstantinov and Cooney provide a definition of a continuous process as "A unit operation is continuous if it is capable of processing a continuous flow input for prolonged periods of time. A continuous unit operation has minimal internal hold volume. The output can be continuous or discretized in small packets produced in a cyclic manner." [1]. They also differentiate between full continuous processes with no or minimal hold volume in the process line or hybrid processes that contain both batch and continuous process operations.

Obviously, the push in continuous manufacturing technologies was initiated by the BioPAT initiative of the Food and Drug Administration (FDA) in 2002 and the published guidance to PAT in 2004 [2], which initially aimed at a better understanding of the connections between product quality and process conditions. This lead to the need to develop quality by design (QbD), that is, the implementation of process analytical tools over the whole developmental pipeline from early product screening over the process development in the laboratory scale and during scale up. The needs for a better understanding of the impact of process parameters on the critical quality attributes (CQA) of the respective product also increased the interest in the development and implementation of novel sensors and analytical

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tools. As a consequence, this better understanding of processes resulted in further process intensification and provided the instrumental basis to approach challenges in relation to continuous operation.

Aside the FDA initiative, there are several drivers for the increasing interest in continuous processing, not only in the pharmaceutical industry but also in the industrial (white) biotech industry. On one side, we see an increasing demand and thus also increasing production scale for industrial bioproducts (enzymes, small molecules, and bioenergy market) with a need for reduced costs for the products and increased competition. Considering that production scales are steadily growing and that a scale reduction close to factor 10 would be possible by continuous processing, plant sizes and the efficiency of bioprocesses could be increased significantly. On the other side, the opportunity of the selection of new biocatalysts and its implementation in the chemical synthesis for integrated chemoenzymatic processes (i.e., processes which combine chemical and enzymatic reactions) have to be competitive with the existing chemical processes and need to be integrated into the chemical production schemes. Here, continuous processes offer clear advantages.

In biopharma for recombinant proteins, antibodies, highly complex proteins, recombinant enzymes and blood factors, the efficiency of the cell factories, and production systems have dramatically increased during the last decade. Opportunities for high cell density processes with a higher volumetric product yield and quality, as well as the changing situation in view of the intellectual properties by the termination of many patents for important drugs with novel commercial opportunities for new biosimilars and biobetters are a strong driver in increasing the competition especially from emerging markets. In parallel, there is an increasing demand for establishing local production sites for defined regional markets, rather than having single production sites. Strict cost calculations as a developmental driver demand for smaller and effective, but also flexible production plants. This directs interest to evaluate continuous bioprocessing opportunities to minimize investments for production facilities, and thinking about parallelization rather than larger scales. Parallelization would also be an advantage in processes with longer plant cycle times [3] as, for example, cell culture-based products. A nice example that shows the opportunities in significantly decreasing operational and capital expenses by changing from conventional bioprocessing to continuous bioprocessing in the case of production on monoclonal antibodies (mAB) and other non-mAB processes is shown by Walther *et al.* [4].

However, despite the obvious opportunities of continuous processes there are many challenges to solve, mainly the demand for fast realization and risk minimization. Currently, it seems to be easier to transfer a batch process into production than to start a new, longer, and more expensive development of a continuous process even though it is expected to be more efficient.

These scenarios show that there is a big need in strategic methods concerning the development of continuous process strategies for either new products or to derive a continuous process from existing batch type processes. As early-phase product development can practically be only performed as batch processes, a key question in product development is how we can transfer a batch strategy to a continuous operation in a large process.