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Perspectives on integrated continuous bioprocessing — opportunities and challenges

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Biopharmaceuticals are currently produced almost entirely using batch operations. Integrated continuous processes have the potential to revolutionize bioprocessing, leading to significant reductions in manufacturing costs and facility size while improving product quality through enhanced uniformity in the microenvironment. This paper examines the potential opportunities and challenges in implementing continuous processes for the production of high value biological products. Although regulatory agencies seem highly open to continuous processing, there are significant technical and practical issues that must be addressed to move the industry in this direction, including the development of effective alternatives to traditional downstream processing operations. Continuous processing could provide unique opportunities for the production and delivery of low-cost biopharmaceuticals for solution of major global health challenges in the coming decades.

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Introduction

The commercial-scale manufacture of high value biological products is currently performed using batch processes in which each unit operation is completed in sequence, with the product outflow from one unit typically collected in a holding tank before moving to the next processing step. Batch operation facilitates the design and optimization of the individual unit operations, often by individuals/teams with very different expertise (e.g., upstream vs downstream or membrane filtration vs chromatography). Batch processing is also attractive given the relatively small scales needed for most biological products, and it easily accommodates off-line measurements of key product quality attributes between processing steps.

The transition from batch to continuous processing has been a hallmark in the development of the modern chemical and pharmaceutical industries. For example, Kreps' early analysis of the history of sulfuric acid production noted that [1]:

"Chemical research and technology gradually coalesce discontinuous processes into continuous ones, replace batch operations by complete unit operations. . .and thus reduce operating charges and increase productive capacity per unit of investment."

Similarly, soda ash production in the 18th and 19th centuries was dominated by the Leblanc process, which involved the batch reaction of sodium chloride with sulfuric acid to produce sodium sulfate which was then reacted with coal and calcium carbonate to form sodium carbonate (with calcium sulfide as a by-product). The Solvay process, developed in the 1860s by Ernest Solvay, was a continuous process in which carbon dioxide was reacted in an aqueous solution of NaCl and ammonia yielding sodium bicarbonate (with NH_4Cl as by-product) that was then converted to sodium carbonate by calcination [2]. Within 30 years, more than 90% of the global production of sodium carbonate was based on the continuous Solvay process; companies that had invested in the Leblanc process were almost entirely supplanted. As discussed by Stephanopoulos and Reklaitis [3], the Solvay process was one of the first examples highlighting the advantages of process systems engineering — it improved yields and productivity, reduced environmental pollution and manufacturing costs, and enhanced safety.

Drivers for continuous bioprocessing

There are two primary drivers behind the current interest in continuous bioprocessing. The first is economic. Biomanufacturers are faced with increasing pressure to reduce the price of biotherapeutics, particularly in light of efforts to increase the availability of life-saving therapies to patients in developing countries. In addition, there is growing competition from lower cost manufacturers, many of whom are focused on the production of biosimilars, that is, generic versions of biological molecules that are now off-patent. There is thus tremendous interest in finding ways to reduce the cost of all aspects of drug discovery, clinical trials, and manufacturing.

A recent economic analysis by Walthe *et al.* [4••] concluded that an integrated continuous biomanufacturing platform could reduce costs (net present value) by 55%

relative to conventional batch processing. Even greater benefits were found for non-monoclonal antibody products — the expected operating cost was reduced from \$1230 g^{-1} for a batch process to less than \$250 g^{-1} for a continuous process with more than a 3-fold reduction in capital costs. Similar cost-savings were identified by Hammerschmidt *et al.* [5] for production of a monoclonal antibody product using a continuous process based on precipitation instead of batch column chromatography. Continuous processes could also facilitate the design of flexible multi-product manufacturing facilities with much lower initial capital investments, which would allow biomanufacturers to more effectively manage rapid changes in product portfolios/demand and could be an enabling strategy for production of more personalized biotherapeutics.

In addition to cost, continuous processing also has the potential to provide significant improvements in product quality through enhanced control and uniformity of the microenvironment within the manufacturing process. Biotherapeutics produced using current batch processes have wide variability in 'experiences'. For example, a monoclonal antibody secreted by a Chinese Hamster Ovary (CHO) cell at the start of the cell culture is produced in a nutrient-rich environment with few lysed cells, but that protein will remain within the bioreactor for multiple days before subsequent downstream processing. The situation is dramatically different for a protein produced right before harvesting. Several studies have shown that much of the variability in glycosylation profiles [6], extent of deamidation [7], and level of degradation/aggregation [8] is due to the wide range (and very long) residence times inherent in batch processes. In addition, protein aggregation and denaturation can occur when proteins are bound to chromatographic resins for long times due to protein unfolding and intermolecular interactions involving other adsorbed proteins [9–11]. Proteins that are loaded on the column at the start of a typical column chromatography step remain in the bound state for well more than an hour, while proteins near the end of the load remain bound for only a small fraction of that time.

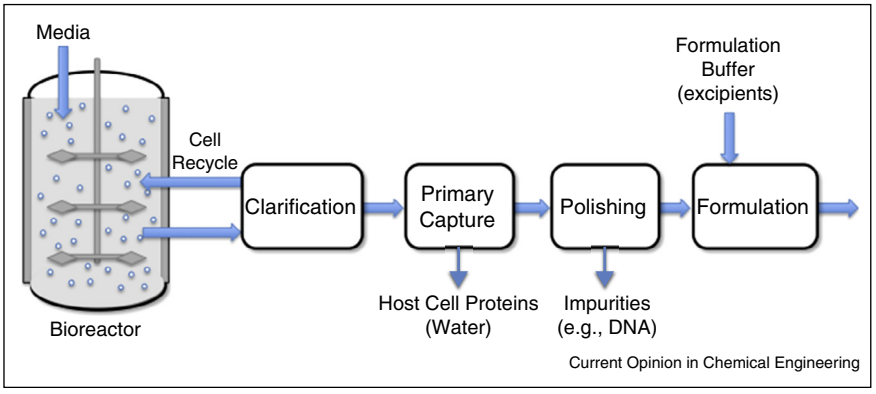
The FDA's recent Regulatory Science Strategic Plan [12] specifically focused on the use of Quality by Design (QbD) to improve the manufacturing process to ensure and improve product quality. As part of this effort, the FDA identified three new areas that would support increased manufacturing quality, one of which is the use of 'continuous processing where materials constantly flow in and out of equipment' [12]. Janet Woodcock, Director of the Center for Drug Evaluation and Research, recently identified continuous manufacturing as a key enabler in modernizing pharmaceutical manufacturing [13].

Technologies for continuous bioprocessing

There have been several recent Reviews of available technology for continuous bioprocessing [14,15••,16••]. Figure 1 shows a schematic of a generic continuous process that would be appropriate for purification of a secreted product like a monoclonal antibody (mAb). The overall process includes a perfusion bioreactor, clarification (with integrated cell recycle), initial product capture, product polishing, and final formulation. Additional steps (e.g., cell lysis) would be required for intracellular proteins or cellular products (e.g., viruses used in the formulation of vaccines).

The technology for continuous cell culture was developed more than 30 years ago [17]. The use of perfusion bioreactors with continuous addition of nutrients and removal of product is well-established for production of both monoclonal antibodies (mAb) and highly labile enzymes and cytokines [18]. Approximately 20 marketed monoclonal antibody products, with annual revenues around \$20 billion, are currently produced using perfusion systems [19]. Voissard *et al.* [20] have reviewed available methods for cell retention in perfusion culture of mammalian cells, including filtration, centrifugation, and gravity settlers. The most common approaches are

Figure 1



Schematic representation of a generic continuous downstream bioprocess.
Source: Adapted from Ref. [16••].