White Paper on Continuous Bioprocessing May 20–21, 2014 Continuous Manufacturing Symposium

KONSTANTIN B. KONSTANTINOV,[1] CHARLES L. COONEY[2]

[1]Late Stage Process Development, Science, Genzyme- A Sanofi Company, 45 New York Ave., Framingham, MA 01702
[2]Department of Chemical Engineering, Massachusetts Institute of Technology, 77 Massachusetts Ave., Cambridge, MA 02139

Received 10 October 2014; accepted 17 October 2014

Published online 21 November 2014 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.24268

ABSTRACT: There is a growing interest in realizing the benefits of continuous processing in biologics manufacturing, which is reflected by the significant number of industrial and academic researchers who are actively involved in the development of continuous bioprocessing systems. These efforts are further encouraged by guidance expressed in recent US FDA conference presentations. The advantages of continuous manufacturing include sustained operation with consistent product quality, reduced equipment size, high-volumetric productivity, streamlined process flow, low-process cycle times, and reduced capital and operating cost. This technology, however, poses challenges, which need to be addressed before routine implementation is considered. This paper, which is based on the available literature and input from a large number of reviewers, is intended to provide a consensus of the opportunities, technical needs, and strategic directions for continuous bioprocessing. The discussion is supported by several examples illustrating various architectures of continuous bioprocessing systems. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 104:813–820, 2015
Keywords: continuous bioprocessing; perfusion cell culture; continuous purification; integrated continuous biomanufacturing; cell culture; chromatography; separation science; biotechnology; regulatory science

INTRODUCTION

Process intensification through conversion from batch to continuous manufacturing has been applied effectively in industries such as steel casting,[1] petrochemical, chemical, food, and pharmaceuticals with great effectiveness.[2–6] Despite vast differences between the product types, the advantages of continuous over batch manufacturing are consistent and include steady-state operation, reduced equipment size, high-volumetric productivity, streamlined process flow, low-cycle times, and reduced capital cost.[7] An example of industrial importance in the therapeutic field is the ongoing project at the Novartis – MIT Center for Continuous Manufacturing that targets a holistic redesign of the pharmaceutical manufacturing process to achieve fully integrated end-to-end continuous flow.[8]

There is a growing interest in realizing the benefits of continuous processing in biologics manufacturing. To this end, a significant number of industrial and academic researchers are actively involved in the development of continuous processing systems.[9,10] The results reported so far point to the transformative potential of this technology on the manufacturing of biological drugs. The development efforts are further encouraged by guidance expressed in recent US FDA conference presentations.[11,12]

Continuous bioprocessing technology, as a paradigm shift in biologics manufacture, will benefit from standardizing on common terminology, as well as from the alignment of expectations and goals. An objective of this document is to propose such a common understanding and to define strategic directions for further development that will address the current challenges and technological gaps. Although the concept of fully continuous bioprocessing will likely face some skepticism, it is important to consider the lengthy but highly successful evolutionary path of the continuous manufacturing in other industries,[1,7] which is seen today as a "disruptive technology" that moved these businesses to a new level.[13,14]

DEFINITIONS

As with other industries, the classification of a biomanufacturing system as continuous depends on the nature of the unit operations and its integration into the final system. Therefore, it is appropriate to first provide a working definition of the term "continuous unit operation."

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.

A process is continuous if it is composed of integrated (physically connected) continuous unit operations with zero or minimal hold volume in between. To emphasize that all the unit operations are continuous and integrated, such processes are also referred to as fully continuous or end-to-end continuous. A process is hybrid if it is composed of both batch and continuous unit operations.

Continuous processing is a rich technical field that encompasses various concepts, such as flow, systems approach, integration, and model-based control. For further discussion of these and other related topics, see Badman and Trout.[15]

CHALLENGES OF CURRENT BIOMANUFACTURING TECHNOLOGY AND THE OPPORTUNITIES OFFERED BY CONTINUOUS PROCESSING

The overarching business drivers for accelerated development times and cost control under stringent quality/regulatory

Correspondence to: Konstantin Konstantinov (Telephone: (508) 661-1644; Fax: (508) 271-3452; E-mail: Konstantin.Konstantinov@genzyme.com)

Journal of Pharmaceutical Sciences, Vol. 104, 813–820 (2015)

requirements continue to dominate the biotechnology industry. At present, biopharma companies often need to flexibly accommodate large-, mid-, and small-volume drugs (e.g., niche or orphan drugs), preferably within the same manufacturing facilities. The same is true for therapeutic proteins of different natures, for example, stable proteins, such as antibodies, and highly complex (less stable) proteins, such as recombinant enzymes or blood factors. Furthermore, the ability to rapidly adjust production capacity to accommodate fluctuating and/or misforecasted market demands is also needed. Mounting pressure to reduce cost is impacted by growing competition from biosimilar products and by government regulations. As a result, concerns about the long-term sustainability and reproducibility of the traditional batch manufacturing facility model with multiple 10–20kL batch bioreactors and downstream trains involving large chromatographic columns have been repeatedly raised. As a consequence of major improvements in upstream product titers and the identification of high-potency products, a trend toward the utilization of smaller, possibly single-use bioreactors, and purification columns has emerged, which addresses some, but not all, of the limitations with current technology. Below, we enumerate the main challenges of current batch or hybrid biomanufacturing systems, and review the opportunities offered by integrated continuous processing to address these issues.

Cost

High capital investment costs are associated with traditional stainless steel fed-batch facilities because of the larger equipment size and low equipment utilization rates. Continuous processing offers significant opportunity to reduce capital costs through radical reduction of facility and equipment footprints that result from: small bioreactors and chromatography columns; elimination of intermediate hold tanks and nonvalue-added unit operations; very high-volumetric productivity; high equipment utilization rate; and single-use technology. The volume of the continuous bioreactors and purification columns can be multifold smaller than the corresponding fed-batch equipment because of significantly higher cell density in perfusion systems and the downstream equipment utilization rate. These small footprint facilities can be constructed and commissioned more expediently than traditional large-scale facilities. Additional savings in operating cost are also expected from the improved resin capacity utilization and accompanying decreases in buffer volumes that are offered by continuous chromatography systems. The functionally closed process will require lower environmental class and therefore drive down capital and QC environmental testing costs as well. Other cost savings will occur through an increase in automation and reduction in operator labor. Further improvements in perfusion processes to increase MAb titer through process and media optimization are needed to achieve COG competitive with current fed-batch processes. As media cost is reduced through systemic development, its impact on COG will become less significant.

Flexibility

The growing diversity of product pipelines within the industry (including large-volume and small-volume drugs; mAb and nonmAb products) and associated market complexity create a need for production flexibility. Continuous processing offers a significant advantage as it allows rapid capacity adjustments through "numbering up" (addition/removal of parallel production lines) when compared with traditional volumetric scale up. The multifold smaller and potentially mobile equipment that is used in continuous processing further enhances this advantage. Another scaling factor in continuous processing is time—the duration of the process can be modulated based on product demand. In combination, these factors allow the utilization of a single bioreactor scale of a few hundred liters for the production of small-volume drugs (<10 kg/year) and large-volume drugs (>100 kg/year). Furthermore, the reduced equipment footprint and the universality of the platform allows high-process mobility and portability, either within the same facility or between different manufacturing sites, which can be strategically distributed to serve local markets.

Standardization

The diversity of biological products has resulted in the development of a variety of production systems with limited standardization. For example, relatively stable proteins (such as a mAb) are typically produced in fed-batch systems, whereas less stable molecules (such as blood factors or enzymes) are produced in hybrid systems (perfusion upstream and batch downstream). There is also significant diversity in production systems even within the same technological category, which complicates knowledge management, technology transfer, speed of development, and the ability to capture incremental process improvement. Continuous bioprocessing offers the opportunity to implement standardization, that is, all biological drugs are manufactured in a common manner. Multiproduct facilities then can be designed using a standardized continuous platform. Furthermore, because of small equipment size, full process standardization can now be realized across process development, clinical production, launch, and commercial manufacturing, as identical equipment and control systems can be used in all these areas. Standardization will also facilitate compliance with local government regulations in emerging markets, as small, predesigned facilities can be rapidly and inexpensively built in such regions in a decentralized operating model.

Furthermore, standard bioreactors of modest volume can be used for the production of both small-volume and large-volume biologics. For example, a single 500-L bioreactor operated continuously at cell density of 80e6 cells/mL for a total of 280 days/year would produce more than 400 kg/year at crude harvest, assuming cell-specific productivity of 40 pg/cell per day. The same 500 L perfusion bioreactor can be used in much shorter campaigns for the production of low-volume drugs. By scaling with longer production cycles, a range of market demands can be met.

Additional improvements can be achieved through equipment interchangeability and standardization of interfaces between continuous process equipment. Because of the small, mobile nature of the directly connected continuous unit operations, interface standardization is facilitated by single-use technology (e.g., disposable tubing, tubing sealers, and tubing welders).

Speed of Scaling

Historically, scale-up and transfer to manufacturing has been a time-consuming activity, often associated with the identification of various technical challenges. The utilization of a standard production platform for protein drugs would facilitate and