Introduction to Continuous Manufacturing: Technology Landscape and Trends

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The classic and largely predominant approach to bioprocessing, both upstream and downstream, remains batch processing, with manufacturing batch fluids essentially moving incrementally en mass as a bolus from one process step and set of equipment to the next. This assembly line-like, finish-one-step then move all the process fluids to the next, approach certainly works well but a number of technological advances and related trends are making continuous bioprocessing attractive. Continuous bioprocessing strategies are making advances and are being adopted or considered for many new drug bioprocesses being implemented. Meanwhile some established bioprocessing facilities are being retrofitted and upgraded for more continuous operations. Continuous upstream bioprocessing is actually not new, with fiber-based perfusion bioreactors widely used for classic fused-cell hybridoma culture, e.g., in the 1980s, when it was replaced by recombinant antibody manufacturing methods.

We can expect higher future adoption of bioprocessing by continuous methods[1,2]. Already, about a dozen or more marketed recombinant protein products are manufactured using perfusion or other continuous bioprocessing technologies. Leading adopters include Genzyme and Bayer. Most adoption of continuous bioprocessing has involved upstream processes, with continuous downstream purification tending to lag behind. Thus, it is currently common for new bioprocesses being implemented to combine continuous upstream processing with conventional batch purification. Continuous chromatography technologies, such as simulated moving bed (SMB) and periodic counter-current chromatography, are generally not yet ready yet for commercial-scale adoption. Regulatory barriers to continuous bioprocessing, such how to define lots, have been resolved, and continuous processing fits better than batch processing with automation, QbD and PAT. These aspects are making the benefits of continuous processing increasingly attractive to biopharma manufacturers.

Continuous upstream bioprocessing generally involves retaining production cells within the bioreactor at a fixed volume and fixed cell concentration on a continuous basis, such as for 30-90 days or even longer. The bioreactor fluid has a much higher cell concentration, with cells retained within the bioreactor by various methods.

The current leading method involves use of specialized filter-based equipment. Other methods for cell retention are done by centrifugation and use of capillary or other fiber-based and microcarrier reactors where cells self-attach to fiber or particle substrates.

There are many benefits to operating bioprocesses continuously rather than in batch mode, with many of these similar and complementing those of single-use and modular systems. These benefits include:

a) Reduced costs: Operating continuously allows use of much smaller-scale equipment, with a smaller volume bioreactor (and smaller sizes for most other equipment) operating over time resulting in as much product as much larger equipment operated in fed-batch mode. Besides smaller-scale equipment generally costing less, this allows much smaller facilities and equipment foot-print, with less space and utilities required, particularly when single-use systems are used.

b) Increased productivity: Because much of the bioprocessing equipment is operated continuously, there is little need for large transfer/storage vessels and no halts between processes. Bioprocessing thus tends to move much more smoothly. Much higher bioreactor cell densities can be attained, providing higher product yield and concentration. Also, the number of bioprocessing staff required is decreased, and their work at large scale is less physically demanding.

c) Improved quality: Biological molecules are naturally produced continuously, and compared to batch culture, continuous culture tends to be more controllable, less intense and stressful, including less shear and media nutrient levels kept constant. Product variability, e.g., later

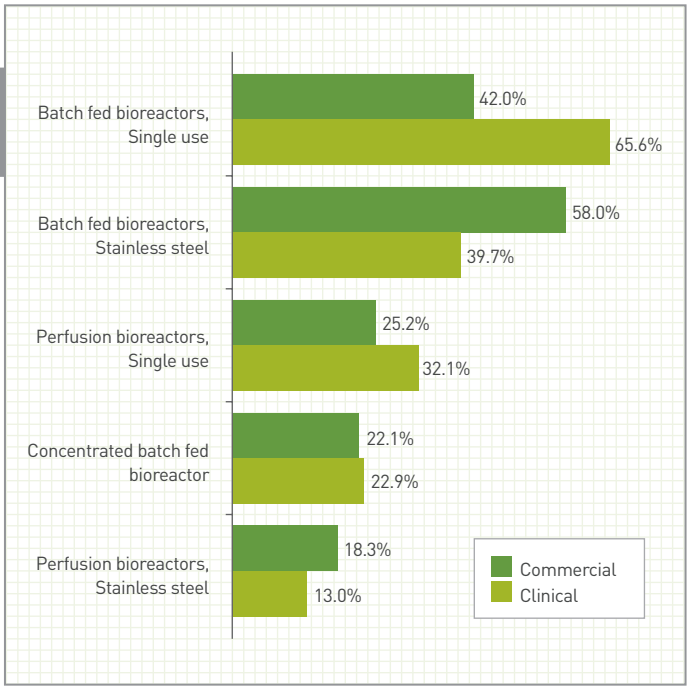
culture stage-related loss of cell viability or altered glycosylation, is reduced, with continuous bioprocessing inherently more consistent and robust. Problems associated with proteolytic or other degradation over time in bioreactors and other vessels can be avoided or minimized. And if any problems do occur, only part, not the entire, production run likely needs be rejected.

d) Increased flexibility: Continuous manufacture enables more adaptability and efficient facility utilization, similar to the advantages of single-use devices. Bioprocessing becomes much more portable, and facilities more clonable. Couple this with the trend for adoption of modular bioprocessing systems, multiple smaller continuous bioprocess lines in smaller facilities worldwide, and we expect this approach will be increasingly adopted for commercial manufacturing.

The BioPlan 10th Annual Report and Survey of the Biopharmaceutical Manufacturing evaluates key trends and aspects of the bioprocessing industry. We surveyed the attitudes of 300 industry professionals towards perfusion and continuous processing in 2013 [3,4]. Attitudes are common with relatively new bioprocessing technologies. Overall, respondents saw more problems associated with perfusion/continuous vs. fed-batch processing. "Process complexity" was the primary concern, cited by 69% (% indicating this factor either "much bigger" or a "somewhat bigger" concern), followed closely by "Process development control challenges" noted by 64.7%. Other issues included "Contamination risk" at 58.6% and "ability to scale-up" at 54.3%. In comparison, for the same aspects, concerns over batch fed processes were noted by very few (single-digit percentages) respondents. Much of this perception will likely change as the industry is increasingly exposed to the successful application of continuous technologies in clinical and commercial scale bioproduction.

'When specifying bioreactor types for a new [Clinical] or [Commercial] scale biologics facility, how likely are you to specify" % "very likely" or "likely"

Fig.1: Likelihood of Implementing Bioreactor, by Type



Source: 10th Annual Report and Survey, Biopharmaceutical Manufacturing, April 2013, BioPlan Associates, Inc. Rockville, MD

In fact, continuous processing equipment manufacturers and users rather uniformly report that many of these problems have been resolved with application of current technologies, including single-use equipment. Perfusion/continuous processing is now generally significantly less complex, less prone to contamination and more readily scalable than fed-batch methods. Industry perceptions of perfusion/continuous vs. fed-batch are lagging, and likely reflect a lack of direct exposure or experience with the technology. When those surveyed were asked what types of bioreactor they would implement for a new facility coming online in 2 years, as expected, over two-thirds cited batch-fed single use bioreactors, while 32% and 25% cited single use perfusion bioreactors at clinical and commercial scales, respectively.

BioPlan Associates expects increased and rapid adoption of continuous bioprocessing at all scales, including commercial manufacture. The imperatives of cost-savings, flexibility and product quality will increasingly drive the industry to explore continuous processing. This, in turn, will expand the industry's current knowledge and experience base, when making major changes in manufacturing platforms. Particularly, as perfusion and other continuous bioprocessing technologies are improved and increasingly adapted for single-use equipment and modular systems, adoption will further accelerate. Many upcoming continuous bioprocessing technologies are actually very novel. For example, a single 5 L bioreactor currently in development will be able to manufacture the same quantity of product, often at better quality, comparable to a 5,000 L over the same time period using the same amount of media [1]. Case studies and other reports of such performance will further promote rapid adoption.

We predict increasingly rapid adoption of single-use systems for the majority of new commercial manufacturing facilities over the next 5 years, and we expect continuous bioprocessing, particularly for upstream processing, to follow a similar trajectory. Use of these products is likely to further increase with hybrid systems that use bolt-on-type technology, that retrofit components unit operations for existing systems. Other conventional technologies, such as centrifugation, will also seen increasing adoption in coming years. Potentially revolutionary capillary fiber perfusion bioreactors and other new technologies, including those for downstream processing, will be likely coming online and be more widely adopted for commercial manufacture over the next 10 years.

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