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Publisher: Taylor & Francis

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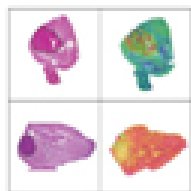


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Accepted author version posted online: 03 Nov 2014. Published online: 15 Dec 2014.



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To cite this article: Suzanne S Farid, Bill Thompson & Andrew Davidson (2014) Continuous bioprocessing: The real thing this time?, mAbs, 6:6, 1357-1361, DOI: [10.4161/mabs.36151](https://doi.org/10.4161/mabs.36151)

To link to this article: <http://dx.doi.org/10.4161/mabs.36151>

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Continuous bioprocessing: The real thing this time?

10th Annual bioProcessUK Conference, December 3–4, 2013, London, UK

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Keywords: Biopharmaceutical manufacture, continuous bioprocessing, cell culture, fed-batch, perfusion, continuous chromatography, process economics

The Annual bioProcessUK Conference has acted as the key networking event for bioprocess scientists and engineers in the UK for the past 10 years. The following article is a report from the sessions that focused on continuous bioprocessing during the 10th Annual bioProcessUK Conference (London, December 2013). These sessions were organized by the 'EPSRC Centre for Innovative Manufacturing in Emergent Macromolecular Therapies' hosted at University College London. A plenary lecture and workshop provided a forum for participants to debate topical issues in roundtable discussions with industry and academic experts from institutions such as Genzyme, Janssen, Novo Nordisk, Pfizer, Merck, GE Healthcare and University College London. The aim of these particular sessions was to understand better the challenges and opportunities for continuous bioprocessing in the bioprocessing sector.

Introduction

The 10th Annual bioProcessUK conference was held in London on 3–4 December 2013, with the theme 'Biopharmaceutical Innovation: a Vision for the Future'. The EPSRC Centre for Innovative Manufacturing in Emergent Macromolecular Therapies was host sponsor for the conference. The Centre was invited by the conference organizer, bioProcessUK, to arrange and chair a plenary session, as well as a workshop on the "Operational and Economic Challenges of Continuous Bioprocessing" in response to the resurgent interest in this topic. Companies are now asking whether they should choose conventional batch technologies or invest in novel continuous technologies, which may lead to lower production costs. This has led to several companies evaluating continuous technologies [e.g. ref. 1–4] to see if they can leverage

their benefits, which include potentially allowing smaller facility footprints and higher equipment utilization rates. This report summarizes the presentations and discussion arising from these sessions.

Plenary Session

Konstantin Konstantinov from Genzyme-Sanofi presented a plenary lecture with an industrial perspective on advancing the case for integrated continuous bioprocesses.^{1,2,5} Dr Konstantinov opened by highlighting the lengthy but highly successful evolutionary path of continuous manufacturing in other industries such as steel casting, which enabled these businesses to operate at a different level of industrialization. He highlighted that investigations into continuous manufacture for biologics are being encouraged by the recent US Food and Drug Administration's strategic plans⁶ and Quality by Design (QbD) initiatives. He presented Genzyme's successful implementation of an integrated, closed and fully continuous biologics processing platform. Recent results were shown for the production of both stable (monoclonal antibody) and less stable (enzyme) proteins in an uninterrupted manner over extended periods with consistent time-based system performance and product quality. The platform demonstrated the integration of a perfusion bioreactor with 2 continuous chromatography steps for capture and polishing of protein therapeutics. Dr Konstantinov presented a vision for a future universal platform for the production of protein therapeutics that relied on continuous processing with a dramatic reduction in the facility footprint, elimination of non-value-added steps and reduction in the number of unit operations to a minimum. Such examples are important demonstrations of proof-of-concept for the sector and of the transformative potential of integrated continuous bioprocesses.

Workshop

The aim of the workshop was to address the drivers, costs, risks and benefits that influence the implementation of continuous bioprocessing. **Suzanne Farid** (University College London)

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<http://dx.doi.org/10.4161/mabs.36151>

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chaired the workshop and introduced the discussion topics that were prioritized under the following 4 core themes:

Theme 1: Fed-batch versus perfusion culture for stable products?

Theme 2: Is there a business case for continuous chromatography linked to fed-batch or perfusion culture?

Theme 3: How do you balance COG savings with continuous bioprocesses with cost of development and flexibility?

Theme 4: Is tomorrow's process a hybrid of batch and continuous operations?

Each theme was introduced with an industrial perspective to kick-start the roundtable discussions. Over 80 industrial and academic participants attended the workshop. The topic of this workshop was similar to one co-chaired by Dr Farid at the Engineering Conferences International's Integrated Continuous Bioprocessing Conference held in Barcelona, Spain in October 2013.

Theme 1: Fed-batch vs. perfusion culture for stable products

Patrick Sheehy from Janssen Biologics (formerly Centocor) shared insights from his experience with both perfusion and fed-batch culture up to 1000 L scale for both clinical trial and in-market supply. The company's early commercial antibodies, such as abciximab (Reopro[®]) and infliximab (Remicade[®]), were originally based on perfusion culture using internal and external spin-filters to retain the cells.⁷ Now extensive use is made of more recent retention devices such as the external alternating tangential flow (ATF) filtration systems in conjunction with perfusion for products such as golimumab (Simponi[®]) and ustekinumab (Stelara[®]).⁸ Practical challenges encountered with perfusion processes developed in the late 1990s and early 2000s relate to equipment fouling, high costs for proprietary media and the expertise required for these more complex processes. Equipment failures were seen with early perfusion processes due to fouling of internal spin filters that led to termination of the cultures. Although all retention devices foul during perfusion cultures, the rate of fouling seen with ATF filters was lower and not considered a major concern given the capability to replace the filters out without too much disruption to the perfusion culture.

Although perfusion processes continue to be used for marketed antibody products, Janssen has moved to fed-batch processing for future stable antibody products going into clinical trials. From Janssen's perspective, fed-batch offers lower complexity and lower risk of failure, as well as higher titers. Lower complexity means processes are easier to operate and product changeovers are simpler, an important consideration for multi-product facilities. Janssen's choice is also influenced by the fact that its development products are quite stable antibodies, and these can be more suited to fed-batch processing than more labile products.

Looking forward, Dr Sheehy noted that the choice of process route would be kept under review. New perfusion processes are very different from those originally developed 10 years ago. Higher cell densities and productivities are achievable and better bioreactor control is available. The potential use of disposables helps make continuous processing a lower capital cost choice for the upstream operations, although there are scale limitations.

Theme 2: Is there a business case for continuous chromatography linked to fed-batch or perfusion culture?

James Pollock from Merck shared cost of goods (COG) insights from his doctorate research on evaluating the potential of continuous processes at different stages of the development lifecycle, carried out in the Decisional Tools team at University College London Biochemical Engineering led by Dr Suzanne Farid and in collaboration with Pfizer. He addressed the following topical questions:

- How well do continuous bioprocess steps need to perform to compete with the traditional batch steps?
- Is there a business case for continuous bioprocessing for early phase manufacture?
- How does the business case change for commercial multi-product manufacture?

He presented 3 industrial case studies⁹⁻¹¹ that provided economic and operational perspectives on the decision to select batch versus continuous processes for upstream, downstream and integrated continuous processes. On the upstream front, Dr Pollock illustrated how the choice of fed-batch vs. spin-filter and ATF perfusion culture depends on the scale of production, failure rate and cell density increase achievable. ATF perfusion processes were predicted to be more competitive for single-product commercial facilities if the cell density increase was above a critical threshold (3-fold higher than fed-batch in this commercial antibody production case) and the process economics savings were considered more important than operational feasibility. The savings with ATF perfusion processes were due to the smaller footprint upstream and downstream suites enabled by their higher cell densities and volumetric productivities, the ability to use single-use bioreactors and to replace a fouled retention device during a culture. In contrast, spin-filters generally did not match the cost or robustness benefits of either fed-batch or ATF processes.

Several of the major biopharmaceutical companies are assessing continuous chromatography from suppliers such as GE, Tarpon and Novasep. Such systems are in reality semi-continuous, utilizing 3–12 columns in a periodic counter-current configuration. Dr Pollock showed that continuous capture chromatography enabled more efficient utilization of Protein A which is particularly significant for early phase manufacture where materials represent a greater proportion of the COG. This can have a large effect on clinical manufacturing costs considering the high clinical attrition rates. Extending this to integrated continuous bioprocesses for multi-product clinical and commercial manufacture, the analysis predicts that an integrated continuous strategy (ATF perfusion, continuous capture, continuous polishing) is cost-effective for early phase production and small/medium-sized companies. However, the ranking of strategies switches for commercial production and large companies to the hybrid strategy with fed-batch culture, continuous capture and batch polishing since this avoids the need for multiple parallel trains with the scale-limited perfusion systems.

The insights from the analysis act as a valuable test bed for assessing the potential of novel continuous strategies to cope with different

scales of operation, phases of development and company sizes. The analysis demonstrated that continuous processing can offer COG benefits in different scenarios. Further considerations outside the scope of this work include the impact of adopting continuous processing on process development efforts. This was discussed in Theme 3.

Theme 3: How do you balance COG savings with cost of development and flexibility?

Haleh Ahmadian from Novo Nordisk considered the balance between cost, quality and time when introducing continuous bioprocessing. She first addressed the dilemma of cost for biopharmaceutical manufacture. On the one hand, COG is a minor percentage of the high prices of biopharmaceuticals. For instance, drug substance COG values for monoclonal antibodies are reported to be around 100 USD per gram, while the sales price of final product varies in the range of 2,000–20,000 USD per gram.¹² There is thus little financial incentive to spend money to bring COG down while ensuring positive return on investments. On the other hand, the pressure from capacity constraints, biosimilars and price differentiation for some products are in favor of reducing COG. She commented that, although price pressures from biosimilars may be considered by some not to be compelling, it is expected that this will change as the sector matures. Examples of efforts to enable price differentiation included post-approval changes to optimizing manufacturing for insulin and growth hormone products so as to reduce their COG.

She presented a managerial view to address the question of how to reduce timelines and COG without compromising quality. From an organizational perspective, her view of the solution is to build up an organization that will support this with strategic alignment, standardization, platforms and most importantly, early technology development to make sure that new technology does not delay time to market.

Dr Ahmadian presented Novo Nordisk's 2-stage process development model where the first stage focused on development of an initial process to cover early phase material with limited experimentation and the second stage on design to manufacture for process robustness. However, for new technologies such as continuous bioprocessing, this model does not work and technology development needs to start early to remain off the critical path.

Dr Ahmadian then brought the time to develop new processes into the equation considering both risk and quality. New technologies that offer favorable COG values still pose a risk since they may not be very well characterized and may incur extra process development costs to develop a process that delivers a high quality product. She stressed that the balance between COG savings and the cost of process development would need to be assessed on a case-by-case basis and would be product-dependent (e.g., different solutions for coagulation factors versus insulin) and be affected by whether the product was registered in the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research in the US Food and Drug Administration.

Novo Nordisk has experienced situations where continuous bioprocessing was proposed but the cost of development could not be justified, and, conversely, a case where continuous bioprocessing turned out to be the most feasible and practical option.

Theme 4: Is tomorrow's process a hybrid of batch and continuous operations?

Karol Lacki from GE opened by drawing parallels with the industry's response to "lean" manufacturing a few years ago and "continuous" manufacturing now. Both encourage the removal of non-value added steps such as intermediate filtration and wash operations so as to lead to leaner processes that translate into time and cost savings. Dr Lacki presented a helicopter view of hybrid options, including current commercial hybrid processes using perfusion culture and standard batch processes for purification. He then addressed the question of whether downstream processing can be operated in a continuous mode. He outlined the different continuous chromatography technologies currently available for capture chromatography from vendors that each aim to improve the utilization of the resin capacity. These include the periodic counter current (PCC) system (3–4 columns) from GE Healthcare (Uppsala, Sweden), BioSC (2–6 columns) from Novasep (Pompey, France), BioSMB (6–12 columns) from Tarpon (Leiden, Netherlands) and SMBC (4–8 columns) from Semba Biosciences (Madison, WI).

Dr Lacki then discussed challenges connecting continuous capture and polishing steps. He highlighted efforts reported in conferences from Genzyme, GE Healthcare/Janssen, Amgen and Sanofi that have led to a number of quasi-continuous purification trains. The trains comprise chromatography steps connected in series with no break-up times or hold-up times. These efforts have focused on in-line adjustment of process streams between columns to enabling continuous flow operation (e.g., GE/Janssen's "straight through processing"¹³ or careful selection of buffers to avoid the need for pH/conductivity adjustment between steps (e.g., Sanofi's ASAP system¹⁴).

Dr Lacki felt that both hybrid and continuous manufacturing scenarios will co-exist in future. Yet, certain conditions must be met. The clear advantage of continuous capture steps where the consumption of expensive resin is reduced is less evident for polishing steps which may operate discontinuously. Despite a few successful examples of continuous or semi-continuous chromatography operations, certain purification steps such as virus inactivation with its incubation time can turn a continuous purification train into a hybrid one. Although there have been efforts to operate virus inactivation in a continuous mode such as Merck's tubular reactor design,¹⁵ Dr Lacki presented the dilemma of whether the industry should consider removal of steps where continuous solutions do not exist or identify ways to work around them.

The View from the Audience

The roundtable discussions led to a lively discussion that tapped into the experiences of the audience, which were primarily with batch rather than continuous processes. However, a quick survey of the audience revealed that over half were considering evaluating continuous processes for both upstream and downstream in the near future. Some already had begun the evaluation, but had not yet implemented it in manufacturing.

On Theme 1, the roundtable discussions revolved around challenges when dealing with the extra complexity posed by continuous culture. The viewpoints on complexity varied based on the exposure of the delegates to continuous bioprocessing. Delegates from small companies noted that, although in the models there were cost advantages for using perfusion systems, there were also some challenges. The difficulty in process definition at a small scale and disadvantage of potentially having to change to fed-batch processing later represented increased risk and uncertainty. The robustness of equipment over long runs was also raised as a concern, as was the ability to define and trace batches unambiguously. For some small companies, speed into clinical trials was more important than the cost of goods and using simpler and more familiar processes with reliable scale-down tools for development offered a faster and lower risk option. Companies with experience running continuous culture for stable antibody products and labile products, such as enzymes and blood factors, commented that the batch definition challenges have been addressed and that the number of process deviations are comparable to fed-batch processes. They recognized that addition of retention devices adds complexity, but that the evolution of retention devices with lower failure rates and faster time to recover has increased the robustness of perfusion culture runs.

On Theme 2, the discussions focused on the business case for continuous processes and the benefits needed to balance the perceived risk in switching to continuous. Representatives from larger companies were careful to balance the potential cost savings of continuous upstream processing against the increased process complexity and uncertainty. For one contributor, performance in terms of production quantity per reactor per unit time would have to double and the cost would have to halve to balance the increase risk and uncertainty. Without the prospect of such a large benefit, it would not be possible to justify the risk in exploring the continuous option. The market size of a development product may not be clear until after the early phase clinical trials, and in this situation a fed-batch process may allow the critical decision point to be reached more quickly and enable a fast-to-failure strategy across a development portfolio. When the market requirements are clear, and there is a good commercial case, continuous upstream processing can be made to work.

The potential payback is very much influenced by whether the proposed plant is a greenfield plant or a retrofit of an existing plant. The balance of risks and benefits can also be significantly different for more labile products where continuous processing offers some real advantages. The lack of reliable scale-down tools for continuous processes was mentioned by a number of the audience as an additional challenge.

On Theme 3, the development effort required for continuous bioprocesses was debated. The majority of the delegates considered that the consequences on the cost and time of development would take priority over COG savings when considering the implementation of continuous bioprocessing. There were some exceptions (e.g., for biosimilars) where COG savings can be more critical to competitiveness in the market. New technologies

also pose risk due to uncertainty about their performance, but can ultimately lead to processes that are more robust. The audience debated whether continuous processes had the potential to offer increased robustness, and whether that would also outweigh COG.

Roundtable discussions on validation highlighted that there were differing views, with some people believing continuous processes could streamline validation efforts, while others believe it is more complex to validate and could lengthen development times. This will depend on the product and when the development starts. The argument for streamlining development and validation efforts relies on the fact that there would be no need to scale-up the process as it moved through the development cycle and higher demands would be met by addition of parallel production lines. For companies with in-house expertise, running continuous perfusion culture for commercial processes the transition to integrated continuous bioprocesses could save development times. On the continuous chromatography front, validation challenges relate to control software and equipment performance qualification.

There are also differing views about quality obtained from continuous processes. Genzyme and others (see for example ref. 16,17) have reported that steady-state operation for antibody production gives less heterogeneity in glycosylation profiling than fed-batch cultures. The heterogeneity in antibodies in fed-batch might have clinical significance; this is not known, but remains a big question mark.

On Theme 4, the discussions focused on whether tomorrow's process would be a hybrid of batch and continuous operations and the gaps that exist to create an integrated continuous bioprocess. Several attendees felt that a continuous bioprocess will rely on smaller equipment that is operated more frequently with a higher level of automation. The audience recognized that a major challenge affecting the uptake of continuous bioprocessing relates to the availability of robust online analytics and control strategies. They considered that the necessary process analytics to run continuous processes should be available in a 5 year time frame. The ability of tomorrow's processes to adapt easily to different manufacturing scenarios, including both batch and continuous operations, without changes in basic downstream technologies was also considered important as the sector advances.

The Final Word

In summary, the final views from the audience on issues to consider when evaluating a transition toward integrated continuous bioprocesses were:

1. Media development will become important for optimizing the costs and logistics in perfusion systems;
2. Continuous bioprocessing (particularly in downstream) needs better online process analytics (PAT), control and hardware reliability than is currently available, but in 5 years' time that issue may be resolved;

3. Development cost is a more important consideration than manufacturing cost (at least in the early stages), and until that changes, significant investment in COG reduction alone will be difficult to justify;
4. Single-use technologies could reduce COG as much as continuous processing;
5. The complexity of continuous bioprocesses may be mitigated by using single-use or disposable technologies and this combination could accelerate industry uptake;
6. The choice between batch and continuous operations will depend on the long-term objectives of the facility (e.g., clinical vs. commercial manufacture), the level of in-house expertise with the technologies, the level of support from the organization and its strategic and operational philosophy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Acknowledgments

This workshop was sponsored by the “EPSRC Centre for Innovative Manufacturing in Emergent Macromolecular Therapies” hosted by University College London in collaboration with Imperial College and a consortium of industrial and government users. The authors would also like to thank the industrial speakers Konstantin Konstantinov, Patrick Sheehy, James Pollock, Haleh Ahmadian, Karol Lacki for their active participation during the plenary and workshop sessions and feedback on the article. The help and encouragement in setting up this workshop from Mark Bustard and Annette England from bioProcessUK is also gratefully acknowledged.

Funding

Funding from the UK Engineering & Physical Sciences Research Council (EPSRC) and support from the user consortium is gratefully acknowledged.