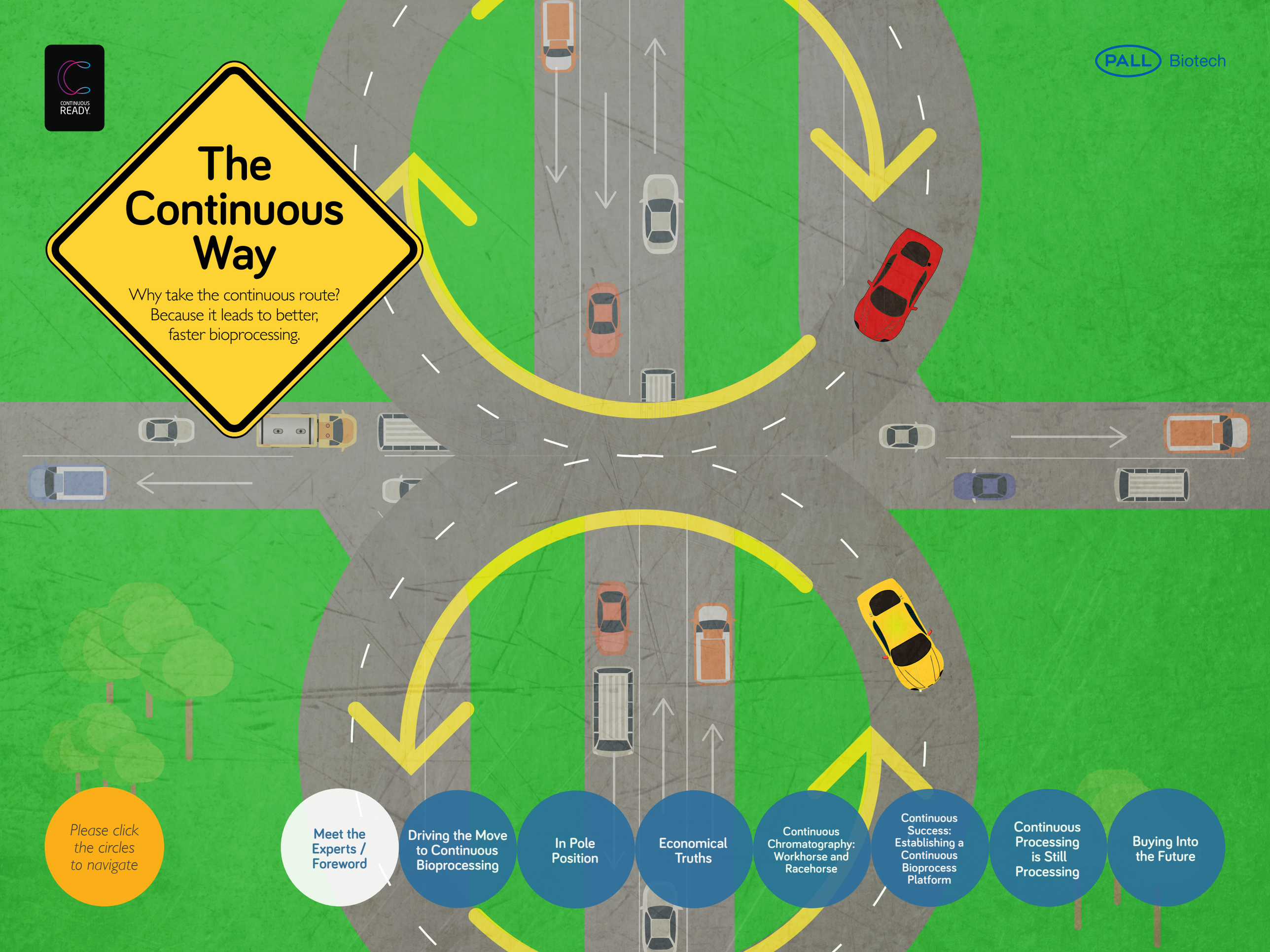
CONTINUOUS READY

# The Continuous Way

Why take the continuous route?
Because it leads to better,
faster bioprocessing.

PALL Biotech

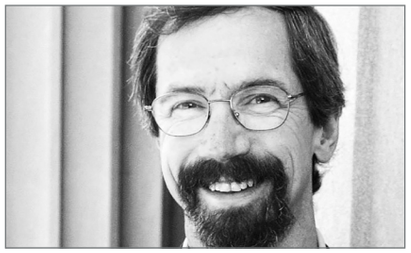


*Please click the circles to navigate*

# Meet the Experts

**Marc Bisschops**
*Director SLS, Continuous Bioprocessing, Pall Biotech*

**Jessica Chia-Yun Sun**
*Senior R&D Engineer, Pall Biotech*



**Charles Cooney**
*Robert T. Haslam (1911) Professor of Chemical and Biochemical Engineering, Emeritus, Department of Chemical Engineering, Massachusetts Institute of Technology*

**Jonathan Hummel**
*Bioprocess R&D Engineer, Pall Biotech*

**Mani Krishnan**
*Vice President Technical Services & Scientific Affairs, Pall Corporation*

**Howard Levine**
*President and CEO of BioProcess Technology Consultants, Inc*

**Peter Levison**
*Senior Marketing Director, Downstream Processing, Pall Biotech*

**Mark Pagkaliwangan**
*Bioprocess Engineer, Pall Biotech*

**Mario Philips**
*Vice President and General Manager, Pall Biotech*

**Rachel Quesenberry**
*Senior R&D Engineer, Pall Biotech*

**Mark Schofield**
*Senior R&D Manager, Pall Biotech*

**Martin Smith**
*Chief Technology Officer, Pall Corporation*





## A New Chapter for Continuous Biomanufacturing

*At last, the industry is entering the era of continuous bioprocessing and improved production efficiencies*

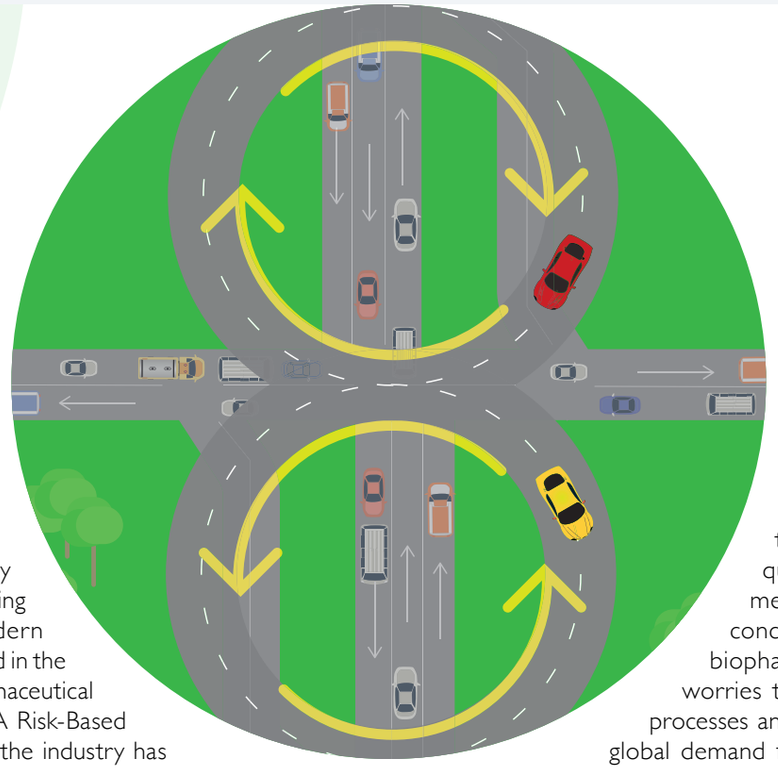
The sunk costs of large stainless steel plants, together with regulatory barriers to process change, have traditionally disincentivized the departure from tried and tested batch manufacture. Recent years, however, have seen dramatic changes, not least growing cost-containment pressures on healthcare providers and systems. This, together with the emergence of innovative products and processes, is making the switch to continuous increasingly attractive.

As with all evolutionary change, the appearance of continuous bioprocessing is the end result of a gradual process. Change began some 15-20 years ago with demonstrations of the cost savings that could be derived from replacing stainless steel systems with single-use components, and continued with the introduction of even more efficient modular systems. Put simply, continuous processing is the natural next step, and the evolution of this approach is reflected in the rate of adoption of continuous processing across many industries. As with single use, biologics manufacturers want reassurance in the form of data before they make the change; in particular, they require evidence of scalability before investing in new process technology. Since data on many continuous technologies is only generated at small scale, it sometimes seems that the clinical or production scale viability of new technology relies on aspiration rather than demonstration!

At Pall, we ensure that our innovations are supported with data, especially with scale up. Using economic models, we provide demonstrably compelling data for the superior cost-effectiveness of continuous systems; this important information is discussed in more detail on page 8. Our data-driven approach has enabled us to introduce a portfolio of continuous processing innovations. More recently, we turned our attention to diafiltration – the one unit operation of biomanufacturing processes that had never before been modified for continuous operation – and our inline diafiltration product was launched in 2017. Future advances will include acoustic wave separation methods for continuous clarification of perfusion cell culture.

My conclusion? This is a new chapter for biologics manufacturing; the time has come for continuous processing to be broadly implemented in biomanufacturing. The economic advantages are irrefutable, and the disadvantages associated with regulatory risk or system complexity no longer exist. Pall has invested broadly and deeply in this field, and stands ready to support companies in each phase of this continuing evolution.

Peter Levison
*Senior Marketing Director, Downstream Processing, Pall Biotech*



# Driving the Move to Continuous Bioprocessing

**Why turn away from established batch manufacture? Because continuous bioprocessing can deliver increased efficiency and improved economics.**

*By Howard Levine*

Batch processing has been the norm in pharma and biopharma manufacture for decades, so why should the industry consider continuous processing? Simple: continuous processing has been the natural evolution for manufacturing in a number of industries that have already made the switch, including petrochemicals, food and automotive. With continuous technologies for pharmaceuticals – and more recently biopharmaceuticals – now becoming available, companies finally have the opportunity to embrace the benefits offered by continuous processing – and it's fair to say that the industry is long overdue an update. In 2011, at the AAPS Annual Meeting, Janet Woodcock famously remarked that manufacturing experts from the 1950s would "easily" recognize the pharma manufacturing processes of today. She also added, "It is predicted that manufacturing will change in the next 25 years as current manufacturing practices are abandoned in favor of cleaner, flexible, more efficient continuous manufacturing".

In the past, the FDA was perceived to have an "enforcement first" mentality, but Woodcock's comments signaled that the agency was open to manufacturing innovation that could benefit product quality and patients. In fact, the agency had already been encouraging companies to examine how they could improve their manufacturing processes, with many modern manufacturing concepts included in the agency's 2004 guideline, "Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach". It's fair to say that the industry has taken some time to embrace continuous processing – the first regulatory approval of a continuous process for a small-molecule drug product (Vertex's Orkambi®) came in 2015 – but the tide is turning, and now it is time for the biopharma industry to get on board. From my perspective, continuous bioprocessing offers several compelling advantages for manufacture: it is more efficient, it is more economical, it is more flexible, and also improves overall product quality and consistency – an aspect that is of particular interest to regulators.

## Defining continuous

A continuous process can mean different things to different people. From a conceptual standpoint, a continuous process basically means something that, once turned on, continues indefinitely – processes in the steel industry and the automotive industry are often run this way. However, in the biopharmaceutical industry, a continuous process may be slightly different. For example, a process that runs for a defined period of time, with minimal intervention and without significant breakpoints in the process.

In the traditional pharma sector, there is a growing trend towards larger scale manufacturing to produce increased quantities of product to meet global demand. This concern has spread to the biopharma sector, as well as worries that some current batch processes and facilities may not meet global demand for high volume biologic products. Continuous processing lends itself very well to the ongoing production of large quantities of product, and so could provide a solution to this potential issue. At the same time, many companies are also developing drugs targeted to smaller, niche markets with fewer patients. For these products, there is concern that traditional batch manufacturing at small scale may not be cost effective, especially with growing pressure to reduce the cost of medicines worldwide. Once again, continuous manufacturing could provide a solution by bringing increased flexibility and the ability to produce more drug product in less time, using smaller facilities and lower capital investment than batch manufacturing.

Continuous systems also allow for much higher rates of equipment and facility utilization as traditional batch processes, using fixed stainless steel systems or even single-use systems, are not used as efficiently as possible. For example, cleaning and changeover times for a large stainless steel production bioreactor may approach the actual production time for the reactor. Switching to continuous processing allows manufacturing assets to be run 24/7, which can have a significant impact on cost of goods sold, as well as the size of a facility. Smaller facilities mean smaller workforces and lower capital investments – hence, lower costs. Small facilities making

LINKS

**Webinar**
*Modernizing BioPharmaceutical Manufacturing: From Batch to Continuous Production*

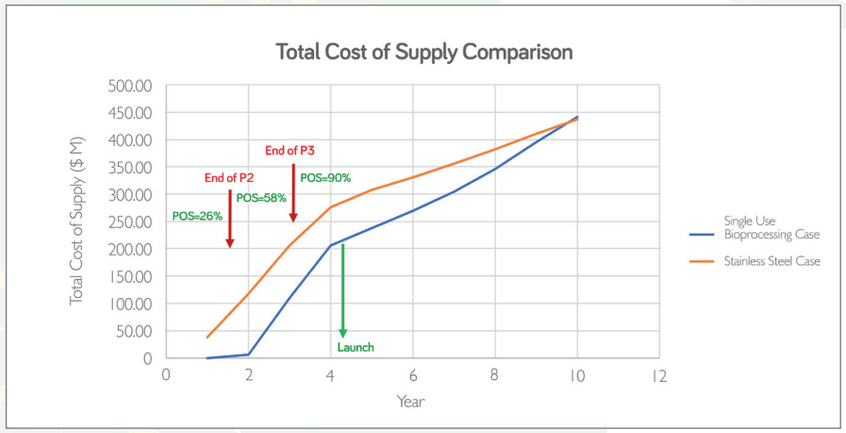



Figure 1: Estimating the value of a flexible supply chain. Use of flexible technologies reduces the overall manufacturing investment from development through commercial launch, while reducing risk.

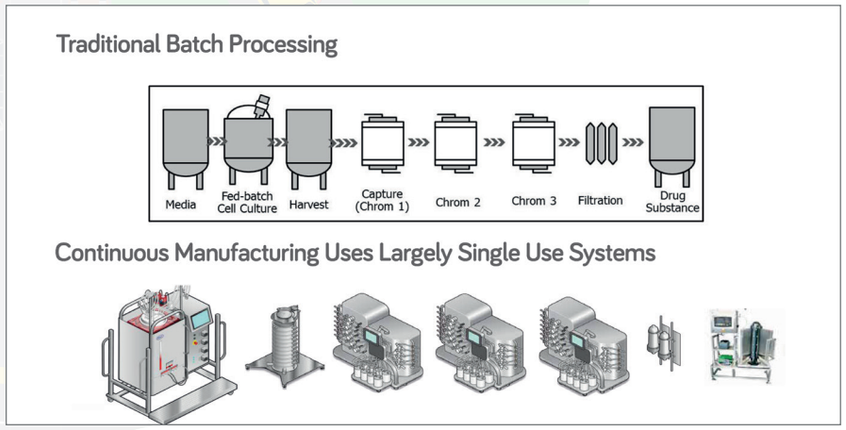



Figure 2: Continuous bioprocessing will allow for the use of smaller, integrated equipment.

maximal use of single-use systems, modular design, and continuous processing technologies (the three complement each other very well) are faster to build, meaning that investment decisions can be delayed until later in the development cycle of a new drug or until sufficient information regarding expected demand is available. Start up of a new continuous manufacturing line may require only a few months, as opposed to several years for a large stainless steel factory.

Aside from lower costs and more flexible manufacturing solutions, continuous manufacturing may also reduce the "waste" associated with biologics manufacturing, including batch variation, equipment and facility down-time, costs of transporting product from one unit operation to another, quality control at the level of individual unit operations, and variation of raw materials. Continuous processing, coupled with advances in Process Analytical Technologies (PAT) may also further reduce the quality control burden on manufacturing, further streamlining manufacturing operations.

Although much attention around continuous bioprocessing has focused on process economics, the time benefits are also significant. It is widely known that manufacturing costs have a relatively small influence on the final price of a drug. A far larger influence is exerted by the need to recoup the costs of failed drugs in the company pipeline. Because of this, companies are seeking to develop technologies that allow them to accelerate development and determine sooner whether or not a potential drug candidate will work sooner to allow them to cut their losses and move on. Small-scale continuous bioprocessing can enable the rapid, cost-effective production of clinical trial material, allowing companies to reach the failure point sooner – as developing manufacturing processes and producing clinical trial material is often the rate-limiting step to initiating clinical trials. Shorter development times and faster manufacture would speed up the transition from product concept to a first-in-man clinical trial, accelerating drug development and inevitable failures.

## Embracing change

The biopharma industry is currently split between those who believe there is a future for continuous processing in our industry and want to embrace the technology and those who feel it is unnecessary. In many cases, it is the larger, established companies who fall in the latter camp, rejecting continuous bioprocessing, perhaps because they have already invested heavily in stainless steel facilities and batch manufacturing. Some companies also have the erroneous belief that continuous processing is difficult or unproven, even though it has been effectively implemented for years in many other industries. That said, not all large pharma companies are standing idly by; companies such as Sanofi, Bayer, Novartis and Amgen are actively developing continuous bioprocessing programs.

Continuous manufacturing for small-molecule drugs is becoming increasingly common – particularly for new product launches. Continuous bioprocessing, however, is still in its infancy. As with any new technology, change is difficult for myriad reasons. Typically, the mentality of "but we have always done it this way and this way works very well" persists until there is an issue that the current way of working cannot solve! The move to continuous bioprocessing may seem daunting, but the technology relies upon single use, which is now well established in the industry. In addition, with suppliers like Pall garnering experience in the field, the switch does not have to be made alone.

Given that the FDA has embraced continuous processing so enthusiastically, it is hard to imagine a future for bioprocessing that does not involve continuous technologies. In fact, industry experience across sectors suggests that, if companies are to reduce costs and remain competitive, continuous processing is not optional, but essential.

*Howard L. Levine, Ph.D. is President and CEO of BioProcess Technology Consultants, Inc.*

# In Pole Position

**Continuous bioprocessing has always had the potential to make a big difference in biopharma manufacturing, but someone had to lead the pack. Pall is the first supplier to truly embrace continuous technologies.**

*By Martin Smith and Mario Philips*

Continuous Lab at Pall Biotech's New England Center of Excellence - Westborough, MA, USA.

Discussions around the potential of continuous bioprocessing started over a decade ago – there were many conferences around the topic, but the lack of technology solutions, as well as uncertainty over how regulators would react, prevented any serious changes from taking place. At Pall, we have always viewed ourselves as a premium technology supplier, as well as a market leader in our fields of activity. Indeed, we have been at the forefront of biologics production since its beginnings in the eighties and we are also a Tier I supplier in the markets we serve. We made the decision to commit to continuous bioprocessing a few years ago. Why? Mainly because of the many changes occurring in the industry. Every government in the world is trying to drive down the costs of their healthcare systems, there is growing competition in the biopharma space, and a move towards niche medicines that cater to smaller numbers of patients.

The industry needs more cost effective and flexible manufacturing – and continuous bioprocessing is the answer. For change to take place, however, companies need to start committing. Pall is the first company to provide continuous bioprocess options for each step of the downstream process.

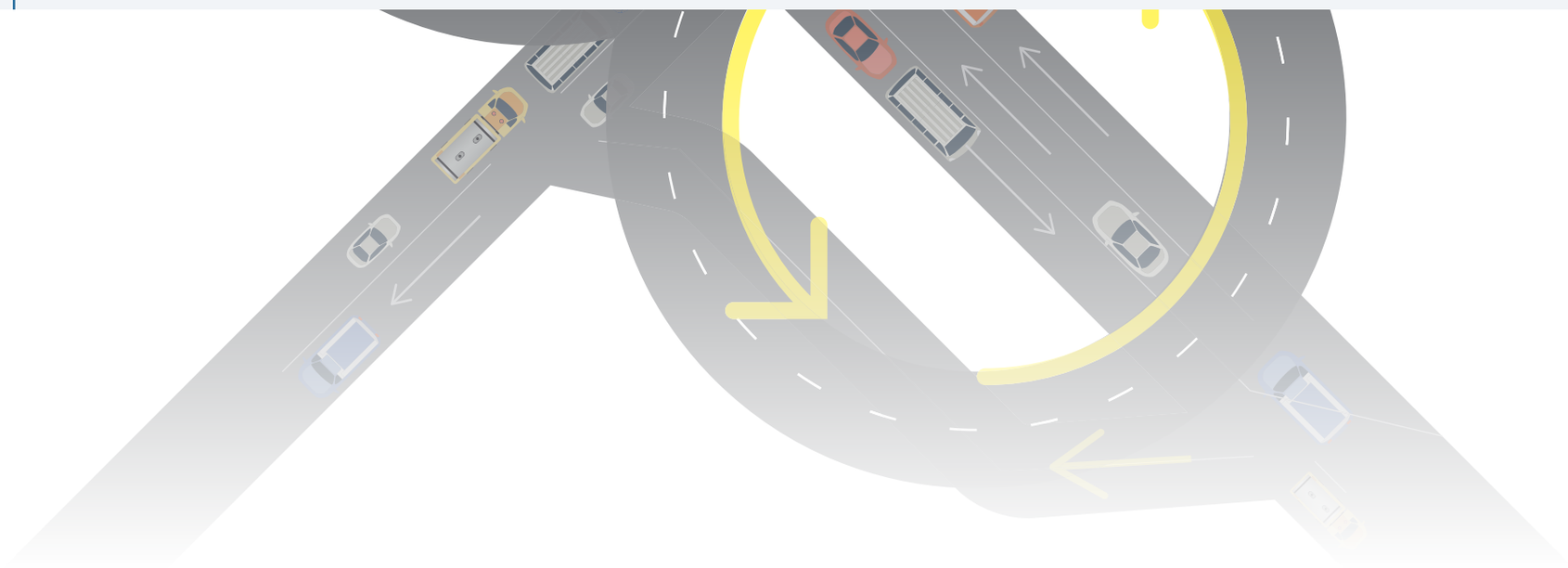
It is neither useful nor effective to create a continuous bioprocess simply by bolting together old batch operations and the technologies therein; integration requires careful management of flow rates, titers and so on – and such constraints must be addressed by new technologies and systems specifically designed for continuous operations. Pall has re-engineered every single stage of the downstream biopharmaceutical process, and we now have a fully continuous, end-to-end, in-house manufacturing system in Westborough, MA, USA (no bigger than a normal wet lab). By the end of 2017, we had also launched a range of different continuous systems that allow our customers to remain in continuous mode from process development through to fully scaled-up operations.

## It really works!

Not every player in the biopharma industry has bought into continuous bioprocessing, and we hear common concerns. Perhaps the most prevalent misconception is that continuous technology simply "doesn't work" – but it really does! We have demonstrated continuous chromatography, continuous clarification from a bioreactor, and continuous concentration of a fluid stream. We offer an on-site trial program to show customers that their unit operations will work in a new, continuous modality. Another frequently raised issue is the idea that the regulators won't accept continuous, but this is also a falsehood. Regulators want better drugs to reach the market faster, and their desires for more streamlined biologics production can be met by continuous bioprocessing. They clearly still need to see validation data, but this is not the same as being antagonistic to the concept.

LINKS

**Video**
*Pall End to End Solutions: From Design to Implementation*



It is true, however, that continuous processing is not a good match for every company. A multinational pharma company will have needs and constraints that differ from a biosimilars company, for example, and a biosimilars company will differ from a small biotech. That said, one of the great advantages of continuous processing is its flexibility: it can accommodate the demands of a top ten pharma company looking for an end-to-end continuous process, but can also be applied to individual unit operations or clusters of unit operations that might be of interest to smaller companies.

When a company is first looking to explore continuous bioprocessing, it can be challenging to know where to begin, but it is no longer necessary for companies to rely completely on their own resources. At Pall, we have experienced the implementation of a continuous bioprocess, so we understand the issues that may arise and how they can be fixed. We started out by designing and running small-scale bioprocesses on a continuous basis, but today our Westborough lab runs a line that produces monoclonal antibodies at large scale, on a continuous basis. Our initial target was to produce 100 grams of monoclonal antibody in 24 hours, starting from a 200 liter bioreactor – and we have accomplished this. We now feel that we could produce more product in the same time from a higher titer culture! We have also expanded our suite of continuous process instrumentation to address some of the aforementioned regulatory requirements.

Customer feedback on our products and development efforts has been very enthusiastic, but we find that most prefer to adopt continuous systems in a step-wise fashion; for example, manufacturers may wish to intensify two or three steps out of fifteen. Very often, the driver for change is to reduce the cost of manufacture, such as by using less protein A in the chromatography stages; when we explain that continuous chromatography requires seven-fold less sorbent than batch process chromatography, we usually get people's attention! As a starting point, customers may implement continuous chromatography, but retain conventional batch processes upstream and downstream of that.

In time, as continuous bioprocesses become more established, we expect to see customers reviewing their development pipelines to identify which new products can employ continuous bioprocessing from the very beginning. We are already being asked to support clients in setting up fully continuous lines, similar to our Westborough set-up, for clinical grade production. Integrating many different continuous operations into a single, efficient and seamless system is not trivial at any scale, so an experienced partner can make a big difference. In addition, for clients that do not have the time to rigorously evaluate and develop a new continuous system, Pall can do it for them off-site, and then transfer the process across at a convenient time.

## Continuous development

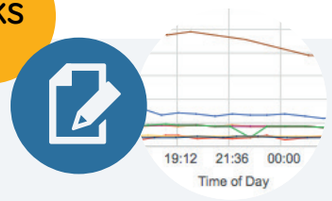
At present, Pall can offer four individual clusters of bioprocess intensification:

- bioreactor, clarification and sterile filtration operations
- in-line concentration, chromatography, virus inactivation and sterile filtration operations
- chromatography polishing
- viral filtration, concentration, final formulation and filling operations.

We are also pushing ahead with the development of advanced automation systems for monitoring and controlling continuous processes, which will be essential to truly advance the field of continuous bioprocessing. However, technology is not the only important enabler of continuous bioprocessing; Pall has not become a leader in the field just by selling products to people – it is because we work with them to overcome the challenges. In developing our continuous bioprocessing expertise, we have placed a heavy emphasis on external collaboration, such as working with key opinion leaders. We know that continuous bioprocessing can make a significant impact on making medicines affordable and getting them to market faster, but now manufacturers, suppliers and regulators need to work together to see real benefits.

*Martin Smith is Chief Technology Officer at Pall Corporation, and Mario Philips is Vice President and General Manager at Pall Biotech.*

LINKS




**Poster**
*Process Analytical Technology (PAT) for Continuous Bioprocessing*

# Economical Truths

**When it comes to hard cash and cost-savings, data do not lie – new economic models developed by Pall Biotech expose the real value of continuous processes.**

*By Mark Schofield and Jonathan Hummel*

Historically, the biopharma industry has not prioritized reduction of manufacturing costs – instead the main concerns have been quality, safety, and time to market. However, the industry is facing cost pressures from increased competition from both biosimilars and multiple treatments for the same disease. Additionally, as patient populations grow and new drugs are introduced, drug pricing increasingly becomes a societal issue. Hence, the issue of manufacturing costs has started to become a serious challenge for the industry. At Pall Biotech, we recognize that continuous bioprocessing offers the greatest potential for cost savings in biomanufacturing. Accordingly, we have developed a portfolio of continuous processing technologies and supporting consumables. We continue to expand this portfolio through in-house development programs. Our aim is to develop a complete suite of products applicable not just to commercial-scale drug manufacture, but also to early stage drug development. In all cases, the focus is firmly on maintaining or improving biopharmaceutical quality and lowering costs.

## Not just another supplier

The philosophy at Pall is that for customers to get the most out of continuous bioprocessing, the supplier must do more than simply supply products. We believe that the future involves working closely with biopharmaceutical companies to optimize their processes and deploy the best systems for their particular needs.

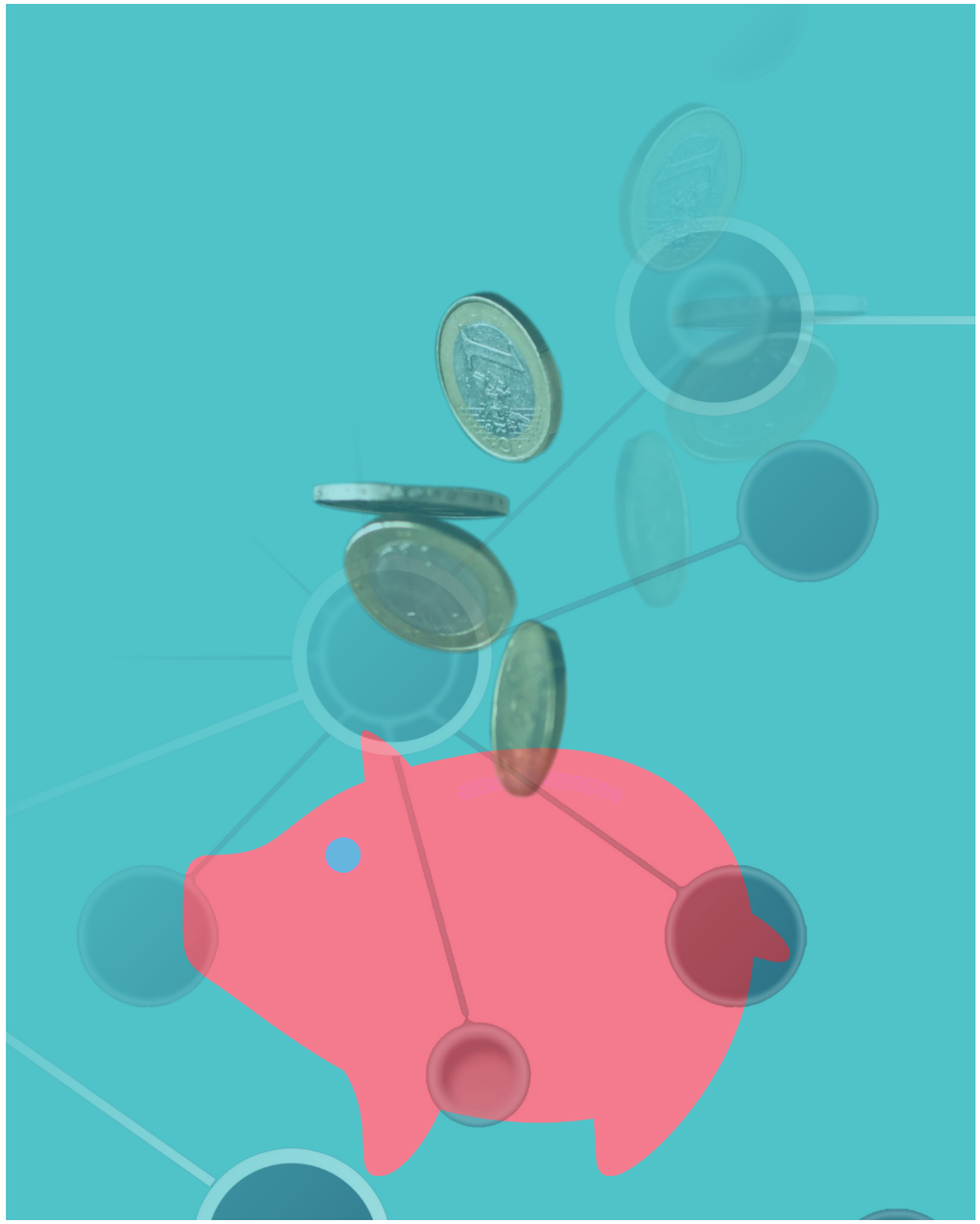
One of the great advantages of continuous bioprocessing is that it permits a reduction in the size of single-use components – this is because of the implementation of more purification cycles to produce more product as an alternative to scaling up. The most striking example is protein A chromatography sorbent, which is commonly discarded after a few batches in clinical stage processes. Continuous bioprocessing spreads process operations over more time, which allows manufacturers to reduce the component size and cost per batch. For example, we see reductions as high as 80 to 90 percent by moving to continuous purification. Therefore, there is a huge advantage to be gained from switching to continuous bioprocessing, which uses these consumables more efficiently. Single-use batch processes use disposables at a relatively large scale and hence suffer from inefficiencies related to large tanks, large buffer-storage bags, or large volumes of protein A sorbent. To get the best out of disposable technologies, they must be coupled with continuous operation; single-use per se is relatively expensive to scale up, but continuous systems permit reduced size of disposable components at a given scale. Overall, this means that continuous manufacturing is less sensitive to consumable prices, and therefore more likely to be viable in a cost-competitive environment.

But are these assertions verifiable? Historically, data to support the economic advantages of continuous bioprocessing have been hard to gather, mainly because there are few examples of continuous processing in real-world biopharmaceutical manufacturing. However, Pall employed Biosolve Process to model and compare the relative costs of continuous, single-use batch and stainless steel downstream processes in monoclonal antibody production (1).

## New systems, new model

The modeling was initiated to enable the analysis of a wide range of downstream purification scenarios. In particular, the model was used to represent clinical and commercial design spaces, respectively. These two design spaces allows us to distinguish between (i) cases with very high disposable turnover and few batches per year (clinical scenario), and (ii), cases where all parameters have been validated, levels of consumables re-use will be higher, bioreactor titers will be higher, and more batches per year will be produced (commercial scale operations).

Modeling various scenarios in these two full-factorial design spaces (Figure 1) has generated uniquely detailed data regarding the comparative cost advantages of different strategies for downstream manufacturing. The modeling indicates that for all scenarios, single-use batch and continuous single-use processes are more cost-effective than stainless steel systems (Figure 2). Continuous processes are generally the most cost-effective; 78 percent of all of the scenarios investigated are most cost effective when performed continuously; single-use is more cost effective for the other 22 percent of scenarios. These scenarios are at low volumes and low



LINKS

**Webinar**
*Process Economics of Continuous Downstream Processing*

*Clinical Factors (0.1 - 19 kg/year)*

| Process | Stainless Steel Batch | Single Use Batch | Integrated Continuous Bioprocess Platform |
|---|---|---|---|
| Volume (L) | 200 | 1000 | 2000 |
| Titer (g/L) | 1 | 3 | 5 |
| Batches/Year | 1 | 2 | 3 |
| Sorbent Reuse* | 200 cycles or 1 year | | |

*Commercial Factors (17 - 1600 kg/year)*

| Process | Stainless Steel Batch | Single Use Batch | Integrated Continuous Bioprocess Platform |
|---|---|---|---|
| Volume (L) | 200 | 6000 | 12000 |
| Titer (g/L) | 1 | 5 | 9 |
| Batches/Year | 15 | 20 | 25 |
| Sorbent Reuse* | 200 cycles or 3 years | | |

** Chromatography membrane adsorbers are reused for maximum duration*

Figure 1: Specific assumptions per design space (clinical versus commercial). Three downstream purification formats were evaluated across these design spaces: stainless steel batch (SS Batch), single-use batch (SU Batch), and an integrated, continuous bioprocessing platform (ICB Platform).

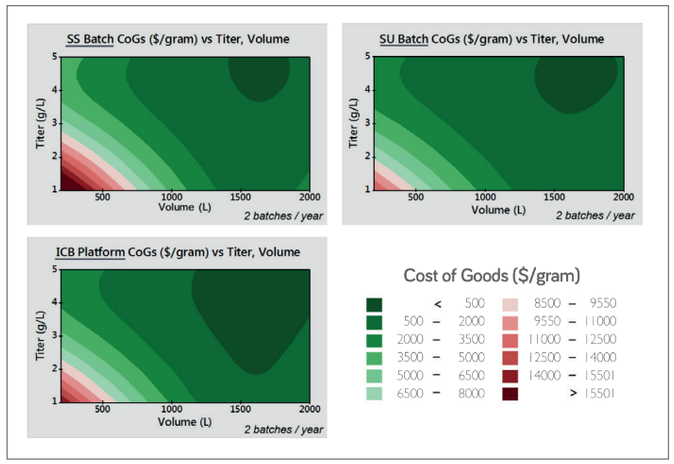



Figure 2: Comparison of cost of goods (CoGs) per gram in the clinical design space: stainless steel batch versus single-use batch versus continuous processing. The data generated via the modeling clearly indicate that stainless steel systems are the least cost-effective of the three processes. Continuous processes are the most cost-effective option except at smaller scales (< 2 kg/year), where single-use batch processes can be more cost-effective than continuous processes.

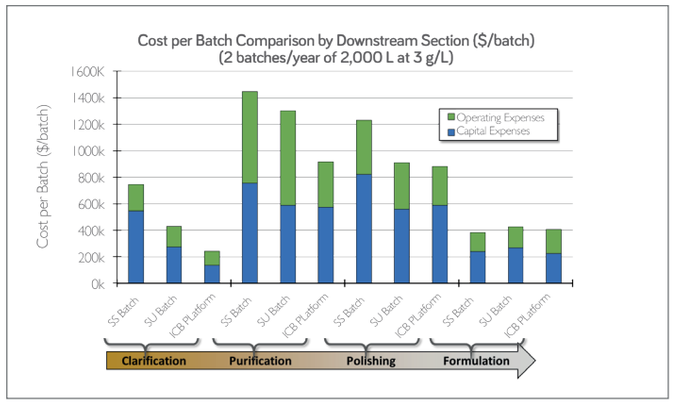



Figure 3: Cost comparison for a single clinical design space case: stainless steel versus single-use batch versus continuous processing. Sources of cost-savings per process in the clinical design space are clear: massive reductions in capital requirements (blue bars) arising from dispensing with centrifuges and filter holder purchases (clarification), and reductions in consumables (green) due to more efficient use of sorbent, filters and bags purification. SS = stainless steel; SU = single use; ICB = integrated continuous bioprocess.

titers, where the modest amount of product produced (< 2 kg/year) do not support the increased capex of continuous manufacturing equipment.

The specific sources of these cost-savings per process scenario, in the clinical design space, are shown in Figure 3; the effect on capital requirements resulting from avoiding the need to buy a centrifuge, as well as reduced operating expenses due to lower volumes of protein A sorbent and fewer single-use filter holders, is clear.

At the commercial scale (Figure 4), the continuous platform provides the lowest costs for all scenarios. For the very lowest volumes and titers, continuous and single-use batch processes are of similar costs, but at larger volumes and higher titers continuous is clearly the most cost-effective option. We attribute this to the lack of sensitivity to scale noted above; continuous manufacturing benefits from upfront capital savings by using disposables, but also makes savings from employing smaller disposable items, and from operating more efficiently. The longer operation times of continuous systems permit smaller consumable items, which means less sensitivity to the scale of monoclonal antibody throughput. This is possible with a shorter total downstream processing time than batch, due to the ability of continuous systems to operate at the same time after start-up operations conclude.

In the commercial design space, breaking down the cost savings by category (Figure 5) shows that continuous processing, again, generates large capital and operating cost savings. Operating cost reductions still largely derive from the need for fewer consumables, including protein A sorbent. Labor cost savings also play a role, due to the reduction of cleaning and buffer preparation activities, particularly in the purification and polishing steps.

Our model also allows us to predict the percentage cost savings achieved across the entire project lifetime by adopting continuous bioprocessing (Figure 6). At 5 g/L and 20 batches/year, switching from a single-use batch process to continuous would save 15 to 20 percent in costs, and switching from stainless steel to continuous would save 34 to 39 percent.

Do these predictions reflect the real world? Like any model, ours is based on assumptions, but it's important to note that our assumptions were developed using feedback from an independent third party (BioProcess Technology Consultants, Inc.) and from current users of Pall systems. This approach does not perfectly fit every manufacturing scenario, but does supply a broad indication of the available cost savings and the scenarios where continuous purification can be employed most effectively. One strength of this approach is that the modeling can be adjusted to reflect a particular manufacturing scenario so that the outputs can be relevant and tailored to a particular biopharmaceutical company's needs. Hence, we are confident that we have developed a tool that is sufficiently robust and flexible to apply to the vast majority of real-world situations.

Interestingly, the data from our model can provoke two opposite responses: people from a batch processing background think the projected savings are too high, and people from continuous processing backgrounds think the anticipated cost reductions are too low – sometimes people just see what they want to see! When people are sceptical about the data, all we can do is reiterate what we have done and provide more detail as necessary. The only way to counter scepticism is through transparency regarding data,

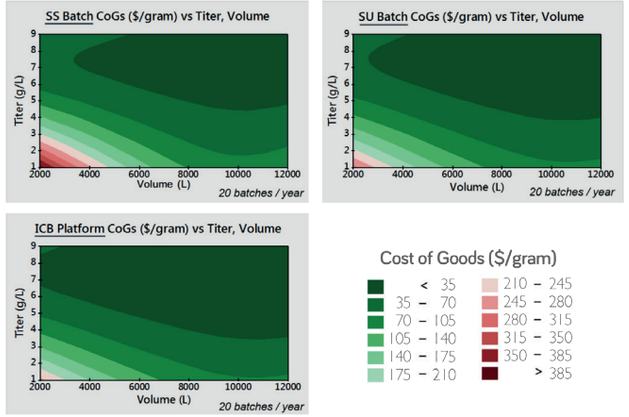



Figure 4: Comparison of CoGs per gram in the commercial design space: stainless steel batch versus single-use batch versus continuous processing. In the commercial design space, continuous processing offers cost advantages at all scales; cost-savings become greater at larger scales.

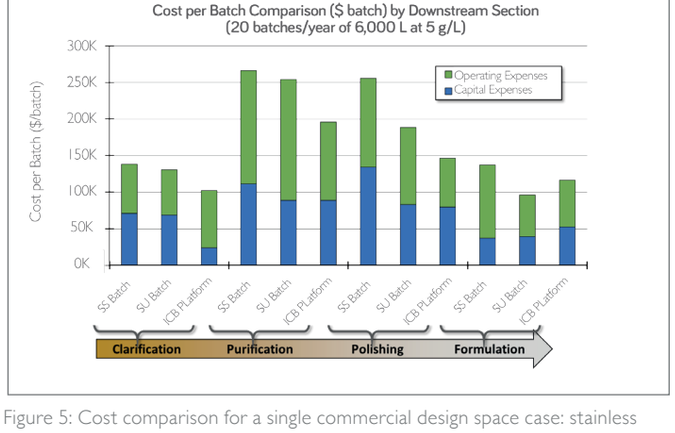



Figure 5: Cost comparison for a single commercial design space case: stainless steel versus single-use batch versus continuous processing. Sources of cost savings for the continuous process include capital (blue) and disposables (green), as well as labor costs (green), particularly in the purification and polishing steps. This is partly a consequence of the reduced need for buffer preparation and clean-in-place protocols.

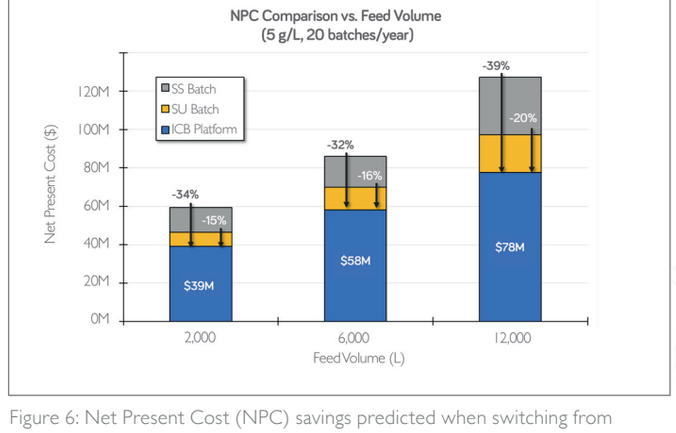



Figure 6: Net Present Cost (NPC) savings predicted when switching from stainless steel or single-use batch processes to continuous processes. The model clearly shows that switching to continuous processing will save costs over the project lifetime.

methods and assumptions, which either leads to a "aha!" moment, or an even stronger model.

## Future: progress will be continuous

The continuous process of the future will be a highly automated and very efficient process based on real-time analysis and feedback. Instead of testing the drug product at the end of the process, prior to release, future manufacturers will rely on operating within a design space according to quality by design principles, resulting in only minimal testing requirements at the process end. Maintaining operations within certain critical parameters throughout the process will be sufficient to ensure a high quality product. This is already a reality for small molecule drug manufacturing.

Given the current dearth of experience with continuous bioprocessing systems, many manufacturers would benefit from partnering with a supplier that has real-world expertise in the field. Pall is now very well positioned to offer advice in this area – and our recent process economics study has generated a body of knowledge that, going forward, will allow identification of specific cost-containment solutions in the context of the constraints associated with a client's specific bioprocess. This is important, because every bioprocess is different, and each is impacted in different ways by the capital and consumables costs associated with biomanufacturing.

So the evolution of bioprocessing towards continuous systems is well underway, but has not nearly reached its full potential. More and more continuous technologies will be brought to the market and processes will become more streamlined to bridge the gap between the current and the future state. The cost-saving potential of continuous manufacturing has only just started to be exploited.

*Mark Schofield is Senior R&D Manager and Jonathan Hummel is Bioprocess R&D Engineer, both at Pall Biotech.*

*Reference*

1. *J Hummel et al., "Modeling the downstream processing of monoclonal antibodies reveals cost advantages for continuous methods for a broad range of manufacturing scales," Biotechnol. J., Epub ahead of print (2018). PMID: 29341493*

## Key Assumptions Used in Pall's Processing Model

- New facility capital estimation
  - 10-year project lifetime, 10% future value, 12% cost of capital
  - Supporting equipment and floor area building costs are included
- Only downstream costs are modeled for all processes
- Same downstream mAb yield and final titer are assumed for each process
- A moderately challenging harvest is assumed (~40 $m^2$ depth / 1000 L feed)
- Formulation membranes are re-used per year (campaign)
- Batch and Cadence™ BioSMB chromatography flow paths are re-used per year (campaign)
  - Cleaning validation capital investment is included
- Sorbent, pre-packed column, and membrane adsorber re-use assumptions are dependent on the design space (clinical versus commercial)


# Continuous Chromatography: Workhorse and Racehorse

**Why try to improve an already established technology like chromatography? Because a continuous approach can help get drugs to the finishing line faster.**

*By Mark Pagkaliwangan and Mark Schofield*

Chromatography is the workhorse technology for bioprocess purifications. After clarification – the removal of cells and crude impurities from bioreactor harvest – chromatography is essential for the removal of remaining contaminants, both in the primary capture step and in subsequent polishing steps. Thus, chromatography systems are critical to the production of biologic drugs of acceptable quality, and have been so for many years. Given that the technology is so established, does it make sense to introduce continuous chromatography? In our view the answer is yes – because continuous systems offer significant cost savings and the potential for higher quality. To achieve the desired productivity gains and cost savings, optimizing the number of columns needed to operate a process is key, especially with the advent of higher titer upstream processes.

## Racing ahead without handicap

Chromatography steps are typically the most cost-intensive parts of a downstream bioprocess, with the primary capture step being particularly expensive, protein A sorbents, for example, cost in excess of ten thousand dollars per liter. Decreasing the volume of sorbent used in a bioprocess and reducing other consumable costs can create significant cost savings in the context of an entire bioprocess. Continuous chromatography can enable reductions in buffer by increasing operating binding capacity at faster flowrates, and reductions in sorbent by increasing productivity.

To study this phenomenon, multiple Cadence BioSMB scenarios are examined in Figure 1, each with a different column configuration. Cadence BioSMB Scenario 1 has two columns in series in the load zone, with one or more columns free to perform non-load process steps of elution, regeneration and equilibration. Cadence BioSMB Scenario 2 has three columns with a primary and two secondary columns in the load zone, with one or more columns free to perform non-load steps. The schematics for these loading configurations are shown in Figure 1. High capacity is maintained by running multiple columns in load at the same time (Figure 2); the additional load columns enable the first column to be overloaded without loss of product (product that breaks-through the first column is captured on subsequent columns), thereby improving capacity utilization (1). It is clear that the Cadence BioSMB system enables higher capacities at much shorter residence times, which leads to higher productivities.

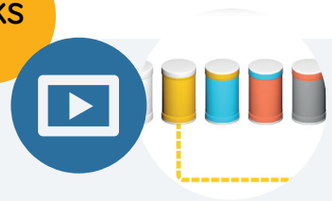
However, the cost reduction associated with continuous technology is not simply a function of increasing productivity and capacity to reduce consumables; continuous chromatography systems also deliver time and labor savings. Human interventions are minimized; less time is required to process the biologic; and shorter column residence times mean the desired product is processed more quickly. Furthermore, Pall's integrated, continuous approach permits many steps to be operated in parallel, allowing for the operation of higher numbers of smaller columns, and permitting more run cycles per unit time. This has pragmatic, real-world benefits: our recent study indicates that processes which add more columns can be up to 65 percent more productive, especially at feed concentrations above 5 g/L.

In addition, capturing product in less time not only makes it cheaper to produce, but also makes the production system as a whole more agile, which in turn facilitates process development (PD) and reduces PD costs, since the manufacturer can test more production methods and more biologics in less time.

## Horses for courses

Every bioprocess, however, is different; column numbers and configurations must be optimized on a case-by-case basis. The Cadence BioSMB system can accommodate many different types of processes, and allow the manufacturer to optimize the process

LINKS



**Video**
*Continuous Purification Using Cadence™ BioSMB Systems*

**Application Note**
*Continuous Chromatography Scalability from Process Development to cGMP Manufacturing*

*Sponsored by* PALL Biotech

*Produced by* the Medicine Maker

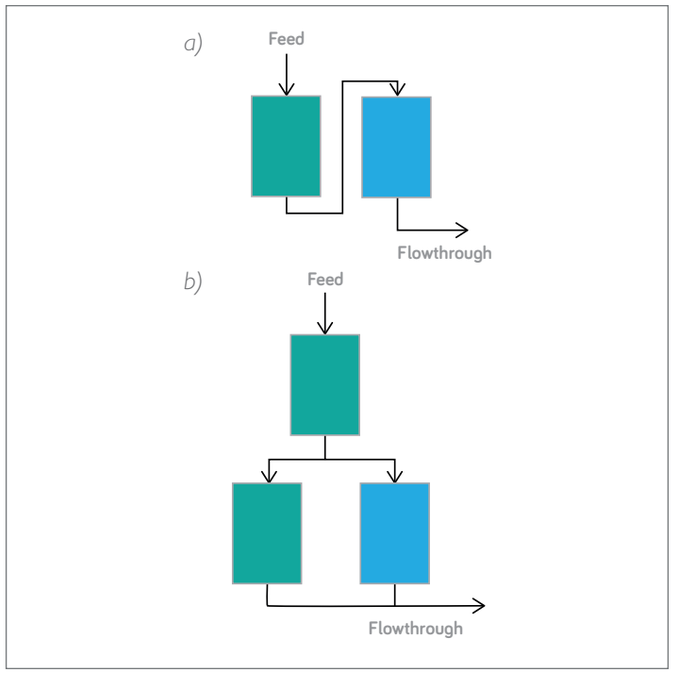



Figure 1: The two Cadence BioSMB system loading scenarios examined for this article. Cadence BioSMB Scenario 1 (a) and Cadence BioSMB system Scenario 2 (b).

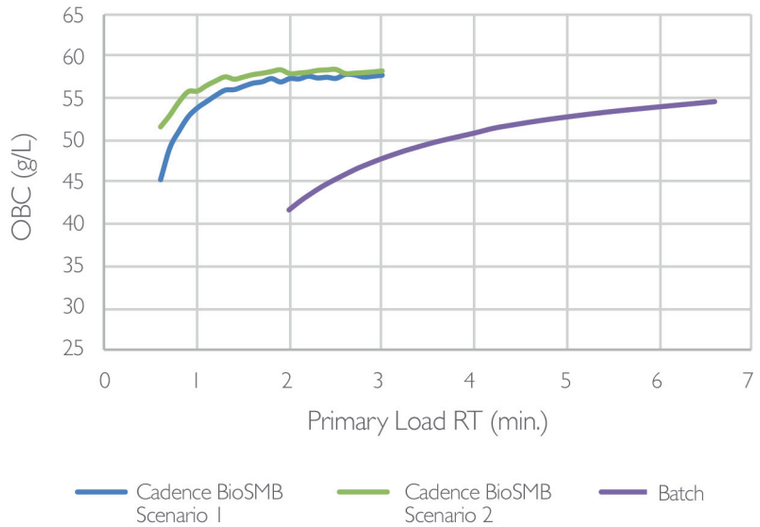



Figure 2: Operating binding capacity (OBC) versus load residence time (RT) across a single column. An investigation of the operating binding capacity for batch capture and two Cadence BioSMB scenarios across a range of residence times, using a feed titer of 5 g/L, assuming a 99% yield for continuous or 60% of 10% breakthrough for batch. The data show that, at short residence times, adding more columns to the load zone results in higher binding capacities (2).

with reference to many different factors, including binding capacity (which permits reduction of buffer consumption); productivity (which permits minimization of sorbent use); and workflow (to minimize time).

The usual procedure is to choose a titer indicative of the upstream product, and to then optimize the column numbers for that target. A total of three columns is often adequate for low titers; at higher titers, however, the loading steps are very short, requiring additional columns to manage the non-loading steps (washes, elution and clean-in-place). This behavior is shown in Figure 3, where the most productive process for each capture scenario is plotted as a function of the number of process columns at three different titers. Although such specific productivity values may vary with process specifics, the trend of increasing productivity with higher titers, and the subsequent requirement for more process columns, remains constant.

At Pall, we have developed our own tools to assist with calculating the optimal column numbers from given parameters. We can predict optimal column numbers and sizes according to the envisaged scenario and, if columns are already in place, the scenario can be adjusted to optimize the process according to the existing column configuration. In any case, the ability of the Cadence BioSMB system to accommodate up to 8 columns allows users to specify a range of operating conditions that provide both high capacities and high productivities, and thus reduce consumables use (Table 1).

Moving from batch to continuous bioprocessing requires careful consideration of many factors. For example, the relationship between productivity and operating costs is complicated by the fact that columns are only sold in discrete sizes – hence, the most theoretically productive process is not necessarily the most cost-effective given a specific processing volume and time. Pall is always happy to help work through these kind of technicalities to develop the process that is best based on particular user requirements. One example is our management of the design and scale-up of a continuous process at Merck (2). Pall began with method development using batch chromatography, then moved to small-scale PD with Cadence BioSMB-based continuous purification, and finally scaled up 150-fold to the large Cadence BioSMB system (350) for full GMP manufacturing with continuous purification. This project was based on feedstreams derived from fed batch bioreactors of up to 2000 L; note that scale-up required no changes to sorbent, buffer systems or quality assays. Furthermore, the entire project was completed in under three weeks!

It's worth noting that increasing process sophistication usually entails increased complexity. For example, the greater number of columns associated with continuous chromatography may require a greater number of valves and pumps. But this principle applies to any industry: consider how automotive technology started with

LINKS

**Webinar**
*Case Study: Merck Presents Scale-up of Continuous Chromatography using Cadence™ BioSMB Process System*

| *1 g/L* | *Number of Columns* | *Column Internal Diameter (ID) (cm)* | *Sorbent Volume (L)* | *Buffer Usage (L)* |
|---|---|---|---|---|
| Cadence BioSMB Scenario 1 | 3 | 30 | 11 | 1100 |
| Cadence BioSMB Scenario 2 | 4 | 25 | 10 | 1100 |
| Batch | 1 | 63 | 20 | 2000 |

| *5 g/L* | *Number of Columns* | *Column ID (cm)* | *Sorbent Volume (L)* | *Buffer Usage (L)* |
|---|---|---|---|---|
| Cadence BioSMB Scenario 1 | 5 | 30 | 18 | 5100 |
| Cadence BioSMB Scenario 2 | 6 | 25 | 20 | 4600 |
| Batch | 1 | 100 | 47 | 8200 |

| *8 g/L* | *Number of Columns* | *Column ID (cm)* | *Sorbent Volume (L)* | *Buffer Usage (L)* |
|---|---|---|---|---|
| Cadence BioSMB Scenario 1 | 4 | 45 | 32 | 7000 |
| Cadence BioSMB Scenario 2 | 7 | 25 | 26 | 7100 |
| Batch | 1 | 100 | 65 | 13100 |

Table 1: Column, sorbent and buffer requirements of the most cost effective process: 2000 L bioreactor, 8 hours run-time, titers of 1, 5, 8 g/L, total of 25 column volumes of rest steps (2).

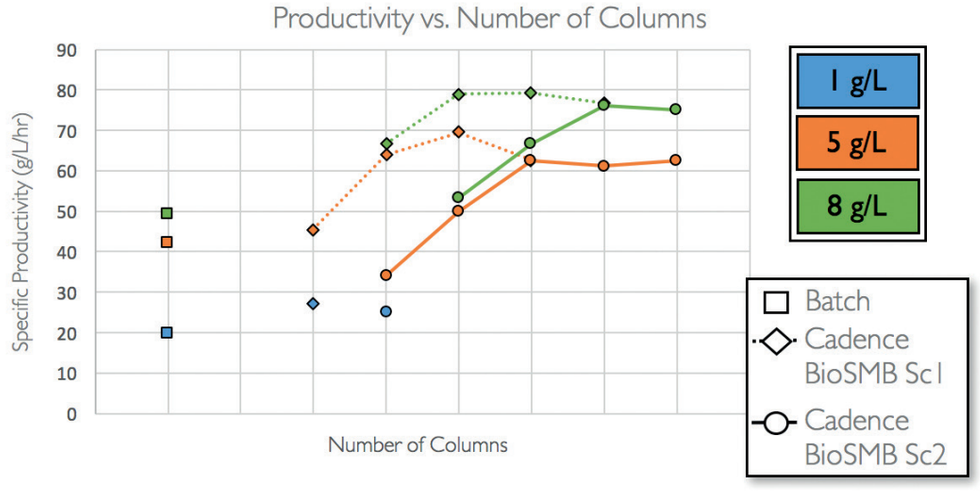



Figure 3: The most productive processes for each batch and Cadence BioSMB scenario at three different titers. Increasing the total number of columns leads to increasing productivities at higher titers.

one-cylinder machines, and now has evolved into twelve-cylinder engines with hybrid power trains. Additional complexity is simply the compromise we must make for improved performance. The real point is that Pall makes no compromise regarding reliability – Cadence BioSMB valves are tested over many cycles to ensure there are no concerns about their operation.

## Finishing lines

Optimizing column numbers with a continuous system has a number of benefits. Primarily, it reduces the use of sorbent, one of the most expensive bioprocess consumables, and so has a direct and significant impact on cost of goods. In addition, the ability to vary column number so as to run a given process at faster flow rates and/or higher feed concentrations allows more biologic to be processed per unit time. This, together with the labor savings associated with continuous operation, suggests that implementing technologies, such as the Cadence BioSMB process, will be highly advantageous in terms of process economics.

Pall provides three Cadence BioSMB systems for unparalleled flexibility of scale, from early PD to high-volume manufacture, while retaining process consistency and compatibility with single-use flow paths. In this way, the Cadence BioSMB system enables manufacturers to develop the optimal process for their specific requirements, and the tools to run that process as they see fit. In the race to get cost-effective drugs to market, older chromatography technologies may increasingly prove to be a handicap for manufacturers.

*Mark Pagkaliwangan is Bioprocess Engineer and Mark Schofield is Senior R&D Manager, both at Pall Biotech.*

***References***

1. *X Gjoka et al., Pall Application Note, Multi-Column Chromatography: Number of Columns Required for Optimizing Capacity and Productivity, (2017). Available at http://bit.ly/2j4nvrl*
2. *Pall Application Note: Scale-Up of Multi-Column Chromatography Using the Cadence BioSMB Process System (2016). Available at: http://bit.ly/2Cj8jiY*

LINKS

**Webinar**

*Reviewing Continuous Chromatography Solutions and The Effect The Number of Process Columns Has On Specific Productivity and Binding Capacity*

# Continuous Success: Establishing a Continuous Bioprocess Platform

## Adopting new technology can be difficult, not least in bioprocessing. What are the dos and don'ts, and how can Pall help?

*By Jessica Chia-Yun Sun, Rachel Quesenberry, and Mark Schofield*

The bioprocessing industry, like many other industries before, is turning towards continuous processing. The advantages of continuous processing for food, petrochemical, glass and steel industries include decreased footprint and manufacturing time, which result in economic advantages. In bioprocessing, it is predicted that large economic gains will be made through making the complete process continuous, but in particular the clarification and primary capture steps offer major cost reduction opportunities. Pall has developed technologies and equipment that allow for complete end-to-end continuous processing. For continuous clarification, Pall has implemented acoustic wave separation via the Cadence acoustic separator. For primary capture, Pall has developed the Cadence BioSMB and Cadence virus inactivation systems.

The Cadence acoustic separator enables acoustophoretic removal of cells from bioreactor harvest. This robust single-use technology is scalable and provides a decrease in footprint and buffer consumption. Continuous chromatography relies on the uniquely flexible and scalable Cadence BioSMB systems. This technology permits a variety of column configurations and flow paths to optimize productivity and minimize consumable cost. Economic benefits are evident when considering the reduction of protein A sorbent use by 80-90 percent in certain scenarios. The continuous platform also features the Cadence virus inactivation system, which is automated and employs an alternating synchronous tank strategy to allow continuous virus inactivation. These innovative technologies can be combined with other technologies in the Pall portfolio to develop an end-to-end continuous platform that is robust, flexible, and productive. The Pall continuous mAb manufacturing platform has demonstrated an increase in productivity (from 13 to 50 g/L/h for protein A capture step, and 10 to 60 g/L/h for the mixed-mode CMM HyperCel sorbent polishing step). This increase in productivity leads to reduced capital costs compared to the batch process. A recent publication demonstrates that continuous manufacturing can result in reduction in buffer usage by 44 percent, sorbent use by 95 percent for protein A and CMM HyperCel process, and 74 percent for the anion-exchange Mustang Q membrane process (1). With an advanced technology offering, and an expert development team, Pall can work with you to implement continuous bioprocesses for the efficient and successful manufacturing of drug candidates.

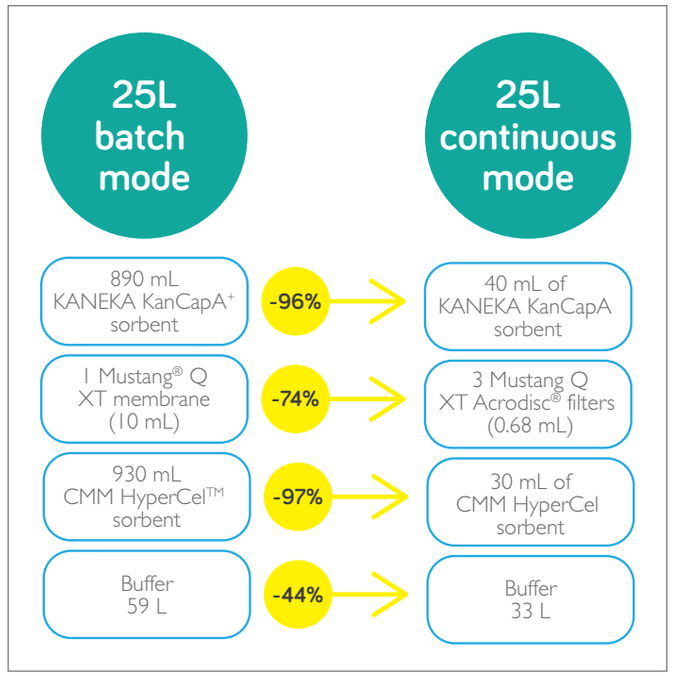



Figure 1: Impact of continuous processing on consumables. Comparison of continuous and batch modes for processing harvested cell culture fluid sample (25 L). Assumptions: (i) both processes employ same sequence of unit operations performed under optimized conditions for each mode; (ii) for batch mode, columns are ideally sized to perform purification in a single cycle.

## Process development for the continuous bioprocess

To adjust the manufacturing processes to continuous mode, the technical expertise of the Pall development team can be a valuable resource for process development (PD) and optimization. Due to the flexibility of the Cadence BioSMB system, there are many options for operating a continuous chromatography process. To leverage this flexibility, simple methods have been developed for optimization and can be customized depending on the individual requirements of the process and facility. Therefore, PD for continuous chromatography can be efficient and streamlined. As with PD for batch mode, each drug target presents distinct challenges with regards to protein characteristics and contaminant removal requirements. One objective of the Pall development team is to assist in the PD of specific drug targets for continuous bioprocessing, resulting in improved contaminant removal, reduced buffer consumption, increased sorbent capacity, and increased productivity. Notwithstanding, the end goal is reduced costs, while

LINKS

**Webinar**
*Making Virus Inactivation A Reality For Continuous Upscaled Processes*

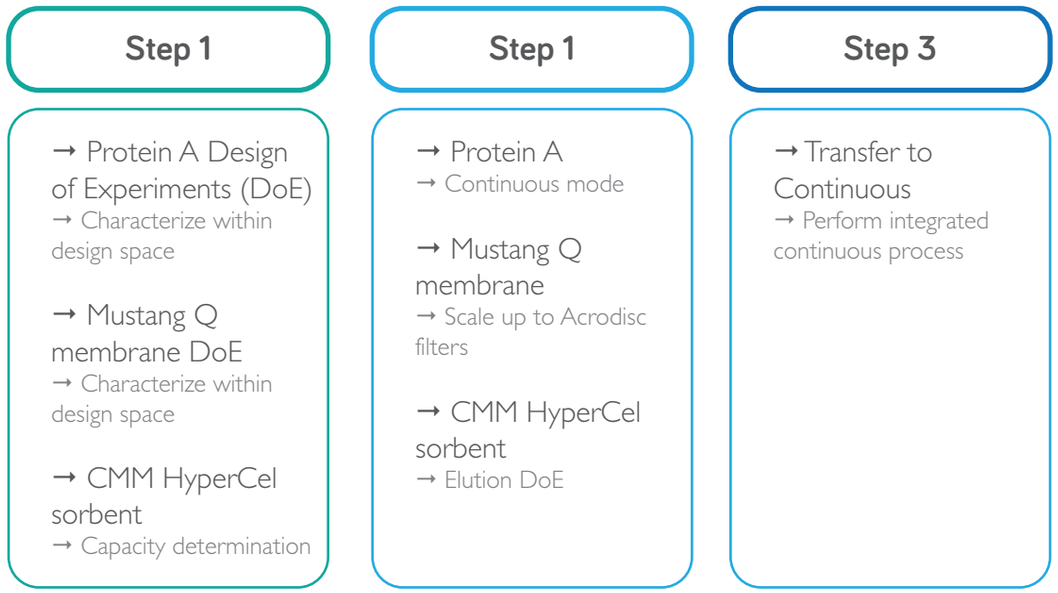



Figure 2: Three-step process development strategy. This strategy was established by Pall's development team to ensure time-efficient PD for robust mAb bioprocessing using continuous chromatography.

## Tips for Success: Process Development for the Continuous Bioprocess

- Process development should be initially conducted in batch mode to define all the operating parameters. This will ensure that all optimal conditions are identified for each unit of operation within the continuous chromatography bioprocess. The PD should be conducted to simulate the continuous mode of operation.
- To develop a streamlined continuous chromatography bioprocess, PD should minimize the steps that would interrupt the envisaged continuous operations, such as buffer exchange and product adjustment steps.
- As the final process is transferred to the continuous mode of operation, column modeling can be implemented as a powerful predictive tool to simulate the column performance in a number of column configurations. Using this method, column capacity and yield can be predicted, which can help maximize productivity of a bioprocess.

maintaining or improving product quality through PD.

Pall's standard three-step continuous chromatography platform for the purification of mAbs consists of a capture step and two polishing steps. Specifically, the platform employs KANEKA KanCapA Protein A sorbent, Mustang Q anion exchange membrane, and CMM HyperCel cation exchange mixed mode sorbent. This platform has been shown to be effective for four mAbs, each with distinct harvested cell culture fluid (HCCF) and protein characteristics. To optimize the continuous chromatography parameters, PD is conducted in batch mode and subsequently transferred to continuous mode with the use of the Cadence BioSMB system (Figure 2). This stepwise process results in efficient transfer from single column batch mode to multicolumn continuous mode of bioprocessing. Pall's development team aims to address specific constraints during collaborations for PD, including final formulation requirements, contaminant removal, proteins with unusual isoelectric points, and proteins prone to aggregation.

## Process development for the continuous bioprocess by Pall's development team

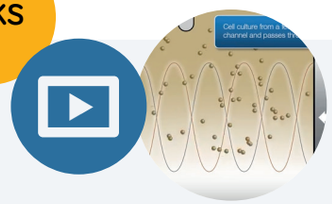
In a recent collaboration, the Pall development team conducted PD for continuous chromatography. Using the three-step strategy, the team was able to deliver two robust mAb bioprocesses within seven weeks: one process was optimized for yield and the other for purity. Using the optimized parameters, the quality attributes of the final product by continuous processing are ≤ 2 PPM HCP, 0.6 percent aggregates, and 86% percent total process yield (or 0.4 percent aggregates and 74 percent total yield when optimized for purity). Through PD and collaboration, the team delivered two robust processes with targeted yield and purity. The strategy for continuous PD was to eliminate buffer adjustments between the chromatography steps. A streamlined process combined with continuous chromatography dramatically increased productivity and throughput compared to the equivalent batch process. The next question we would like to ask is, how can Pall improve your process?

*Jessica Chia-Yun Sun is Senior R&D Engineer, Rachel Quesenberry is Senior R&D Engineer, and Mark Schofield is R&D Manager, all at Pall Biotech.*

***Reference***

1. *X Gjoka, et al., "Transfer of a three step mAb chromatography process from batch to continuous: Optimizing productivity to minimize consumable requirements", J Biotechnol, 242, 11-18 (2017). PMID: 27939321*

LINKS



**Video**
*Acoustic Wave Separation: How It Works*

# Continuous Processing is Still Processing

## Have regulations been updated to accommodate continuous processing?

*By Mani Krishnan and Marc Bisschops*

There is often a perception that continuous processing is a step-change from batch processing that carries different regulatory risks and, therefore, requires a revised regulatory approach. Nobody denies that continuous differs from batch processing in certain respects; if it did not, it would not be the significant advance that we all agree it to be. And these differences can raise challenges: for example, in continuous processing, most unit operations run for longer periods than in batch systems, which can require operators to pay attention to bioburden management and process consistency. It is also fair to say that continuous processing could require more complex instrumentation and this complexity can generate risk; for example, with regard to equipment failure.

Clearly, regulators must understand the risks associated with continuous manufacturing, and how manufacturers intend to mitigate them, but this is no different from the regulatory approach to batch processes. From a regulatory context, continuous processing is not inherently riskier than batch processing and the regulations that currently exist, and that are used for batch processes, are actually agnostic to this difference between batch and continuous manufacturing. Indeed, regulators have repeatedly stated that current regulations make no distinction between batch and continuous processes. Thus, there has been no need to issue any specific guidelines for continuous processing, nor is any such need envisaged.

Rather than challenging regulators, continuous systems present them with opportunities. In particular, the sophisticated instrumentation of continuous systems allows manufacturers to gather more information on process parameters, which means more data to show that the process is operated consistently within acceptable operating ranges. Take the example of chromatography operations; in a batch process, running a column three times generates three elution peaks. These must be compared to assess process consistency, but one will always find some differences between them because each elution peak is inherently unique. In a corresponding continuous process, however, one can generate not three but (for instance) 50 elution peaks. This makes the data amenable to sophisticated statistical analysis, such that you can establish whether observed variance is purely stochastic or is a reflection of an underlying cause. In other words, the number of data points manufacturers can generate are much greater with a continuous process, and the ability to demonstrate that they are running their process as expected is accordingly higher.

Another regulatory advantage of the greater amount of data collected in continuous operations is that it provides a better understanding of the process and permits more consistent generation of high quality products – continuous process involves operating at a steady state, less time between unit operations, and enables you to go from start to finish much faster, all leading to better consistency and higher quality. For this reason, as well as because of the advantages of speed, flexibility, quality consistency and cost reduction associated with continuous, the regulatory authorities have been encouraging the industry to move from batch to continuous. The FDA tends to be very open to innovation – they have laboratories where they can test new systems in-house, which helps them tremendously. The EMA also is very receptive to innovation; hence bioprocessing in Europe is advancing as fast as it is in the US. Both of these regulatory bodies are proactively taking clear, supportive positions with regard to continuous bioprocessing. At the same time, Asian regulators are watching US and EU regulatory developments very carefully, and are likely to move in a similar direction.

### Continuous conversations

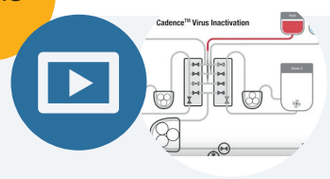
Although the strategic intent is there, implementation of continuous bioprocessing will require industry to help educate the inspectors and reviewers. We have to help them understand the nature of the differences between continuous and batch, and why these differences do not make continuous processes inherently unsafe. This is why we at Pall are engaging with regulators to get the rank and file comfortable with the manufacturing changes that are reshaping the biopharma industry. Our objective is not just to provide technologies and services but to work collaboratively with the industry and regulatory authorities to further this journey.

We believe that, as a whole, the regulators, including reviewers from the FDA, have a remarkably good understanding of continuous manufacturing – and had begun proactively educating themselves even before continuous-based submissions started coming in. It is very encouraging to see them challenge our proposed solutions, such as with regard to viral clearance, from a base of informed opinion.

### Travel companions

Continuous bioprocessing is still in its infancy and we are all learning how to handle the challenges and mitigate the risks; for example, with regards to dealing with microbial contamination in the extended processing times typical of continuous systems. We must remember

LINKS




Video Playlist
*Continuous Bioprocessing*

that regulators will not tell us how to manage continuous bioprocessing, or what specific evidence needs to be provided that demonstrates that the process is meeting all the stated quality expectations. In the end, the adoption of continuous bioprocessing is a journey that industry and regulatory authorities must travel on together. Indeed, it is important to appreciate that the introduction of continuous bioprocessing requires a new kind of relationship between suppliers – as technology providers – end-users and regulators. In particular, the role of the supplier is changing – it is increasingly important for us, as suppliers, to provide guidance to, and learn from, the other two parties. All three parties possess critical expertise, and the more that suppliers, regulators and end-users work as a collaborative team, the better returns we will each get from the adoption of continuous bioprocessing. As one example, Pall is participating in a three-way collaboration to demonstrate virus safety for continuous processing. This requires input from three parties: Pall contributes continuous processing equipment and knowhow and knowledge on data analysis, the end-user provides multiple representative molecules to run through the process, and the regulators provide assistance with experimental design and execution. This tripartite agreement will lead to a thorough understanding of the nuances of virus clearance in a continuous process, to the benefit of all three parties.

## Future moves

In a way, continuous bioprocessing has appeared at exactly the right time. Over the past five to seven years, there has been increased understanding of the importance of Quality by Design, as per ICH Q8, and quality risk management, as per ICH Q9, for batch processes and how to implement these in batch processes. That experience has been enormously helpful for the introduction of continuous bioprocessing. The industry has already gone down that path with batch processing and is now well-positioned to mitigate similar risks in continuous bioprocessing.

That said, the environment is never static, and some evolution of our understanding and methodologies is inevitable. In particular, regulators will increasingly demand more consistency, from a quality perspective, for both batch and continuous processes. This will not require any changes in regulations per se; rather, it will involve increased emphasis on statistical methods, simply because it makes more sense to use statistical analysis on the large quantities of data generated in a continuous process. Most or all end-users are increasingly exploiting statistical analysis to demonstrate consistency of their processes and the resulting product quality; nevertheless, this way of doing things is new to both technology providers and end-users; it is another part of the journey we are jointly undertaking.

As a supplier of technology, Pall is thinking very carefully about how to best integrate these statistical tools with our new equipment – it is critical that the equipment and analytics work together to support real-time decisions. Our philosophy is that, in order to integrate multiple continuous operations, we must be willing to collaborate and combine our technologies with other systems available in the market. Effective integration will rely on open communication and open data sharing.

One of the advantages of continuous processing is that, due to higher overall productivity of the facility, the unit operations are smaller than in a facility utilizing a batch process. Smaller unit operations facilitate the use of single-use technology and the ability to fully close, or functionally close, the processes, which would substantially mitigate the bioburden risks. The use of continuous chromatography, for instance, enables the use of smaller and potentially gamma-irradiated chromatography columns. Furthermore, the columns can be operated to the end-of-life within fewer campaigns, further mitigating the risk of bioburden growth in these high-area systems when operated and stored for extended periods of time.

The future regulatory challenge lies not in safety or quality issues, but in the application of current regulations in the context of continuous bioprocessing. Industry would benefit from more guidance here. For example, in a batch process we design and optimize each unit operation as a discrete step, but continuous processes are different in that a perturbation in one unit operation may be translated to the next unit operation. In a batch process, that perturbation would have been detected during monitoring of the output of that discrete unit operation, giving the manufacturer the opportunity to deal with the variation as appropriate. In a continuous process, by contrast, such perturbations, in theory, could go undetected before the material is processed through downstream unit operation(s). Therefore, continuous bioprocessing requires the development of robust analytical capabilities to enable identification of variations, tracking of any output materials that might have been affected, and determination of whether the product is still within acceptable specifications. Fundamentally, it requires a rigorous understanding of the critical aspects of the process, so that operators may control what needs to be controlled to maintain quality. This type of control is no different from that associated with batch processing – the only nuance in continuous is that we must apply the controls in a slightly different way.

### Key Trends in Continuous

- There is increasing recognition that technology sufficient for batch operations is often too slow for continuous systems: e.g. bioburden assays may require days to deliver results.
- This is driving the emergence of new assay technology, for example nucleic acid-based microbial assays.
- Satisfactory development and acceptance of these new assay techniques requires close collaboration between technology providers, end-users and regulators. One example of Pall's collaborations in the continuous field is an agreement with WuXi to jointly establish a laboratory for continuous monoclonal antibody manufacture (1).
- At the same time, suppliers must be proactive in educating industry on the challenges and opportunities of continuous systems. One of Pall's efforts in this field includes a partnership with the BioFactory Competence Center in Fribourg, Switzerland, to launch training courses (from early 2018) in continuous bioprocessing (2).

*Mani Krishnan is Vice President, Technical Services and Scientific Affairs at Pall Corporation, and Marc Bisschops is Director SLS, Continuous Bioprocessing at Pall Biotech.*

***References***

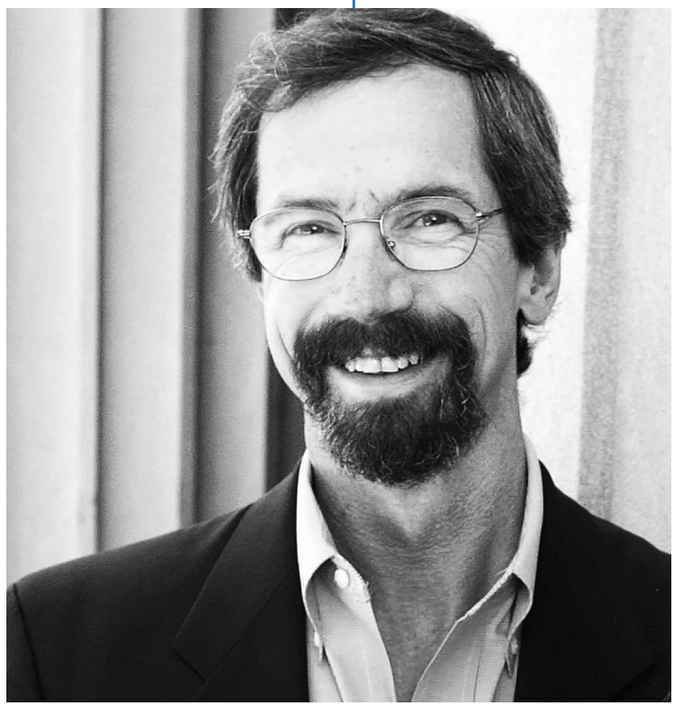
1. *Cision PR Newswire, "WuXi Biologics and Pall Corporation Establish Joint Continuous Bioprocess Laboratory" (2017). Available at http://prn.to/2Bol2Dh. Last accessed December 14, 2017.*
2. *Pall, "Pall Partners with BioFactory Competence Center to Launch Practical Continuous Bioprocessing Courses Featuring Pall Life Sciences' Cadence™ Technologies; Dedicated Training Facility Planned" (2017). Available at http://bit.ly/2AnZRgS. Last accessed December 14, 2017.*

LINKS

**Application Note**
*Cleanability and Re-usability of Cadence Inline Diafiltration Modules*

# Buying Into the Future

**We glance back at the history of continuous processing, and take a look forward with Charles Cooney, Robert T. Haslam (1911) Professor of Chemical and Biochemical Engineering, Emeritus, Department of Chemical Engineering, Massachusetts Institute of Technology, USA.**



What key events or people influenced you to work on continuous systems?

I've been fortunate to work alongside some wonderful scientists. As an undergraduate, I studied under Professor Arthur Humphrey, one of the early pioneers in biochemical engineering, and during my PhD I was advised by Daniel Wang, who also had been a student of Arthur Humphrey. Following my studies, I joined the faculty at MIT, where I focused on the interface between chemical engineering and biology – this exposed me to researchers at UCL, not least Peter Dunnill and Malcolm Lilly, who were tremendously inspiring to work with. A pivotal point in my career was a visit to Genentech in its early days, and meeting with Bob Swanson, the founding CEO; at that time there were only a handful of employees. I still remember sitting across a table from Bob and looking at a large bottle he'd put in front of me. It contained what was then the largest supply of human growth hormone ever seen in any one place. Being exposed to Bob's vision for the future of biotechnology for recombinant human therapeutics made it very easy to say yes when he invited me to become a consultant for Genentech; in fact, that was the moment when I truly bought into the future of biopharmaceutical manufacturing. Another pivotal moment for me was my early involvement as a Board member of Genzyme when we recruited Henri Termeer to be the CEO. I stayed on the Board with Henri for the next 30 years! A third inflexion point in my career was my recruitment as the founding director of the MIT Deshpande Center for Technological Innovation, which had been established with a gift from Gururaj 'Desh' Deshpande and his wife in 2002. It was fantastic to have the opportunity to support innovation across the entire MIT campus and to translate early stage ideas from the laboratory through to market. All of the above individuals were pivotal in my career – they provided leadership that helped drive biotech from early recombinant DNA technology to the current excitement around continuous manufacturing systems.

Why has the biologics community been slow to adopt continuous processing?

Academic interest in continuous bioprocessing predates modern biotechnology. The 1940s to 1960s saw chemical engineers move from batch to continuous systems, and that trend did not go unnoticed by the fermentation community. Even in those early days, we were interested in the concept of continuous processing for vaccines and antibiotics. Indeed, my post-doc at Squibb involved manufacturing penicillin in 60 cubic meter reactors by a process called repeated fed-batch, which essentially was a form of perfusion culture. Continuous bioprocessing is actually not that new, but its adoption in modern biologics manufacture has been slow. Part of the reason is that even a few years ago, the economic and quality benefits of continuous were far less compelling than they are in today's biopharma environment. Also, the dramatic advances in continuous technology over the last five years mean that these systems are now far easier and less risky to implement.

What challenges remain for the development of continuous bioprocessing?

A particular challenge (and opportunity) is in the integration of continuous operations. It is not enough to improve individual unit processes; we must also connect them efficiently. In fact, my opinion is that our future challenges lie not in continuous bioprocessing per se, but in integrated continuous bioprocessing. Remember, continuous bioprocessing is well-established – perfusion culture has been the method of choice for unstable proteins, such as glucocerebrosidase or factor VIII, since they were first commercialized, as they are fundamentally unsuitable in batch culture. Furthermore, each individual step in bioprocessing – culture, separation, purification – is inherently continuous, but we have always chosen to operate them in batch mode in the past. The real challenge now is to fully integrate the different steps in a continuous fashion.

How can we advance continuous bioprocessing?

My firm belief is that the interface of science and technology holds major opportunities, but to find and exploit these opportunities will require an interdisciplinary approach. Bringing together biology, chemistry, computer science and chemical engineering will allow us to take advances from disparate fields and translate them into processes that provide new therapies. Another key success factor will be a willingness to break down silo thinking; focusing only on the silo of immediate interest is too common, and not the way forward.

Similarly, if continuous bioprocessing is to achieve its full potential we must encourage a productive nexus between academics, manufacturers and technology suppliers.

What does the future hold for continuous bioprocessing?

Advances in analytical sciences, from genomics to product characterization, will be absolutely essential to continuous processing. Advanced analytics provide a vocabulary that allows manufacturers, scientists and regulators to have a meaningful conversation. In fact, parallel implementation of new analytical science by both manufacturers and suppliers is now a major enabler of integrated continuous bioprocessing. But clever technology won't get us far if it isn't embraced by regulators – fortunately, the FDA, EMA and Japanese PDMA have all made it very clear that continuous bioprocessing is covered by current regulations and have gone out of their way to encourage innovation in this field.

LINKS

**Podcast**
*Continuous Biomanufacturing Implementation Now and in the Future*