THE CONTINUOUS LEARNING CURVE: SELECTING THE RIGHT PRODUCTS, PLATFORMS, EQUIPMENT

Simon Hawdon, Principal Scientist, CPI's National Biologics Manufacturing Centre

ABOUT

Simon Hawdon is a Principle Scientist at the Centre for Process Innovation in the UK. Simon has over 20 years of experience in biotechnology and bioprocessing previously holding positions at Lonza and Eurofins. Chris and John Bonham-Carter, Vice President of Business Development and Product Management, Erbi Biosystems, discuss the technical considerations for a successful continuous bioprocessing system.

Simon Hawdon,
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John Bonham-Carter
VP Business Development and Product Management, Erbi Biosystems

JBC: Could you give a brief introduction to Centre for Process Innovation to our global audience?

SH: CPI is one of the founding members of the UK government's high-value manufacturing Catapult and it was set up to bridge that gap between the innovative, small enterprises or university labs and the commercialization of products. We were set up to develop capabilities, to scale up, develop, and commercialize the innovative products from UK universities and small enterprises and then turn them into high-value products. We also do collaborative R&D and commercial projects.

We work across a lot of different sectors and the different industries that we work in give us a unique perspective and bring people together across different disciplines.

In the biopharmaceutical area, we run both continuous and fed-batch systems. The Darlington facility has traditional fermentations, so mammalian culture and we do bacterial culture. We also have downstream facilities up to a small, 150-liter pilot scale. We have high throughput process development capabilities, including robotic liquid handling systems. So, we can help from the scale-up processes all the way through to commercial-scale manufacturing.

JBC: When you have a customer or collaborator that comes to you looking for innovation, you take what is often a batch process, why would you make the effort to convert a batch of fed-batch process into a continuous process?

SH: The drive would come from the customer to do that, but the reasons behind it would probably be economics. There are quality advantages too, as the continuous process itself means the product is produced in a steadier state, as such, it's a more consistently produced product, higher quality and more reproducible. Economically speaking, the process is intensified, so the productivity is higher and expensive materials are used more efficiently – the columns are smaller and reused more often, and they're also used to higher capacity.

Also, one of our goals is to work towards real-time release and some of the process analytical testing that comes hand in hand with continuous biomanufacturing. Once you've achieved that, the economic benefits will be huge because it avoids lengthy delays in terms of inventory hold; we all know the further downstream the product goes, the more expensive it becomes. Therefore, having that product sitting in a freezer or a fridge for six weeks can incur a huge cost. Real-time release would cut down on that and that's a huge saving.

JBC: When do these costs start to be more impactful? Is there an optimum time to move to continuous biomanufacturing?

SH: The earlier you do it the better, especially from a regulatory point of view because you would still have to validate everything to the same standard. The sooner you do that, the less you're double-working things further down the line. One of the unique things about continuous is that your development scale could potentially be the same scale as your production scale.

As such, process development could improve the timescale to production because there is no scale-up and, in a traditional batch system, you would do two or three validation batches at several hundred liters, maybe produce grams or kilograms of product but there's no way of cutting that down. Whereas in a continuous system, you could say that once the system has reached a steady state and you've produced some product at a steady state, you could run your validation batches at a much smaller scale, which would be a lot cheaper and quicker. Additionally, you don't need to change the equipment to go to a production scale either.

So, you've eliminated a lot of risk in that scale, particularly if you're going to 20,000 liters, that's an investment in that tech transfer.

JBC: Is there an example where you've had a customer who has benefited in the way you've described? Do you have any case studies you could describe to expand on this?

SH: Automation is nothing new in production. The automation systems we've been using are based on Siemens PCS 7, it's all established, there's nothing new about it. In terms of the equipment, there's a difference between running continuously and in intermittent batches, but most of the time equipment failure rates are measured per hour. In that respect, you could still measure it in a continuous system. Those failures might happen more often in terms of calendar days and months, but it might be less frequent per hour because of the way machinery works, i.e., with seals and things like that, sometimes they're better off working continuously than intermittently.

JBC: If you've implemented automation, you've obviously got to prove that automation is reliable. There's an investment in both time and the human aspect of training, and that interaction also becomes critical, but is it true with that automation there is less human interaction or is that a fallacy?

SH: This is part of what our project is trying to evaluate. I would assume there would be less human interaction if there were more automation. Especially with advanced process control; the aim of that would be to reduce human interactions with the system so there are fewer opportunities to introduce contamination events. Also, these systems are running 24/7, and people don't work well at three o'clock in the morning. As such, I think it would be wise to cut down on human interaction, that's the only way of running with completely automated systems. Why shouldn't a goal here be to have a kind of a black box system where you just switch it on and leave it? That's the ideal situation for any kind of manufacturer, isn't it?

JBC: Is it critical to get new sensors into these processes so you improve reliability? Is it a nice-to-have or are we at a point where it's a must-have to get wider adopters?

SH: I think it's a must-have right now for process development, even if your production is a few years in advance, you'd be in development now. To be able to develop continuous processes, you need inline PAT and there aren't many options, especially if you want to control critical quality attributes. The current benchmark is mass spec but it's unlikely that it's ever going to be real-time and inline. That may or may not be a problem because if you have parts of your process where there are hold tanks, then you could see how you could time the analysis in such a way that it doesn't become a problem.

There aren't many PAT technologies out there now that can be mounted inline, so spectroscopy seems to be the way it'll go.

JBC: So, what happens if or when you deviate, is that something that is hard to handle today or is that a misplaced fear about the deviations?

SH: This depends on process development. When you're talking about an ideal level, you would avoid those variations because you would have advanced process control. That's why I made the distinction about development because in development you would iron all these kinks out. In development, you might have lots of sensors to develop the process, but when you go into production, you might take a lot of those out because you've developed the process.

Another option is residence time distributions, you could use that kind of analysis to kind of divert any product that was out of spec. It can sometimes be possible to reprocess any diverted material for future use or it might have to be diverted to waste. However, you would need inline PAT to do that.

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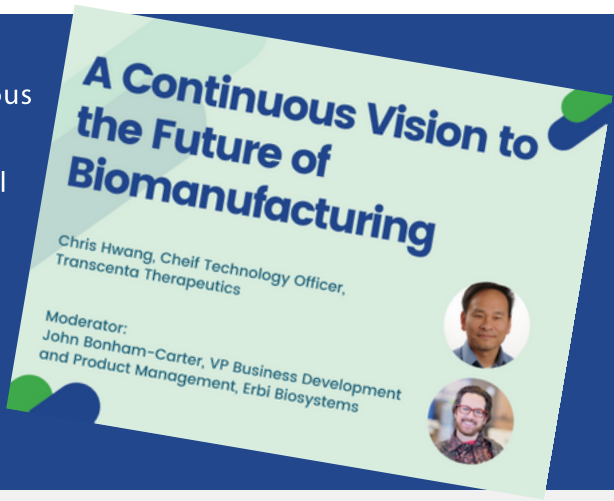
This case study was presented at Evaluating Biopharma's Continuous Bioprocessing – Justifying your Company's Investment virtual networking and educational event which included three additional case study presentations and two interactive networking sessions

Details of future events can be found here.

You can watch Simon's case study in full and on-demand here.



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Evaluating Biopharma is a convener of knowledge, data, and industry leaders within the biopharma and bioprocessing industries. Built upon the foundation of BioPlan Associates decades of data collection and analysis, Evaluating Biopharma brings together top industry experts, innovators, decision-makers, and leading providers so that together they can share, evaluate and discuss critical topics that will help biopharma and bioprocessing leaders advance life sciences.

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