THE FINANCIAL IMPACT OF A CONTINUOUS STRATEGY

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ABOUT

Joseph Shultz is Vice President of Bioprocess and Product Development at Evelo Biosciences. Previously Joseph has led teams at Novartis and Amgen building factories of the future. Joseph and John Bonham-Carter, Vice President of Business Development and Product Management, Erbi Biosystems discuss the financial impact of a continuous strategy.

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JBC: Amgen was one of the first, if not perhaps the first, company to embrace new technology in an intensified maybe semi-continuous mode but that started something which dramatically changed the industry. So, when you were there, what was the thinking of the leadership behind this innovation?

JS: Thinking back, the idea was to challenge whether we've been doing it the right way over the last 30 or 40 years. If you look at biopharma, not much has changed from a manufacturing standpoint, so it was a complete rethink of what drives manufacturing today, i.e., what are the prevailing market forces, and if we're meeting those challenges appropriately.

JBC: When you reviewed those challenges and requirements, did you know everything upfront or to what extent were there challenges you couldn't foresee that perhaps made you change direction on that journey?

JS: The key was setting out a base understanding of the challenges we were trying to meet and with the realization that, along the way, we were going to come across challenges, but also that we had ideas of what tools we could use to meet these challenges. This approach also gave rise to openness to adapt. To be clear, the challenges we saw at the time were:

1. Health care costs were a major driver and the number of people seeking healthcare was soon going to overwhelm the amount of money that payers have
2. New modalities coming to meet that challenge from research, but traditional batch monoclonal antibody plants are limited in their capability
3. The traditional model of the large, centralized giant facilities is outdated and overwhelms most companies with underutilized capital and labor

As such, what we looked to do was to turn that model completely on it on its head so we could get more out of smaller facilities that are nimble, fast to build, and replicable.

JBC: This is quite a significant change. How did the senior leadership get comfortable with taking some of the risks that you did on that journey?

JS: I have experience doing this at two different companies; Amgen was the first and then Novartis, and it was different for both. At Amgen, it was very much driven by the development organization and there was quite open-minded senior management who were interested in pushing to meet the demands for the products that they had at the time.

In the second instance, it was a confluence of a really good situation of very open-minded leadership at Novartis when I was there that, plus a key factor of a reasonably-sized batch network that was completely – or soon to be completely - utilized. The openness was there to rethink the next generation of manufacturing capability.

That's important; if you have unused capacity, you're never going to get the investments because if you're still paying for that unused capacity why add more?

JBC: Was it a different story at Novartis? I guess there was a more risk-averse nature in the senior management?

JS: There was but at the time we initiated the program, there were a couple of key pioneers who were willing to have an open mind and listen to the concept. Then when you lay out the business case and you build it, you do so in a way that everybody sees there's a little in it for them; R&D gets the flexibility they need, development gets to the clinic and to market faster, manufacturing gets cheaper and more flexible, and quality gets simpler systems. The impact this has across the organization is that you're solving problems, so you start with the problem, and you look for solutions, as opposed to how it's worked traditionally, i.e., we find solutions and then go hunting for a problem to solve with it… and that brings us to 'continuous'.

Continuous is an answer, it's a tool, it's not the objective. When you use it as a tool to solve problems, then you're using it right and it serves your business case.

JBC: So, at Novartis, that ability to understand how this tool (continuous) could impact the different business drivers is what led the senior management to realize it's worth backing? I'm sure there were bumps on that road when you could have had design reviews and various other business reviews to say this isn't going right, did you experience any of those things and if so, how did those problems and overruns and costs impact that journey?

JS: Of course, there are always bumps in the road but if I look back, what we said we were going to do at the start is exactly what we did, so the business case is everything. When you have a strong business case – and after a while, your job becomes implementing and reminding people of the business case – so through a variety of organizational changes, the support can be maintained.

However, that's not enough you have to come with data. Part of the original plan was how to implement the business case, step by step with key milestones and progressive building upon previous successes, and while you trip here or there, you get up and dust yourself off and try again. Those who know me, know I like the metaphor 'how do you eat an elephant?' and the answer is bite by bite, step by step.

We started with dipping into disposables which, at the time, was not an industry-accepted thing. We put some of the first GMP clinical disposable bioreactors in play, then extended to perfusion and continuous capture, then to demonstrate that we could do monoclonal antibodies, eight or nine different molecules actually ended up proving themselves out. We never really had a failure in implementing the technology but there are limits to where continuous is the best value and where it's not.

The end goal is to expand beyond monoclonal antibodies into the flexibility of multiple modalities. When you approach it in steps, you don't end up choking on the first bite when you eat that elephant.

JBC: Thinking about this movement to continuous and intensified cultures, why are some making rapid moves into it and building facilities while others are sitting on the sidelines and waiting? How would you view that if you're an independent person evaluating which road is best for you?

JS: I think it's situational and specific to where you are as a company. If you've already invested quite a lot in traditional batch culture it's hard to move away from that, especially if you're underutilized. There are examples in the past where tremendous batch facilities were built then the pipeline didn't come and there's no drive to intensify.

My provocative statement is that biopharma is not very innovative. Other industries tend to innovate, but we tend to keep doing the same thing. What it takes is for somebody to be the tip of the spear and prove that it can be done, then there are quick followers.

Now, on the other hand, I would say that those who don't have a manufacturing network yet have the opportunity to start with these approaches by following the lessons learned from those who are the tip of the spear.

JBC: Is there an optimum? Do you need a certain number of kilograms per year or a certain size of portfolio for continuous to make sense or is this applicable at any time?

JS: I'm a big advocate of continuous or integrated processing for many reasons but part of being the tip of the spear is you get bloody occasionally. Continuous isn't best in all cases, there is a minimum batch size or output mass or output per batch that is needed because when running continuous closed systems, (and there are a lot of nuances that go with this) tools like disposable technologies, sterile connector technologies etc. are very useful but they're expensive currently. This can overwhelm you if you have a low output cell line, I had this failure at one point where we didn't fully understand the cost of the raw materials because we were still building the systems. In the end, when we did the math, it was much more expensive to run a continuous system per gram than the other seven programs that we had tested. Considering this limitation, there's probably a need for a hybrid network if you're going to run these lower demand, lower output products, where batch may actually be the right thing still.

Flexibility is also a key driver, it's not all or nothing. The reality is, in the batch world, you still have CMOs so if you don't want to build the capability you don't have to. Although, often your reactors that you run perfusion on can be run as batch as well.

JBC: So now you've joined Evelo, tell us what you're doing there.

JS: What we're driving is a new modality, which will be akin to monoclonal antibody modality, cell therapy or gene therapy. We're driving extracellular vesicles derived from monoclonal microbials at a price point probably an order of magnitude lower than a traditional biologic. We plan to access the entire world, which means that we have huge demand projections.

So now I'm looking at continuous on an almost unfathomable scale, perhaps 20,000-liter type perfusion systems and the adjoining downstream integrated processes simply to meet the demand and the price points. It's continuous from a completely different angle.

JBC: It sounds to me like you're going need to invent a whole lot of new equipment to handle that kind of volume and a whole different price point on media. Everything is again got to be challenged as you did right from the beginning

JS: Exactly! So never be bored, always find a new challenge.

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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 Joseph'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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