A CONTINUOUS VISION TO THE FUTURE OF BIOMANUFACTURING

Chris Hwang, Chief Technical Officer at Transcenta Therapeutics

ABOUT

Chris Hwang is the Chief Technology Officer at Transcenta Therapeutics. Previously, Chris has led teams at Genzyme and Sanofi building continuous processes. Chris and John Bonham-Carter, Vice President of Business Development and Product Management, Erbi Biosystems, discuss the role that continuous systems have to play in the future of biomanufacturing.

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JBC: Chris, we first met when you were Vice President at Genzyme. It's a fascinating company; it was the first to so publicly state the direction and the thought process about going continuous. There were profusion processes that needed updating but you took it further than that. Can you talk about your thought process and why you decided to take those extra steps? What was important to you as you debated that internally?

CH: Early on, back in 2009 or so, I think we already had this vision of continuous process, looking at how other industries have gone from batch to continuous with all the advantages. For us, because our upstream process was already perfusion, and since we adopted alternating tangential flow (ATF) filtration, the fact that I clarified harvest fully coming out of the reactor already and the fact that we were already looking at some sort of continuous chromatography system in our downstream group, it became obvious that we can connect the two together to gain a lot of the benefits in terms of removing the clarification step as well as the large storage, making the process much more streamlined and economical. So that was really the genesis of implementing a continuous chromatography system and that was important for us because it simplified the operation quite significantly.

JBC: At the time, equipment didn't really exist for the integrated capture, at least not in our industry, so that was quite a risk as you had to invent a unit operation. How did you think about that risk and the eventual outcome? Did you feel justified at the end of it?

CH: We were taking a lot of risks, not just on the downstream, but upstream too, but on the downstream side we were fortunate to have very innovative downstream teams that were already working on aspects of continuous chromatography. Our downstream team were putting together chromatography columns to try to simulate continuous multi-column systems. They did a lot of lab work to demonstrate it worked, and we generated a lot of data to support that this technology can be very robust, certainly focusing on process understanding and equipment understanding. We partnered with GE at the time, who are one of the industry leaders in developing bioprocessing equipment automation to make these things become implementable in the pilot GMP environment. From that perspective and, also, just like any innovation, there were a lot of risks involved.

We take risk management very seriously. We weren't just generating very good data but also did a lot of the FnbA analysis to mitigate all the high risks in implementing something new like this. Then we got the unit in from GE and connected it with our single-use bioreactors and did multiple runs, which demonstrated the system worked as intended. We then generated a lot of very useful data that we approached FDA and EMA on an EGT team and ITF and EMA to get their support and feedback.

A combination of internal and external validation eventually gets us to the point where we feel that we have the information we need to move forward. Given the advantages that I already talked about for continuous, it then becomes obvious that we can convince our management to move forward with this technology.

JBC: It's interesting that you engaged with the regulatory authorities as you went through that process. So, that was one element of mitigating that risk, that you weren't going out too much on a limb, that you understood the data that was going to be required to validate the process. In the end, the facility got built and the experience was very valuable, is that now deemed a success?

CH: It was highly successful, just imagine that if you can replace your 4 by 2000-liter stainless steel profusion bioreactors with one or two 50-liter single-use bioreactors with about two orders of magnitude smaller column compared to your original commercial scale, with whole system fully automated. This gives you a sense that it's a successful outcome and the success was measured by, firstly, convincing management to move forward, which was a daunting task. However, more importantly is to get regulatory approval for these types of technologies. There are more coming, my understanding from my colleagues at Sanofi is they're continuing to use this platform for all future products. To me, that's what success looks like; to develop the technology and implement it and, ultimately, we can benefit patients.

JBC: You're now at Transcenta, where you have a whole set of new molecules and processes, and you've taken a series of extra steps on that continuous line. What does fully continuous mean at Transcenta and why have you made those decisions?

CH: The situation in China is very different and I want to explain the drive to do this. There is significant drug pricing pressure in China, so for any drug that comes to China, its price will typically drop at least 50%. Even if domestic products are highly competitive for you to list your drug in the National Reimbursement List you are required to significantly reduce your drug price. Consequently, low cost of goods (COGs) is not only a competitive advantage for us, but in many cases, it's a go or no-go decision.

Process intensification becomes important when aiming for low COGs. We chose a version of the continuous process to get us there. Right now, we're putting together a five-year plan to develop a highly intensive perfusion process.

We chose a continuous perfusion, steady-state process and integrated it with a capture technology, followed by a flow-through polishing system that we're collaborating on with MilliporeSigma. The whole process is not end-to-end because our facility has a relatively small footprint and we don't want to tie down these new technologies to one product at a time. We want to be able to process multiple reactors and use these technologies to de-bottleneck our facilities. So we decided to implement a hybrid continuous platform to allow us to maximize the output from the highly flexible and small facility that we've built.

JBC: So, you immediately had to consider the cost and evaluate each new operation to determine which would be continuous and which wouldn't. You're not a huge pharmaceutical company with a huge portfolio, wouldn't you have got to phase I trials faster with batch operations, without this investment? Why is continuous best even as you develop the process in preclinical phases?

CH: When I say continuous, I don't mean that we go all in for our early-stage programs. We don't go all in from the very beginning because we're still developing the technology to ensure it's mature and ready to be implemented; we do it incrementally to manage risks. For instance, we may start with perfusion, but our downstream will be batch. We recently converted to perfusion for one of our molecules, we got regulatory agency approval to switch to the perfusion and that was based on our comparability data package.

Then we implement as the technology is ready, i.e., we rely on process change during the product development to ensure that the end goal, the end process, is where we want it to be. Our philosophy is we don't want to risk our programs, but we want to find ways to take risks while keeping our end goal in mind.

JBC: Focusing on those early stages, fed-batch is maybe a two-week process and you move that into perfusion as quickly as you can but that could double or triple your process development time. How do you avoid extending that time? Is there an extension of time that is worthwhile or is that a misplaced way for how to develop a lengthy perfusion process?

CH: A very important criterion for us is the development of this new platform doesn't impact our timeline. In fact, we developed the perfusion as a plug-and-play platform and typically we run our phase I process for no more than 20 to 21 days. However, because it's plug-and-play, there's no development when we go to phase I – you plug in your cell line and run it for the duration that you desire. We can typically achieve, I would say, from top clones to the process block in less than 10 weeks, which is very, very fast.

Typically, our timeline from CMC package to IND is still around 10 months. It hasn't slowed us down, in fact, I think it might accelerate it a little bit in terms of our time to the clinic, from that standpoint, we don't think process development would extend the timeline. There's certainly more work to be done later in the process, but that's not going to become the rate-limiting element, that tends to occur more around the clinical stages. We don't see how implementing continuous technology is going to negatively impact the timeline.

JBC: It's always good to have a vision, but executing on the vision is the hard part, how are you delivering against your five-year plan at Transcenta?

CH: We started this five-year plan in 2018 when our facilities opened in China and we're getting close to being done, 2023 would be five years. COVID has delayed the overall time, about six months but we are well into it.

We started off on this five-year plan by building the foundation for the perfusion. We had to build everything from scratch from the cell line to media and the perfusion platform, but within about a year and a half we had completed the development of this platform and we are now applying it to every single one of our internal products.

We're also partnering with MilliporeSigma to develop this integrated or fully automated flow policy system that combines four unit operations into one, which decreases the cycle time of downstream processing, including the multi-system that we'll implement as well.

So, this platform is almost ready. The combo system is currently in-house, unfortunately, I can't share a lot of information, but I will in the future. This system will be fully ready for GMP operations very soon this year and then the MCC will be later in the year. Our goal is to have the system ready to go for PPQ run in Q1 20203.

JBC: So, you've got some smaller bioreactors and some larger bioreactors feeding into these same pods downstream. So that's four times the volume coming through, how do you match that up?

CH: As we decided not to do end-to-end, so there needs to be a whole point, the whole point, in this case, would be Protein A. From our experience, Protein A is fairly stable and the volume is manageable, but what this allows is that for any product going through, whether it is fed-batch, intensive fed-batch, or in this case, continuous perfusion, we can quickly run through this pre-viral downstream POD processing material in a very short amount of time. Then you follow it with the post-viral POD.

The other reason we didn't go full continuous is that we don't want to tie up not just the pre-viral pod technology, but also the post-viral pod. If you have a continuous, that means you need to have a dedicated post-viral suite for each product, which we don't want to do for a small footprint. So, that's how we process everything up to Protein A and then we schedule, we process through the post, the pre-viral pod very quickly. From typically four or five days of operation, we can make it in one or two days. That allows us to handle everything that's coming from our upstream process.

JBC: There are two technical points I want to finish on. With your development system being the same size as the manufacturing scale system, it allows you high confidence in that tech transfer and a large elimination of risk and time as you do that. Is, that your experience too? Is that, how you run it in the development scale?

CH: It depends on how intensify your processes. From our standpoint, our lab scales are typically benchtop lab scales, so they're typically two liters or so, but when we go to pilot, or in this case, phase I, manufacturing, commercial, typically, the scale will be much larger.

I would say going from phase I process to commercial there's little to no scale-up. You do still have to scale up from the bench top, but, overall, the risks are significantly lower because your phase I process scale and your commercial scale are equal or only slightly larger.

JBC: In your portfolio of products, in what I would call quite a sophisticated large perfusion facility, you've got a smaller number of products compared to large pharma. How do you balance that capacity?

CH: First, our facility is not large it’s about 2000 square meters and our facility was not built at full capacity upfront. Our capacity can expand over time, so you don't have to build full capacity up. With increasing demand, at least for us, because we have a number of internal products that we're developing as well as for CDMO production, then we will increase our capacity as needed to meet the demand.

So that's why these types of facilities are going to become very important. You need to be flexible, not just supporting different types of molecules, but also you can build very quickly and extend the capacity and mitigate sort of the capacity risk.

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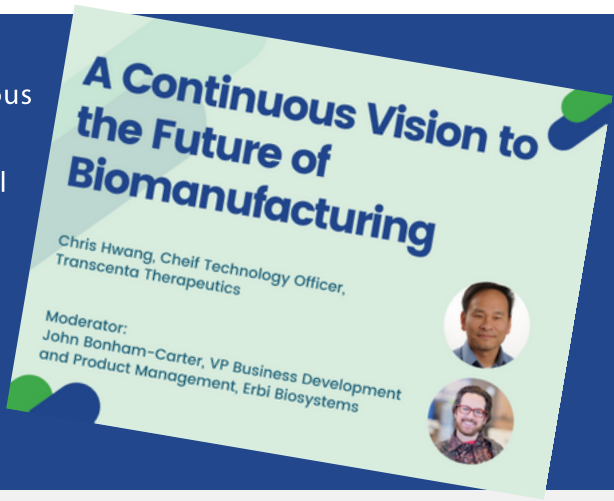
This case study was presented at Evaluating Biopharma's Continuous Bioprocessing – Justifying your Company's Investment virtual networking and educational event which included three additional case study presentations and two interactive networking sessions

Details of future events can be found here.

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



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