JEFFREY BUGULISKIS: Welcome to GENCast, a sponsored podcast series brought to you by *Genetic Engineering and Biotechnology News*. I am your host, Jeff Buguliskis.

Separation. It is an uneasy concept for most people, as we are social beings and thrive on interactions with each other. The simple act of putting up physical barriers is often an affront to the human psyche. Animals are not too particularly fond of the scenario, either, as any dog owner who leaves the house for five minutes can attest to.

But if you are a biotech researcher, well, then, separation is probably your jam. As the isolation of biomolecules using membrane filtration plays a vital role in bioprocessing, as nearly every unit operation utilizes a membrane for process protection.

While there are numerous types of filtration methods that are employed through the biomanufacturing pipeline, late-stage bioprocesses often require large-volume manufacturing to meet supply requirements. And these increased volume demands can create challenging filtration operations. Large-scale volume operations, especially those with low filter capacity and flux, can disrupt facility fit, leading to situations that require time-consuming solutions or undesirable capital purchases.

In this GENCast, we will explore the various troubleshooting techniques that the M Lab Collaboration Center experts employed, together with Biogen, to solve their facility fit challenges. Let us meet our panelists and find out more about the obstacles they face and how they navigated through them.

MITCH GOETZ: My name is Mitch Goetz. I am an engineer in manufacturing sciences at Biogen located in Research Triangle Park, North Carolina. My job function is to tech transfer new products and processes into the manufacturing facility located here at our TP, North Carolina.

THOMAS PARKER: And my name is Thomas Parker. I am a process development scientist with MilliporeSigma.

JEFFREY BUGULISKIS: All right, guys. Well, thanks for joining this GENCast today. Let us begin and discuss some of the topics that we have here. So, Mitch, maybe you could talk a little bit about the unique challenges that manufacturers faced during late-stage bioprocessing and why Biogen approached the team at the M Lab Collaboration Centers.

MITCH GOETZ: Sure. So, as late-stage processing from partners, even from internal, requires that you have everything together and you have all the data, all the

information so that you have a smooth transfer into the manufacturing facility, in addition, our timelines are typically such that we have about three to four months to accomplish this from the time that the pre-tech transfer occurs, where they identify resins and filters, to the time that we actually start the detailed design and actually get it implemented, three to four months.

So, as a result, we had a partner that came in with a process, and they had a number of filters within the process. The issue that we had was that they had a 2K process that we were trying to scale up to 15K, and they were using Biogen nonpreferred filters, ones that we just simply did not have available here on site. And so I approached Thomas and his team with this information and requested that we get some filters that were Biogen-preferred filters sized properly so that we could put them into this process.

THOMAS PARKER: Yeah, Mitch, that is a great summary. And we as an organization engage in similar trials all over the world to solve facility fit challenges, as well as many other areas of process optimization.

This collaboration was unique in a couple of ways, though. Biogen, as Mitch was saying, they were scaling to pretty large volume from a 2000-liter process all the way

up to a 15,000-liter process, and under pretty tight timelines without the luxury of being able to optimize every individual unit operation to make things run really smoothly.

Additionally, we were helping Biogen on an end-to-end basis on this entire process, all the way from harvest clarification to bulk drug substance filtration. So it was not just a single-unit operation that we were helping Biogen with. This was a full-process challenge to understand how one step would impact the next and how we would optimize the intermediate filtrations to ensure a smooth process at 15,000 liters.

We also had to work with the process that we were given and troubleshoot using techniques that did not introduce significant process changes, such as pre-filtration and lower footprint filtration solutions.

JEFFREY BUGULISKIS: So, how did Biogen and the M Lab Collaboration Centers work together to solve this facility fit challenge?

THOMAS PARKER: So this collaboration is a great example of how the M Lab Collaboration Centers are uniquely positioned to help customers not just on individual unit operations, but also for end-to-end process optimization.

Biogen provided representative feed samples from their PPQ campaign, and we generated filter sizing for all intermediates from harvest clarification all the way to bulk fill filtration to ensure facility fit at that large scale.

And where filter sizing data suggested that there would be a risky scaleup, we suggested various process changes or optimized the filter train through pre-filtration to ensure that there would be facility fit. One unique challenge that we faced within pre-filtration in this filter sizing and scaleup was that Biogen had a salt addition at their last column step that was causing a lot of precipitation and turbidity and was really difficult for just bioburden reduction filter to remove alone.

And so we added a pre-filter, and we actually looked at a depth filter there, because of Biogen's previous experience with our depth filter technologies. And that worked really well to protect that bioburden reduction filter.

Additionally, we looked at the Millipore high-area express filters, which provide double the filter area per cartridge, and these technologies, because of their dense pleat structure, have been difficult to scale up into.

They are not exactly representative of the standard pleat structures and do not always scale linearly.

And our research and development team has done a lot of work to develop a scaling tool for those Millipore high-area express filters. And we were able to evaluate those with Biogen and provide confidence in their scalability from this 2K scale all the way up to 15K using a really small amount of feed material.

MITCH GOETZ: Yeah, and adding on to what Thomas said is, this was a unique process to Biogen in that on the feed to the third column, we added the depth filters. This was something that, at Biogen, we had never had to perform before. But again, there was no issue. The depth filters were something new to the partner, but we did have experience with depth filters in further upstream portions of the process. So, you know, we were able to convince them that things would go well.

As far as the high-area membrane, that really helped us out a great deal in that we were able to use our existing filter bases and filter housings without having to change piping or add new capital equipment, because, a couple things. We did not have the time to do that, as well as we did not have the capital budget to do that for this process.

JEFFREY BUGULISKIS: So it sounds like the M Lab Collaboration Center team went through some pretty intense problem-solving to address Biogen's facility fit challenge. What was the ultimate outcome for Biogen?

MITCH GOETZ: The outcome was excellent. Again, this was a PPQ first batch. It was a five-batch campaign. And during that campaign, there were no filter issues. We had no filter following, and we had no deviations associated with filters. It worked really well.

The other benefits here is, we did not have to change our filter configuration, our equipment. No equipment modifications required. No capital expenditures required. As a result, there were no delays in getting these filters installed into the facility.

The other plus that the partner really liked was that the wedded materials that were supplied were the same materials that the partner had used at the 2K process, and so they did not have to worry about leachables and extractables as a result.

In addition, all of the filters that were recommended were filters that Biogen had used before, so there were no new filter specs that were required, which was definitely a time savings, and also the warehouse item codes, we were able to use existing ones with no new additions. So all of

this saved time, was very fluid, and it worked out very well to our advantage, as well as for the partner.

JEFFREY BUGULISKIS: So, guys, with your experience with this project and other projects, you know, what is the number-one tip you would give to other late-phase CMOs struggling with these types of challenges?

MITCH GOETZ: I would definitely work on this early, on the front end of the tech transfer, so that you do not put yourself in a corner, just in case there are issues and concerns. So definitely, work on it early. And secondly, obtain representative samples. So all of these intermediates had to be representative, and we also held them for the total duration of their hold time, so that would be a worst case. So that added to the safety factor in the sizing. So those are the two tips that I would provide to someone performing this exercise.

THOMAS PARKER: And Mitch, you discussed this at the American Chemical Society BIOT meeting earlier this year, giving an oral presentation about this collaboration. And after your presentation, I was approached by another one of our customers, and he said he was really appreciative of hearing somebody talk about intermediate filtration, because it is often something that gets overlooked in large-scale processing as really just not all that

important, because you can just, you know, fill up your facility with filters and assume that it is going to work if you are maxing out your footprint.

And that is really just not the case for all of these processes. You know, as we have discussed, sometimes you are on a very short timeline, and you have moved quickly through the clinic and have just a little bit of time to transfer a process into the facility. And here we were scaling up so large that the footprint differences were quite significant. And, you know, if we had not performed this filter sizing, then it could have resulted in an unsuccessful campaign at that 15,000-liter scale.

So my advice for other late-phase CMOs and manufacturers would be to, you know, just really push to generate this data. It does not take terribly long to generate, and that is what your vendors are here for. The M Lab Collaboration Centers can come alongside customers to help ease the burden of that process development. And as we did with Mitch, we were able to generate filter sizing data, and he just had to supply representative feed sample in a pretty short amount of time, and then work together to determine the best solutions for Biogen moving forward.

So I think just ensuring that you engage with these things and do not overlook them, and allow vendors to partner and collaborate to ensure success in manufacturing.

JEFFREY BUGULISKIS: Gentlemen, thank you very much for joining us today on this GENCast. Thank you for talking about the many challenges that you guys face and how you were able to get around them.

THOMAS PARKER: Thanks, Jeff. Thanks for having us.

MITCH GOETZ: Thank you.

JEFFREY BUGULISKIS: Thanks for listening to GENCast. For *Genetic Engineering and Biotechnology News*, I am Jeff Buguliskis.

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