ENSURING SUCCESS FROM DEVELOPMENT TO GMP - LESSONS IN SCALE-UP

A conversation with Tiffany Rao, Bio Pharma Technical Consulting

ABOUT

Tiffany Rao is a biopharmaceutical consultant with expertise in everything from process development all the way to commercial manufacturing. Susan Dana Jones is a recognized leader in bioprocessing, She has over 30 years' experience in managing complex biopharmaceutical development programs from discovery through late-stage clinical trials and commercialization.

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Tourmaline bio

Susan Dana Jones: Well Tiffany you have a case study you wanted to share with us on the successful tech transfer and scale up of the CHO process so let's set the stage for this whole discussion with your case study.

Yes thanks Susan, I wanted to start with a case study about transferring a CHO-based process, but really the underlying strategy applies to all types of tech transfer no matter what type of organism you're using. What we're going to be talking today about is a CHO process that was developed for an early stage to an early Phase II type of process but it needed to be scaled up.

They couldn't scale it up within their own facility so it needed to be switched to another site. And so as you can imagine after you've been working with the process for a significant period of time, there's a lot of information that is within the organization. And all that information needed to be transferred to the other site. And unfortunately not everyone has exactly the same types of bioreactors and downstream processing units. Even in the old days where we'd say all these two stainless steel vessels are perfectly the same you always got surprises right. And we still get those surprises as we're moving to our different. Single-use [technologies] as well because we have custom bag designs and such.

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So there were some a few differences in the equipment sets as well as the fact that it was being manufactured by a group that did not have the history the other team had. It was a successful tech transfer but not just because we got the product out. It was successful because we were able to transfer and scale up so that we can have more material for our patients. It took work from both groups and it required a cultural fit and communication

SDS: Let's talk more about the equipment differences. That's something we've all faced as we transfer processes between facilities or even between the development lab and the manufacturing floor. You sometimes don't have alignment so how do you manage differences in the equipment throughout the life cycle.

TR: So in preparation for any type of transfer we should be doing a facility and equipment Gap assessment to understand the differences between the development labs and the manufacturing setup. I always encourage you to do a small scale experiment as part of your tech transfer so you know how those vessels scale and the limitations whether there's a gas transfer, whether there's a pH control limitation. All of those things are part of that particular process.

Also and I'm sure everyone has come up against this - and if you haven't just wait – there is the issue of cell counters. Very often different counters do not count in the same way which is a problem, because oftentimes origin sites and destination sites have different counters. Sometimes it's because the cell counter is not supported in that region of the world. Sometimes it is because the developer involved can't get it.

All these things - being able to quickly get that data set and to understand what site-to-site equipment differences – are important to keep in mind when we're designing the process, start designing those small changes in.

You've also got to remember that technologies never perform optimally all the time. A bioreactor or vessel may run slow, it's never going to run perfectly on target - you're always going to be a little bit above, a little bit below. So making sure that we're building those different types of processes into our equipment set is important.

The other thing is that during the earlier stages of projects, we don't necessarily check all the boxes saying have 21 CFR part 11 compliance. Sometimes we're not able to do it because we are using non-compliant equipment. So that's one thing we just have to be thinking about and staying ahead.

SDS: Can you talk a little bit about the importance of communication and collaboration during tech transfer?

TR: So you can imagine as we're doing these tech transfers they're multifaceted. There's development, there's engineering, there's could be multiple manufacturing sites involved. There's the regulatory teams, there's the health and safety teams as well, because sometimes we're putting in processes which we may be able to run them without certain measures in location A but when we move to location B there's quite different regulations.

We need to be communicating early not just the data aspects but the logistics around tech transfer as well. Also, bringing people into those discussions earlier to help with the operations team understand "why do we do what we do?" is very critical.

And then in terms of data transfer, if you take a look at the data we collect within our organizations - we've got online pH, dissolved oxygen, we've got all kinds of information coming off of our chromatography columns. We've got data coming from our analytical labs that are in process and we prepare that as part of our batch records and release status. Being able to get that data transferred back and forth is very key.

I'll give you a good example. In a previous transfer, where we had a bit of a surprise, as I mentioned earlier, was around cell counters. We had a custom cell counter program that was not transferred, as we expected, to the site. So they were getting very different cell counts even though whenever we reprocessed the data we would get the expected result.

So that's where data transfer was very important. We didn't do a good job of transferring our data - which was our method and how we were counting the cells - but we did a good job transferring the data back so that we could do some analysis. This is also part of understanding if our process was transferred appropriately or not as well, because we need to ensure that our profiles are running as expected, we're running in our ranges. That's something we have to negotiate oftentimes with our CDMOs. How much of that in-process data they're going to send back compared to just sending us an Excel type of chart. The data is really important especially as we get closer and closer to starting our process characterization activities.

SDS: So being able to transfer data is also a critical part of tech transfer?

TR: Absolutely. I don't know how many of you guys have had this experience where you have tons of data for a particular tech transfer but it's sitting on people's computers.

And, in this example, some people had retired, some people had taken new opportunities. Other people had forgotten they did the experiments - so just coming up with the data packages and the information to transfer was a challenge. So making sure these data lakes don't become data swaps is important. Data Lakes are bad but at least we can kind of find things. When data lakes become data swamps it's quite a disaster.

SDS: So let's take a look at controlling the process inputs for a successful scale up. What are the things to keep in mind?

TR: This is near and dear to my heart because of the fact that we have amazing analytical capabilities. We have all types of sensors today. We can do conductivity online, we've done pH for years and temperature but we have a lot more analytics that we can do at a much more rapid pace than we have previously. We have these great systems that allow us to control processes very tightly.

But one of the things that we sometimes forget is that while we can control a process when a scientist is watching, when we transfer it to a manufacturing site the process will not be monitored in the same way. Of course operators will be watching the process but they're not setting it and manipulating it.

And different sites operate to different standards. When somebody says they run a a piece of equipment - a bioreactor for example - to a very tight set point. I go, "really how tight is tight?"

You have to also be leery on that. I'm not saying they're not doing it but how are they compressing the data? How are they looking at it? Are they taking a sample every so often – those types of things. Because we know that when we put in a feed for instance we are going to have a change in pH in our bioreactors, so our process needs to be able to manage that.

SDS: Let's talk a little bit about how improving process efficiency can help facilitate product approval? How are those tied together in your mind?

TR: They're hand in hand or they're connected at the hip as they say. The fact is that, in biopharma, we have a lot of very aggressive timelines for a variety of reasons. One of them is we want to get medications to patients as fast as possible. We also have business commitments as well. So the question is how can we front load our processes and our development in order to start designing for manufacturability earlier. One of the things that I like to do earlier - and we've been doing this for tech transfers and other things – is starting to think about what does our FMEA look like, our risk assessment for our process.

You might say, "Well Tiffany we don't know very much in pre-clinical or even Phase I because we're getting our feedback from the clinic." But even during those early stages we do know quite a bit about the process and the history so it sets us up to say okay these are the things that we're going to look at. We might not need be able to look at them today, but we can look at them later on and therefore we can start building that into our process development program. Then when we get to that later stage and everybody's going "Oh my goodness I have to do my FMEA - and it's going to take me you know weeks or months." You can say well we've already started building that data set.

The key is, starting to think about how we can build in opportunities for process improvements earlier. For instance, we don't want to change our cell line late during development - it's just a nightmare! You are never going to get back that time it's going to really set you back.

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TR: That's one reason we work with a lot of different feeds during early development because we don't want to change our base media because it is what we used for all of our stability studies. So by being able to think earlier about the challenges we may have in later stage manufacturing is important.

Another thing is working out how much material do we really need. I think that's a huge question that people are discussing -how much do I need to make for those first batches and will the process that I have today be able to let me reach that next milestone?

So factoring that in has potential advantages from a scientific and a business perspective. Ultimately, if I cannot get the material made in an efficient way, I cannot get it to the clinic and then the patient will never be able to receive it.

This case study was originally presented at Evaluating Biopharma's Biomanufacturing Optimization online and interactive event

You can watch Tiffany's presentation in full and on demand here.
Details of future Evaluating Biopharma events can be found here.

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