PREPARING FOR COMMERCIAL MANUFACTURING OF AN AUTOLOGOUS CELL THERAPY

A conversation with Jonathan Tsang, Kite Pharma

ABOUT

Jonathan Tsang is senior director manufacturing science and technology at Kite Pharma, a Gilead Company. Moderator Ben Locwin is a healthcare executive with quantitative and qualitative analytics expertise. He works with senior managers at biopharmaceutical, vaccine, and medical device companies to market at higher velocity and with higher quality.

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Ben Locwin: How does commercializing an autologous cell therapy product compare with traditional biotechnology products? What are the major differences?

Jonathan Tsang: The first major difference is variability of your incoming starting material, which is derived from the specific patient. Also, they may have undergone previous treatment which introduces further variability.

The second difference is volume. In comparison to a monoclonal, for example, where you may run two batches a month in a small facility, in the autologous space we're running thousands of individual patient batches through our facilities every year.

The last difference is to do with manufacturing speed because we in the autologous cell therapy sector can't carry inventory. We actually just recently published a report at ASH that showed we have an average vein to vein time of 27 days, meaning from patient through our manufacturing process to released and back takes 27 days which is breakneck speed.

So those three are probably the biggest differences between an autologous product and a traditional biotech product.

BL: What sorts of challenges arise as a result of the variability in donor cell material that you mentioned?

JT: Individual patient genetics and the varying phenotypes of their can cells lead to different performance in terms of manufacturing the finished cell therapy.

The challenging part is that when you're doing all your initial process characterization you use healthy cells. But once you start working with patient material from people who've undergone two previous lines of treatment – maybe chemo radiation, maybe stem cell transplants - then your cells may not be as healthy or have different growth profiles from the cells used for development.

BL: How do you go about developing processes that can handle this type of starting material variability? What are the strategies?

JT: I think scientists really need to have this variability in mind when they're going about developing processes. We always talk about characterizing at the edge of failure and all these nice things to have in traditional biotherapeutics but it's even more important when we're talking about autologous cell therapies to really manage that. If you're developing your entire process only at center point of all your process ranges it's pretty much setting things up for failure, so that's one thing to keep in mind.

Then when you're talking about data, I think that's where there are tremendous opportunities. It's never been so important to have process monitoring, process analytics, good CPV programs all these elements to sort of extract data from your active processes. The opportunities to link that data with your clinics that are collecting patient materials are tremendous. You could really understand how patient health is linked with manufacturing success rates.

And then on top of that with data I think there's also a lot of opportunity for improved process analytical technologies. Traditional, in bioreactors PATs measure things like glucose lactate, cell density and dissolved oxygen. However, I think the next generation of advanced processing technology will help us understand patient phenotypes while cells are growing and will really allow us to control manufacturing more precisely. There's a lot of wonderful science to be had in the future

BL: Yeah I couldn't agree more with that. We had a comment come in from the audience which is directly topical here. What critical quality attributes (CQAs) do you look at during process development?

JT: That is such a huge question. It really depends on what your quality target product profile for the patient indication you have.

So it's really hard to tell you which specific CQA you should to look at, but of course you have all your typical ones. To identify the key CQAs, you really need to be able to answer a few fundamental questions: How many cells you need to dose? How healthy are the cells you are working with? And how well is your genetic payload incorporated?

BL: Maybe a subpart to that question would be to look at how you compare CQAs between healthy and diseased patients?

JT: So in terms of the process, the CQAs don't change. For example, you're using healthy donor material to do your process characterization you're still looking at the same critical quality attributes of your product at the end. The real question is how do you go about making sure that you challenge your process across variable process ranges?

Let's just use an example, you have a patient from whom you are trying to harvest cells but they can't provide enough. Well then maybe you should start your process development with the requirement for a lower amount of cells to make sure that they can reach the endpoint number of cells. It's that sort of behaviour, making sure you challenge the process to test it can cope with variability of incoming materials that is the key.

BL: Patient material aside, how important is it to develop processes that can cope with variability in reagents, media etc?

JT: With autologous processes, and cell therapy in general, you're using pretty advanced raw materials. I can think of some past cases at previous roles I've had where media components had an incredibly large impact on cell culture performance. And nowadays you're using even more advanced antibody reagents as part of processes so there is quite a bit of variability

This all goes back into process development. You really need to make sure that you have good relationships with your suppliers of these reagents and really characterize them well to minimize the impact of variability along the way. Otherwise all that variability adds up and the more that spins out of control, the worse the overall output.

BL: How important is it to engage with suppliers to try and tackle variability in reagents etc?

JT: It would help if the raw material providers worked with the process development scientists to really understand what the potential impact of material variation on manufacturing.

An example would be when you have a raw material and it meets all specifications but then when it gets into operations it performs a little bit differently - it's not quite as active or it's too active – which may indicate that there's something uncharacterized in a specification that's actually leading to some difference in performance of that raw material.

And I think that's really hard to do without good coordination between the company and the raw material provider.

BL: Do you have any recommendations for how to establish and execute a proper chain of custody for materials or cells?

JT: When we're talking about what's important for a commercial autologous platform it's really the volume that the facility needs to deal with.

For example you could be handling material from hundreds of patients a week and really the question is how do you make sure you're not mixing up between patients, mixing up the raw materials that are going into them or even mixing up batches themselves? So really when you're talking about chain of custody and chain of identity you must have the appropriate I.T systems in place and also have operational controls that support them. You cannot afford to give one patient another patient cells. That would be disastrous.

BL: Do you have any advice for implementing these systems to help support scale up?

JT: What I would recommend is proactively thinking through these things before you're actually using them and really doing good value stream maps of your entire business process. Let's go back to the traditional biotech example, maybe I make two to three batches in the bioreactor a month. Imagine now hundreds of batches or lots per week - what does that mean for product release or batch record review or deviation investigation? It means now you're taking all those steps carrying them out hundreds maybe thousands of times.

What does that workload look like? What does that look like for the staff that you have? What type of training that needs are there? So all of these things have to be thought out very well up front otherwise it's a bit like trying to build a plane while you're flying.

BL: And for those who haven't done it a value stream map is a visual tool that shows critical steps in a specific process and quantifies the time and material volume required at each stage. Do you have any preferred ways of creating a value stream map?

JT: Well when putting together a value of stream map it's always nice to have someone with a lean background to facilitate it. And then making sure that, when you do perform the map, all your appropriate stakeholders are involved.

Let's use deviations as an example. A deviation occurs on the manufacturing floor and an operator may report that deviation so immediately there's some sort of triage between them and a quality organization. At that point they define the deviation and then that goes to someone in manufacturing sciences for investigation, so you already have quality and manufacturing people involved. Then if the deviation is traced to a raw material you need to be talking to supplier quality management or QC.

So if you look at that sort of branching topic of who is involved in the deviation it looks like this massive web. So when performing a value stream map it is important to make sure to actually understand what that potentially looks like because once you're in operations the number of people involved can multiply by an order of magnitude.

BL: To sum up, what are the most important elements of any cell therapy commercialization and manufacturing strategy?

JT: WI think that maybe one of the biggest surprises for me is how important data is to an autologous manufacturing process. For traditional biotherapeutics, process monitoring is always important. You want to know how the bioreactor is running that day etc. However, they are even more important in cell therapy production because of the scale that we're running at. If you have a problem with the raw material or if you have a problem with a piece of equipment you want to know about it immediately before hundreds of patients have run through your facility.

I think data monitoring and process monitoring is just incredibly important and for them to be successful, data integration has to be thought about very early in the process. The ideal scenario is for a company to be able to get the digital systems in place to really utilize data to control process and avoid potential manufacturing disasters.

This case study was originally presented at Evaluating Biopharma's Cell therapy strategies online and interactive event

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