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Cell Therapy Analytics: Overcoming CMC Challenges

A Conversation with Yeh-Chuin Poh, Senior Director, Cell Therapy Process Development, Beam Therapeutics

ABOUT

Yeh-Chuin Poh is senior director of cell therapy process development at Beam Therapeutics. I this session moderated by Dominic Clarke, chief technical officer, Cell and Gene Therapy, Discovery Life Sciences, Poh shares his experiences and provides advice on how cell therapy companies can better identify and overcome CMC challenges, including: (1) Balancing continuous process innovation and the FDA; (2) Implementing a proper comparability strategy; (3) When to make pivotal product changes; (4) Process standardization—what's possible and what's appropriate.

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Dominic Clarke: Welcome, everyone. We're excited for this conversation about cell and gene therapies. I'm joined by Yeh-Chuin Poh from Beam Therapeutics. Before we jump into the conversation can you give a quick background on yourself and your work?

Yeh-Chuin Poh: I am currently the senior director of Beam Therapeutics. Beam is a company that focuses on base editing using a modified CRISPR/Cas9 system to do single base pair edits. I am currently also the CMC lead for the immuno-oncology franchise, primarily focused on the CAR-T and CAR-NK programs. I've also had some experience with hematopoietic stem cells, CD34 stem cells, and prior to that, it was pluripotent stem cells, differentiating them into pancreatic beta cells. I have about a decade in the biotech industry, primarily focused in cell and gene therapy.

Clarke: When I think about CMC challenges and the challenges associated with CMC and cell and gene therapies, we all know about the impact around the regulatory success of these products. Yet, many companies fail to get it right the first time. We know where we are. We're a developing industry and innovation is running at a speed that's perhaps quicker than the FDA and the regulatory bodies can keep up with. From your standpoint, how have you managed that as a company?

Poh: It's something many people need to start thinking about, not just in the near term, but also in the long term. There's a phrase that many people use—phase appropriateness. What exactly is the phase appropriate strategy when it comes to your CNC strategy? We all have to understand that as we have a CNC strategy, we have to keep the big picture in mind where it's not just the immediate needs which you're trying to address, but further down the line

what exactly are you lining yourself up in order to mitigate, or to accelerate, your program as you progress through the lifecycle of the program? One of the things is managing the improvements to your manufacturing processes. For example, if you have a cell therapy product, you develop a process for manufacturing and scaling up. But many times whenever you scale up, your initial manufacturing process is appropriate for the Phase I clinical trial and it's not always the same process you use when you get the pivotal (trial) or commercial. So, make sure to have in mind what you are hoping to scale to and what is your target number of cells. What you're hoping to accomplish when you get to pivotal and commercial helps you to formulate what kind of improvements need to be put in place. For example, if you were to think about some of the critical materials like guide RNA mRNA, lentiviral vectors, what are the improvements to the manufacturing processes in order for you to get to your pivotal and commercial readiness? At an early stage of the company, you might say, "this is sufficient for us to get to Phase One," but what about the process improvements for you to get to Phase Two and beyond? Those are the things you need to start thinking about, especially as you interact with the FDA.

FDA interactions are also something you have to be strategic about, because many times you don't go straight in with an IND amendment for your improved processes. You usually have a Type C meeting. Especially in those interactions, what kind of specific feedback are you trying to get in order to get your process improvements from one generation to another? And as far as your scale up strategy, how do you get your manufacturing process to scale, and which is pivotal and commercial.

Clarke: We're always trying to strike the right balance. How do you do that when, oftentimes, a company is trying to quickly get to the clinic. It's all about speed, for the most part, so how do you balance that out with your process, your CMC requirements, to separate that from the next phase? Because there are often two different mindsets: getting to the clinic, and then you're going to think about going into the later phases. How do you work that out as you're going into your early stage? How do you not make the mistakes?

Poh: I can tell you with the many programs that I've been involved in, (there was) never one program that was perfect. Mistakes always happens—that is the nature of the industry. You always have deviations, you always have different investigations, and so on. So continuous improvement is something that is natural for this industry. But nonetheless, we still need to have a CMC strategy. When we talk about CMC strategy for the early phase versus the late phase, we need to talk about phase appropriateness. Meaning that in your early phase of your clinical trial, let's say Phase One, what exactly is the target number of patients that you're trying to get to? From there, you can back calculate how many cells do I need to produce in this Phase One? In an allogenic setting you will be thinking about how many batches do I need to generate? In an autologous setting, how many runs do I need to generate? How many manufacturing campaigns do I need to meet the number of patients that I'm hoping to get to Phase One?

So the scale at which you're trying to get to in a Phase One strategy is usually much lower than that of a later stage—and that is totally fine. What you need to start thinking about is how do you show improved processes later on that are comparable to that of the current process and making sure that you have that comparability strategy, even earlier on in your Phase One trial. That is very critical, because you don't want to come to a point at which you're already in your Phase One and realize that we have to make improved processes, we didn't really think about that and how do we actually show comparability? So, your strategy up front needs to inform your strategy later on. Having that broader picture, not just in the next two or three years, but seven, eight, nine, 10 years, that strategy really helps you carve out your CMC strategy.

Clarke: So ,it's balancing the short term and thinking about the long term at the same time. You talked implementing that proper comparability strategy. When it comes to either doing this then transitioning to an outsource manufacturing partner, how do you balance that? How do you work that in from a comparability strategy from your mindset, and also working with a partner to build out that manufacturing?

SD: Poh: Yeah, this is another important thing. When you're selecting your CMO, or when you're selecting your manufacturing partner, it's important to start thinking further down the line, because there are many manufacturing facilities that are ready for the early Phase One clinical manufacturing, but they're not ready for commercial manufacturing. Make sure that you're picking the right partner. If you were to pick a CMO that is appropriate for your Phase One trial and then, after that, switching your manufacturing facility from one to another in and of itself requires comparability data packages. You need to file an IND amendment for that. Ideally, you want to be able to pick someone that you can run with for the next 20 years. But that's not always the case.

So, identify the need that you have right now, and thinking down the line—what is the comparability data package if I were to switch vendors and manufacturing sites? And it's not just a manufacturing site that often changes, you often change your manufacturing process as well. If your Phase One clinical trial manufacturing is with this CMO, you're then switching for your pivotal and commercial to a different CMO, often you also implement process improvements. The important thing is to understand what exactly are the changes. Perform a risk assessment before you execute the comparability study design. This has to be a very well thought out process, because the FDA will ask a lot of questions—and very detailed questions.

It is not just that strategy, but other details such as your analytical comparability, your safety, your identity, your potency, the readouts—those are needed for your process improvements as well. The critical part that comes into play is that as you strategize and make sure that you have proper comparability strategies, you're also thinking about how you have to retain the certain drug product (unintelligible) in your gen-one manufacturing process, such that you can then analyze it later on side-by-side with future generations of your manufacturing process or the new manufacturing site where you're doing it.

Clarke: As you're thinking about the comparability strategy and doing that risk-based assessment, are there a couple of key components that are obvious? Thinking a proper comparability strategy, maybe it's not obviously a one size fits all.

Poh: There are several analytical aspects that needs to be taken into consideration. The first is, for example, in a CAR T program. Many times people use interferon gamma as a potency release. When you get to pivotal that might not be sufficient, you may need to have something that measures the mechanism of action, or something like that. So, you would always have analytical improvements as you move from one stage of your clinical trial to a different stage—a different phase. When you start thinking about how you improve your analytical processes, you're also trying to implement, in parallel, the process improvements or the site change or site manufacturing. You're implementing a bunch of different changes as you're implementing your analytical change at the same time. How, then, do you make sure you are able to show comparability to your first clinical manufacturing drug product, and that's the part where the importance of retaining drug product (unintelligible), especially in an allogenic program, for characterization, for comparability, those are extremely critical. There have been trials where you get to a stage at which you're implementing changes, and you don't have enough retains to compare it with your previous Phase One clinical trial. And a lot of those data are basically wasted. You can't bridge it.

Clarke: So when do we make pivotal changes for the product?

SD: Poh: Before we move on, I just want to mention, as well that the retain files that we were talking about, it's not just drug product. There are also the starting materials. If you think of many of the trials out there, especially in allogenic programs, you start with healthy donor, that starting material, (unintelligible) of dose needs to be retained as well, because it's so important as you go down the later stage of the clinical trials. As far as when to make this change, this is something that is very dynamic and depends on the program. This is where Type C meetings with the FDA are very critical. Those type C meetings are where you come with a clear comparability strategy, where you bring that strategy to the FDA, get them to buy in on it, and you get their feedback. Very seldom do they say everything is good to go and just execute. They always have clear feedback to you. Making sure that you have clear and pointed specific questions

during that Type C interaction will help you define what your comparability data package needs to be.

For example, when you start thinking about where you are in a clinical trial, depending on where you are, the number of ends you need to generate to show comparability may significantly differ. So, if you're still early on preclinical, you haven't dosed a single patient, it's much easier to implement some of those changes and show comparability. Whereas if you're already in your pivotal studies and you're trying to make process improvements, you're trying to make changes during your pivotal trial, you may require a lot more to show comparability. It's really a regulatory and clinical strategy needed to identify the timing of when the CMC changes should be implemented during the clinical lifecycle.

Clarke: Like anything, it's constant communication, and cross functional collaboration with internal groups, your manufacturing partners, the regulatory bodies. I want to touch on one other point here: when you think about where we are, and think about making changes, we'll bring up the topic of standardization. Knowing where we are today are there areas that we can consider?

Poh: Standardization is a critical part of our platform. You can do it internally within your company or you can do it with the broader industry, with your peers. Talking first about your own company, your own organization, many times people try to do things very quickly and they end up doing it one program at a time, instead of just trying to approach it from a platform where you say, "What is it that we can leverage across all critical materials or drug substances? What is it that we can approach as a platform, instead of individually, instead of following multiple ID amendments? Can we take it as a platform and have one single IND amendment that can be applied across multiple different programs?"

Take, for example, those companies that use CRISPR/Cas9. You need a guide RNA and when you have improvements to your guide RNA manufacturing process, often it is it's not just one specific program that has improvements. You want to leverage that improvement, and manufacturing process improvements across all the programs, all the different guide RNAs that you're trying to manufacture for the different drug or different disease types you're trying to target. When you have multiple guides with no multiple INDs, can you take it as a platform approach where when you're following an amendment, or if you're improving the manufacturing process of the guide, can you make it a platform approach where the guide sequence might differ by only 20 base pairs or 20 nucleotides, but a significant amount of that sequence is similar across board?

If we were to think of the industry as a whole, what kind of process standardization is possible, and what is appropriate? There are some things that we could potentially do even as an industry—or maybe a consortium can be formed around this—whereby we start thinking about many of the cell therapy programs are moving towards an allogenic setting. When you get to an allogenic setting, there are so many things that every company is using by themselves, and it's not standardized. Can we come to a point at which the industry is standardized when it comes to 15 liter bioreactors, we should standardize using master flex tubing and now we can have a master file for your specific tubing set that we're using, or something like that. Therefore, we can then just cite or reference in the amendment that we have. That will be tremendously helpful from many of the different companies that are working in cell therapy.

Clarke: I was speaking broadly. There's a company and your own platform—what you can standardize and when—versus the industry. I think both of those go hand in hand. But is there one aspect you'd like to see standardized from an industry standpoint that isn't today?

Poh: I have a pet peeve on tubings. I feel like the tubing set we are all using right now is grandfathered in from the blood industry. Everyone's using PVC. All the instruments such as Prodigy and things like that are all PVC tubings. But it doesn't work for every single program. If we can standardize, especially when we get to a larger scale, maybe we can use a different set of tubing instead of always just using a PVC tubing. That would be something I would love to see as an industry.

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This case study was presented at Evaluating Biopharma's virtual networking and educational event *Cell Therapy Analytics: Overcoming CMC Challenges*, which included two additional presentations and two interactive networking sessions.

Details of future events can be found here.

You can watch Poh's presentation 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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