INTERVIEW with Peter Walters, Advanced Therapy Medicinal Product Subject Matter Expert at CRB and **Kim Nelson**, Senior Director, Strategic Consulting, at CRB.

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Designing your facilities and processes with commercialization in mind

Peter Walters is a process engineer with 15 years of experience. He specializes in pharmaceutical process and facility design. He is an industry-recognized subject matter expert in the advanced therapy medicinal product field and frequently speaks at industry conferences and events. He has a strong technical background designing equipment and processes for multiprocess facilities predicated on maximum flexibility, logistics optimization and technologies that reduce overhead costs, allow for pipeline expandability and produce a higher quality therapeutic. Coupled with his approachable business acumen, he is well respected for guiding clients to understand the impacts of facility design choices and acts as a steward to clients, assisting with the best decisions for their business and bottom line.

Kim Nelson PhD is a Senior Director at CRB. He is a recognized bioprocess design industry leader with more than 35 years of experience in process and facility design. He specializes in process design and scale-up, facility programming, layout and design, cGMP compliance, biocontainment, and contamination investigations for the biopharmaceutical industry. His operational experience includes hands-on pilot plant work as the Manager and

Chief Scientist of large-scale cell culture and microbial pilot plants. Kim has assisted numerous clients with preparing and participating in Type C meetings with the FDA. Current areas of interest focus on cellular therapeutics, gene vectors, gene editing, plasmids and RNA products.

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Q Tell us about technology-related issues for facility design, with tech transfer particularly in mind – how do you work with clients to make this process as efficient as possible?

Kim: Tech transfer is ultimately a clear documentation of the user's requirements and what we look for from a client is what we call a User Requirement Brief (URB). This documents the process, its scale, its manufacturing schedule or cadence, raw materials requirements, automation and the degree of closure.

However, some of our clients are very young, almost boutique firms that may not have a well-documented package. We work with these clients to pull together all the necessary parts for this document. We also take the opportunity at that stage to suggest equipment or closure systems and approaches to them – to help get things built in that the user wants to have in their facility. So it's really an interactive process of asking questions and offering suggestions. Sometimes we go so far as to take the clients on onsite inspections so they can see various technologies in action.

Peter: For cell therapy in particular, the size of the equipment can sometimes make tech transfer easier than it is in other submarkets of the industry – the equipment is often small enough that a client transferring from a smaller facility to a larger facility or pilot plant can literally just pick it up and bring it with them. That certainly lends itself to a seamless transition but of course it doesn't take into account the potential changes in technology that Kim alluded to earlier.

There are also factors that get baked into a facility – things like the distances operators need to travel when moving critical components become inherent parts of the process. It is important when you then tech transfer to another facility that you define which of these parameters are critical and which are less so. You might not be able to have your controlled rate freezers in the same vicinity as you did in the previous facility, for example, you need to know if that's a critical factor and you have to have them immediately adjacent, or if you can allow for a 5-minute walk. That sort of detail is key to ensuring tech transfer is successful.

Q How do you go about facility design with a smooth preclinical-to-clinical production transition in mind?

Kim: With cell therapies, the batch is defined as either a single patient, for an autologous product, or relatively few patients, if the product is allogeneic. What that translates into is autologous cell therapy facilities that scale-out and allogeneic product facilities that do scale-up, but not very much – certainly when compared to protein therapeutics, for example.

Another key distinction to the biopharma world is the dramatically lower number of patients involved in those early clinical trials. This results in clinical manufacturing facilities being able to support trials into a later phase, because they are catering for fewer patients and batch sizes stay the same. They can scale-out sufficiently simply by going with more shifts of work, or they may not even need to do so: in the early stages of clinical development, they may have a patient a week, but in the later stages that may have only increased to three or four patients a week. So the scale-out of cell therapies is pretty straightforward.

Peter: In my experience, the key discussion with companies going through the preclinical-clinical transition is the one around maturity of technology.

At the preclinical stage, you are often dealing with open processes in biosafety cabinets, with highly operator-centric manufacturing. As you transition through early clinical production, you ideally want to start making decisions around upgrading to a more technology-based, closed platform that's more robust. Getting those decisions made before you commit to clinical Phase 2 production is key, in my mind. You want your facility to be flexible enough to not only accommodate the open, operator-centric preclinical process, but to also provide the utilities and sufficient surrounding space to accommodate this technology transition – from an incubator to a rocking bioreactor, for example.

It is also of critical importance to make sure you're in line with regulations throughout, of course.

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Q Can you lay out the factors to consider as you make that transition to commercial manufacture and discuss the pitfalls one might encounter on this journey and how they could be avoided?

Peter: The biggest issue we tend to see as you start to get into commercial manufacture relates to the increase in patient population. This is especially the case with autologous products or single-digit patient scale for allogeneic products. As you increase your patient production needs, you're really scaling-out your facility and whatever philosophy you've baked into your clinical model tends to follow a linear expansion for your commercial model. The key thing for me is that while you're in that transitional period before you get to commercial manufacture, you want to be trying to factor in philosophies that can lead to efficient use of space. The metric I tend to use is patient per year per square foot of manufacturing space, because again, if you're going to a 1,000, 2,000 or 5,000 patients per year facility and you are looking at linear expansion, you don't want to have to grow your facility five-, six-, ten-fold to accommodate demand. You must think about how to do manufacturing in a more efficient manner.

The other pitfall we regularly see relates to the need for large numbers of skilled operators. Again, if you have a process that's very operator-centric, as you scale-out you will need more and more of them. We're seeing clients whose head count model outpaces the availability of operators in their region and they end up without the talent pool from which to hire. That also applies to QC because every lot has to undergo full release testing – QC then becomes either a bottleneck, or you end up with a huge QC lab and a large lab head count as well.

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Kim: I think that's a very good point about QC – that is a real bottleneck. What I have seen is a number of clients are interested in the opportunities for integrating or automating that QC workflow, in order to manage the huge number of individual patient samples that have to be analyzed.

What I think is really important for the transition from clinical to commercial manufacturing is trying to have the facility and building systems that satisfy full GMPs, and then using the phase-appropriate GMPs to guide procedural SOPs, controls and the CMC data packages that are being developed.

Q How should you build commercial logistics considerations into your process and facility, and at/by what point in development should the necessary changes be implemented?

Kim: Cell therapies can be manufactured using one of two different models. One is centralized manufacturing and the alternative is distributed manufacturing.

Centralized is where you have samples shipped to a manufacturing site, they're processed and returned through a logistics supply chain back to the patient. There are different extents to distributed models, but the ultimate would be to have a bedside or hospital-based manufacturing system that could do the processing and be able to return the materials without having to transport them at all, or at least without having to transport them very far.

Those are radically different models, obviously. With centralized manufacturing, which is what is currently being used for the licensed products out there, the utilization of cryogenic freezing for the cell material has made it possible to enable an easier and less risky supply chain. There's been a great deal of experience over the last several years with blood and bone marrow transfers between sites and even internationally. That experience in shipping and handling blood and bone marrow is something that might be leveraged by advanced therapy companies. There has also been a recent increase in the number of additional players getting into the supply chain support sector, offering distribution, delivery and supply chain management services.

The alternative to cryopreserving is to utilize fresh material. Dendreon did so with their Provenge product, using a fresh material supply chain to and from their centralized manufacturing facility. They did this very successfully, but the challenges are huge: coordinating the draw date of the blood from the patient with the precise manufacturing slot that would be available to process that sample, and then coordinating the return date of that fresh material with the clinician so the patient is primed and ready to receive the therapeutic product, with any necessary conditioning regimen accounted for.

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Consequently, there has been interest in distributed, hospital-based manufacturing models. Lonza just recently announced a partnership with Canada-based Octane Biotech for their Cocoon cell processing system. It is self-contained, fully automated modules that can be used for individual patients and should enable a distributed model. It's going to be very interesting to see how well that works out – it's certainly an exciting development.

Q How do you see models across the broad spectrum of centralized and distributed manufacturing evolving and what are the key issues to be addressed for you in this regard?

Kim: One aspect of this is the manufacturing model within the plant itself: is it going to be one patient per room, where all manipulations are done in that room, or are companies going to go towards more of an assembly line where there are specialized spaces or rooms that variously handle the initial processing of the cells, the expansion and the harvesting and processing? In that model, each area is more streamlined for those individual operations and you get better equipment utilization, as opposed to having a lot of duplication and equipment that lies unused until a new patient comes into the room.

Peter: To my mind, if you go with a centralized model, transport logistics will remain a big issue. Kim talked earlier about storage and transportation of cryogenically frozen cells – that helps reduce the risk and complexity somewhat, but then there are other challenging aspects like tracking. Having backup options in place for when those systems fail so that you can still get the dose to the patient in time will be critical.

In terms of distributed manufacturing, I think there are a lot of questions around how you ensure quality across all the different sites: how do you manage your QC testing across all sites? How do you ensure that staff are doing the same steps in the exact same way? Certainly, I think the solution is a fully contained, automated manufacturing system like the Lonza-Octane Cocoon or the Miltenyi Prodigy, for example, but it will be very difficult to ensure reproducible quality product across multiple sites with an operator-centric process.

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Q What is key to ensuring a facility has sufficient flexibility to meet future technological demands and capacity needs in such a rapidly evolving space as cell and gene therapy?

Peter: Future-proofing is a tough task in this industry, just because it's so new and the technology is evolving so rapidly. It seems as though every year there is a smattering of new designs and approaches coming out that need to be evaluated. In terms of where we are going to be in 5 years, we could be talking about equipment that hasn't been alpha tested yet, or even released to the public as a concept.

However, there are two main points I would strongly recommend. One is to be really smart about decisions around your manufacturing philosophy. Build in flexibility to enable you to pivot into different uses of more future-thinking equipment as it arrives. Even if it doesn't currently exist, you can set the stage for it.

Secondly, as you are selecting equipment and making decisions about what your manufacturing platform needs to look like, ideally before clinical Phase 2 stage, look at isolators or ways to close down your process through automated equipment that is currently available. I think that approach will definitely help lay the groundwork and get you better set-up and ready for future developments than sitting back on your heels and waiting for a magic bullet to come down the pipe.

Kim: The use of isolators is growing quite rapidly for the residual number of operations that may still be open, and that is something that, at this point in time, companies really shouldn't have a lot of hesitation in adopting. It's been well proven over the past few years. That is one way to future-proof the building part of it because you don't have the air locks and the high classifications and the small inoculum transfer rooms that might be Grade B. That helps out a lot.

On the technology side, I see nothing but more trending towards fully closed operations.

One thing we haven't touched on is some of the other types of cell therapies out there that will come to the fore. For example, stem cell therapies are going to be coming into their own over the next few years, and they will bring a whole range of new challenges with them. They're going to require somewhat larger bioreactors, but they're also going to need very tight control over the conditions in those bioreactors: for the shear

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impact on the cells, the additions at very critical timepoints of cytokines and activating chemicals, differentiating compounds, etc. That's going to be a whole new field of challenges for the industry.

Q You both encounter a great deal of new technology – how do you assess and evaluate it, and do you see any particular trends in cell and gene therapy space in terms of novel tech development?

Peter: Whenever we're evaluating a new piece of tech in this environment, as much as I can, I like to get my hands on the system so we can evaluate its usability. We can perform a GMP review to make sure it checks all the regulatory requirement boxes.

The key item is being able to accommodate the process needs. We had an interesting experience recently with cryogenic freezing technology that we were evaluating.

The client had a specific challenge, which called for cryogenic freezing of large lot sizes under controlled conditions and in a very short space of time. We had to go to a custom controlled rate freezing manufacturer or vendor. In that particular example, it was a case of ensuring we had temperature uniformity across the entirety of the freezer in all dimensions: that one sample in the corner wasn't going to be freezing at a dramatically different rate than a sample in the middle; that the fans were appropriate for the size of freezer to turn over the air flow consistently and provide a reproducible profile of freezing every time you went to use it.

I think we go through a lot of those kinds of challenges with other pieces of equipment, too. Closed processing systems involve a lot of looking at the tube sets and the flexibility of the system to be able to adapt to future processing changes.

In terms of novel technology development, I think we're seeing a lot of novel design elements coming out of isolator vendors. Historically, isolators have been used for either sterility testing or for filling lines, but now the vendors are definitely seeing the need for their use in cell therapy. And importantly, they are not just trying to shoehorn a cell therapy process into a filling line isolator, for example, where the glove ports might not be at the correct locations, or the way you're bringing materials in and out of the isolator might not be fully appropriate for the number of iterations you're doing.

So looking at transition methods, I think we're seeing a lot of innovative ideas starting to come out and becoming reality in the isolator world. We seek to get our hands on these new systems – to visit the vendors in order to 'kick the tires' and also to get tours of sites that are actually using the equipment in practice. We interview the people who are alpha testing some of this brand new equipment: 'you've been using it for a year now, what are the pitfalls you've seen with the equipment, where has it worked really well and where has it not worked so well?' And we've also taken on some of the responsibility of getting feedback from the clients and giving it to the vendors, so these novel technologies can continue to iterate and become more appropriate, more flexible and more adaptable to the specific needs of the cell and gene therapy market.

Q And finally, what is your vision for the commercial cell and gene therapy facilities of the future in light of the directions in which you see the sector moving today?

Peter: In terms of cell therapy, I certainly expect to see a continuation towards process closure, and increased adoption of new technologies that are not only closed but also automated, to help reduce the requirement for skilled, trained operators. We will see increased availability of inline monitoring, providing valuable data so that processes can be adjusted in real time. This will be vital given the variability in quantity and quality of the starting materials for some of these cell therapies – it will allow for a process that is adaptable to those varying conditions.

As I touched on earlier, I believe we will see processing systems that are able to be integrated vertically, so as you look towards commercial manufacturing for much larger patient populations, you will be able to maximize the number of patient treatments per square footage of your facility, without the need to grow your facility a great deal.

And then as Kim mentioned, we'll see not just the automation of manufacturing process but also of QC testing, and maybe even automation of portions of the warehousing, because the number of materials is going to be immense for all the individual products and processes.

Kim: What I see coming is really a higher level of automation, but that automation is not going to solely take the form of a robot or a machine. I think we're probably going to see more of a cooperative operator-robotic system that's sometimes been called 'cobotics'.

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It leverages the strengths of the operator in their flexibility and adaptability to respond to changing conditions, while utilizing the strengths of the robotic system for repetitive movement; a robotic system is very amenable to transport insertion and removal of items, whereas an operator is much better at doing connections. To have a robotic system make tubing connections is not really very doable at this point, so it would require a reworking of the designs of these systems. That can be done, but whether or not that's going to be the most efficient way to do things remains to be seen.

But I think when you look at automation, what we have to keep in mind is that sometimes perfect is the enemy of good. In terms of getting a product onto the market and producing it at a reasonable manufacturing cost, automating something may not actually be the answer – it could even conceivably raise manufacturing cost, if it was over-automated.

Peter Walters, ATMP Subject Matter Expert at CRB;
Peter.Walters@crbusa.com

Kim Nelson, Senior Director, Strategic Consulting at CRB;
Kim.Nelson@crbusa.com

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