INTERVIEW

Fixing the weak links in the cell therapy manufacturing chain: processes, people and partnerships

PHILIP G VANEK Phil is General Manager of GE Healthcare's Cell and Gene Therapy business strategy, a business initiative funded in part by GE Healthymagination, a $6 billion strategy to revolutionize the world's health by improving the quality, access and affordability of care. Prior to joining GE, Phil was Head of Business Development for Cell Therapy, and later Head of Innovation for Lonza's Pharmaceutical division, helping to drive new technology initiatives focused on cell, protein and viral therapeutic manufacturing. Phil's career has included a number of innovation, business and market development roles at Becton Dickinson, Invitrogen and Life Technologies, as well as two start-up biotechnology companies in the Washington, DC area. Additionally, Phil was an Instructor for Johns Hopkins University Advanced Academic Programs teaching Biotechnology Marketing for several years while working at BD and Lonza. Phil received his PhD in Biochemistry and Molecular Biology from Georgetown University Medical Center and subsequently held an IRTA fellowship at the National Cancer Institute in the Laboratory of Molecular Oncology and the Hollings Cancer Center in Charleston, South Carolina. Phil is an active board member of the Alliance for Regenerative Medicine and the ARM Foundation, as well as the Centre for Commercialization of Regenerative Medicine (CCRM) in Toronto. Phil has published a number of industry position pieces and serves on the Editorial Board of *Cell and Gene Therapy Insights*.

Q In our previous interview in 2016 we talked about manufacturing lagging behind the remarkable clinical progress we were seeing with CAR-T therapies. Do you feel that manufacturing capabilities are still playing catch up?

PV: I think they are. Philosophically, there have been a lot of advances in the technologies being made available to the companies developing and

commercializing these therapies. The problem is it takes time and investment to bring a new technology to the market. But we are getting closer to the point where reagents, consumables and ultimately new devices, are starting to catch up to the demand in the market.

The other challenge we have is the pace of change in this field. For the CAR-T sector in particular, we're already on generation 2, 3, 4 CAR-Ts. While these therapies are evolving and advancing rapidly, tool companies like GE are trying hard to keep up with that pace of change.

We must anticipate what a therapeutic manufacturing model might look like in 2 to 3 years and design new tools with that vision. However, I think with such a fast moving field, there will be a consequential lag with any of these technologies, just trying to keep up with the pace of therapeutic advancement.

Q Do you think the conversation has changed over the last few years – has manufacturing come to the forefront in terms of its importance?

PV: I don't want to short shrift the other therapeutic modalities that are also evolving like gene therapies and allogeneic therapies but talking about the CAR-T scenario and other autologous therapies, there are two proof points to consider.

The big question being asked at conferences recently is – what's changed? Well of course the biggest change is that these therapies are now becoming commercially available and are being prescribed to patients, offering potentially transformative benefits. With Kymriah and Yescarta coming to market, we've now demonstrated proof of concept that these therapies can be commercialized. With that comes the confidence that the industry will now start to take shape, that we can retire some of the risks in the supply chain, and we can knock down some of the challenges that remain.

So for us and the many companies in the sector, we now have confidence that the market is real, investment will continue, and therefore the whole ecosystem and supply chain will continue to advance and evolve around that new reality we're in.

Q When you look across these complex supply chains where do you feel the biggest opportunities lie for innovation and improvement in manufacturing?

PV: As the common expression goes – the strength of any chain is only as good as its weakest link. If we look at the supply chain for autologous

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therapies, these are patient-specific therapies, so all the complexity and orchestration have to take place from vein to vein. The process includes collection of patient materials, delivery of those materials to the manufacturing center wherever that may be, processing of that material, transduction to genetically modify cells, the downstream processing, fill and finish, and finally the cold chain distribution back to point of care for re-administration.

There are several weak links in that process today. We've worked on some of the manufacturing challenges. For instance, expansion of cells is routine now and several platforms are available for undertaking that work. But the weakest link remains in the viral transduction and virus-mediated genetic modification steps. The weakness there is really the lack of ability to effectively and efficiently manufacture the viral particles for transduction.

Whether it's lentivirus or gamma-retrovirus, the methodologies and technologies for producing them as a raw material in manufacturing are poorly developed. The efficiency and recovery, and ultimately infectivity of those materials is still low. It's an expensive, cumbersome and slow process. The demand for those materials is starting to increase with new technologies and that is driving some of the improvements and efficiencies we will see in the coming months to years.

But there is a pent up demand for those materials. If you talk to CMOs that manufacture these for the therapeutic customers, there's a backlog and demand for them to be produced, provided and delivered to the point where they will be used.

Other weak points in the supply chain include the orchestration – the scheduling and integration of all the different individual unit operations. In the manufacturing processes alone, there could be 100s of different steps requiring lots of labor and potentially a lot of manual intervention; the handoff from one device to another. Because these devices are evolving as the industry develops and are being cherry picked from what's available in the market, not many of them currently connect [to one another] digitally and consequently there are multiple data entry requirements. They're not necessarily connected to the LIM systems or quality management systems, so there's a lot of inefficiency in that part of the workflow.

And then ultimately if we look at the cold chain, this is still a process that requires liquid nitrogen and shippers that are transported around the world. People haven't yet reconciled whether we are going to do manufacturing at a geographically central location or at multiple regionally distributed manufacturing centers and that will ultimately have a huge impact on the cold chain requirements.

All in all, the challenges mainly pertain to three different areas: viral production, orchestration and digitalization of the workflow, and then ultimately the cold chain and distribution, which will have to be addressed in the next few years.

Q How is the collaboration between GE and CCRM seeking to address these opportunities and weaknesses in the chain to improve the cell and gene therapy manufacturing pathway?

PV: When we started the discussion with CCRM we really understood that as a technology provider we had limited access to the real therapeutic challenges that manufacturers of these therapies faced on a day-to-day basis.

To that end, we wanted to set up a center of excellence through which we could do better than just asking: "what are your pain points, where are your challenges in the workflow"? We recognised we had to roll up our sleeves, get our hands dirty, and actually work on the processes in lock step with these therapy providers to enable us to develop next-generation technologies.

We set up a fairly sophisticated process development laboratory at CCRM, not only with GE equipment but with technology and equipment from lots of providers throughout the industry, and a very comprehensive analytical capability to really understand what the impacts are when we introduce a technology or new step, or remove a step, from a customer's work flow process. This really helps us understand what the implications of a change to their workflow can have on the subsequent process steps and outputs. So not only does our therapeutic provider and partner benefit from an improved process, but we learn along the way. That makes us better, smarter, and gives us the opportunity in our next generation tools and technologies to provide a much more streamlined and sophisticated reaction or response to those needs our customers face.

Q In some cases, the achievement of commercial success will hinge upon the speed at which these companies can move to commercial scale manufacture. What approach does GE take when working with a company looking to transition to commercialization?

PV: The approaches we take are driven by what our therapeutic client requires. It is true that there is a race to bring the next-generation CAR-Ts to market and this is mainly for two reasons: economic benefit to the company; and more importantly the desire to improve the lives of patients around the world.

To that end, like most of our peer companies, we are being approached by our therapeutic clients, whether it's at a clinical center or a biotech

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company, to assist them in identifying and improving their processes. Through our collaboration with CCRM, we are able to undertake this process development approach.

The second service we provide is bringing our Flex Factory and Enterprise Solutions where we look at the existing workflow of any of these operations, then analyse and make better recommendations about different types of equipment and kit. We then acquire and install that equipment in the workflow as part of what we call Flex Factory, which is really a front-to-back manufacturing operations workflow.

For instance, we can bring an upstream cell selection technology, expansion process, transduction process, or provide capability for viral upstream and downstream manufacturing, bring in different components as required by the therapeutic client into the workflow, and make recommendations. Taking it a step further, we can acquire, install, perform validation, IQ/OQ and then get it operational so that our clients can focus on the therapy and their clinical studies, and we can focus on operationalizing their workflow.

Furthermore, when a client gets to a point where scale becomes limiting to them we can perform scale up for them. We can provide greenfield manufacturing capabilities, what we call Kubio, that is a turn-key, ready-to-go GMP manufacturing facility. We can install the Flex Factory into that facility, and then provide a fully comprehensive, turn-key capability, where they have a completely operational and validated factory for producing any number of cells or doses they might require.

Those are some of the approaches we're taking on the manufacturing side: providing a holistic front-to-back, soup-to-nuts capability to our clients.

We can also bring digital capabilities into the workflow, through our relationship with Vineti, a spin out of GE, in partnership with the Mayo Clinic. We can bring a whole layer of digital orchestration into some of that scheduling and sequencing, chain of custody and chain of identity for the patient.

This approach enables us to support a therapeutic developer by bringing a comprehensive capability, whether they require individual unit steps, unit operations, a fully-fledged and validated workflow, or as a full factory.

Q How much time can you potentially save a company by implementing this modular approach to manufacturing?

PV: We've done some time estimations based on modeling of the different workflows and the optimizations. There's two ways we save time and

money. One is opportunity cost – if you're focusing on both clinical and manufacturing development, the manufacturing piece is logically going to take some of your time and energy and investment away from clinical development and running your clinical trials. We allow a therapeutic company to invest their time and energy in developing and delivering a high quality therapy. In about 18–24 months, we can provide them with a factory workflow ready for operation. The time would even be shorter if it's just a Flex Factory or some of the components that go inside the factory. We believe we can save anywhere from 10 to 50% of time depending on the process and complexity.

The second factor to consider here is the staff expertise. Only very few people in the world have the real-world expertise in running a cell therapy manufacturing enterprise. By conserving that engineering know how and capability, it can provide quite a significant time saving. If you lay on top of that the time required to train into a facility and get someone fully operational on a GMP floor, that can easily take 6 months. By allowing them to focus on personnel training and development and providing this technology we can multitask across a lot of these time components, and therefore shorten some of that time. So it's a dramatic time saving.

Q Continuing our discussion on skilled personnel, there are concerns about skills gaps emerging in this sector. Is this a reflection of reality in your experience, and what can we do to address that?

PV: It absolutely is. My advice to anyone thinking about what career path to follow in the biotech industry, is to look at the cell therapy sector. We absolutely need skilled operators and skilled therapy developers.

This is an area that is going to take off in the next few years, with the advancement of the autologous therapies, allogeneic therapies, all the way through tissue engineering – and all of these require a very foundational biotechnology GMP manufacturing competence and skill set that is hard to find.

If you think about where companies are hiring from today, and where some of the real high-quality skill sets are coming from – first and foremost they're coming from the biologics industry. But biologics and cell therapy are quite different. There are a lot of elements in cell therapies that depart quite a bit in terms of a manufacturing process from the biologics industry.

While we can translate some of those skill sets, like GMP qualification and working in clean rooms for example, there's a great deal more complexity and nuances to cell therapy manufacturing, and the industry needs

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more people developing this specialized knowledge – everything from process developers to floor level manufacturing supervisors and operators of the facilities and equipment.

What can be done to address these skills gaps? The industry is talking about partnerships, and consortia are exploring various deliverables such as the education, development and training of individuals – from associate level all the way up through PhD level programmes in the USA, as a way of growing capabilities in this field.

If you go broader than just manufacturing: regulatory personnel, transportation, logistics, supply chain management – all these roles require some very unique skill sets to make this industry work. Digital programmers, people who understand automation, people who understand the factory workflow and factory floor production logistics, supply chain, all these things will be needed.

The lack of skillset is something industry has faced in the past. At present people are seeking the talent that exists in the market as it is today, but there is a need for the skills to be developed further.

Q Could you share your insights into the exciting partnership between GE and CBMG in China to help them expedite their CAR-T manufacturing process?

PV: The pace of adoption of CAR-T and other cell therapies in China is like nothing I've ever seen before: 5 years ago there was a lot of attention in cell therapy and in the last 2 years it's just caught fire!

The Alliance for Regenerative Medicines website cites over 120 clinical trials running in Asia, the bulk of which are running in China. Two things are essentially happening in China: one, the sheer intensity of investment and energy being put into running these clinical trials and getting these therapies to market there is driving commercial development. And secondly, the number of patients eligible and available in any of these markets is huge. So it's no surprise that China will be one of the most important markets for cell therapy in the next 5–10 years, simply because of the population and the high quality of research. China's moving very quickly through clinical trials and the only thing they're lacking at this point in time is the infrastructure, the logistics and supply chain.

That's one of the reasons why CBMG chose GE as a partner, we have that expertise and experience in building an industrializable supply chain around a number of industries, in particular in cell therapy where there's a real unmet demand.

Q We previously talked about your vision for the factory of the future. Two years on, how close do you think we are to this becoming a reality?

PV: We're getting there! I think people are having the conversation about what would it take to develop that factory of the future.

The factory of the future is one that can manage a multitude of different cell therapies, gene-modified therapies, non-gene-modified therapies, autologous versus allogeneic therapies. It's a very flexible environment that can put through a large number of doses and patient samples through that enterprise.

What does that require? Again it looks at each of the bottlenecks of the process and knocks them down one by one. Where are the costs being driven into the factory? Costs are being driven largely by labor and overhead. The first thing we'd love to do is take out the clean room entirely and to do that you need closed devices that can operate in more of a declassified environment, and that requires a different type of approach to developing the entire manufacturing consumable, as well as the equipment and hardware that operates that consumable. It also requires new packaging and competencies around reagents that are used throughout that workflow. In addition, it requires an integrated supply chain with logistics, distribution and cold chain management processes.

All of those elements will come as the processes and as the therapies start to coalesce around particular types [indications], which is what we are starting to see with CAR-Ts. Making that seamless closed and digitalized workflow available in environments that are somewhat, if not entirely, declassified, will really enable that vision of a future factory. And whilst it is still some years away, people are having the conversation about what would it take to enable that factory of the future and working towards that goal.

AFFILIATION

Philip G Vanek
General Manager of GE Healthcare's Cell and Gene Therapy business strategy

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