AUTOMATION OF CELL AND GENE THERAPY MANUFACTURING: FROM VEIN TO VEIN

SPOTLIGHT

INNOVATOR INSIGHT

Critically Evaluating the Benefits of Automation in Commercial-Scale Manufacture

Nina Bauer leads Lonza's Autologous Cell Therapy business, with manufacturing sites in the US, Europe and Asia. As part of this role, she is also in charge of establishing novel manufacturing technologies to remove bottlenecks and enable commercially viable services for patient-scale therapies. With more than 12 years' experience in the Regenerative Medicine sector, Nina has held Business Development roles at the Cell Therapy Catapult (UK), and the University of Edinburgh, and worked as a Life Science Consultant for a wide range of Regenerative Medicine businesses. She holds a PhD in Neuroscience from the University of Oldenburg (GER), an MBA from the University of Edinburgh (UK), and conducted post-doctoral research at the Weizman Institute (ISR), Salk Institute (USA), and the University of Edinburgh (UK)."

Q The recent approval of the first CAR-T therapies is a key milestone for the field, but thus far approved cell and gene therapies are for relatively small patient groups. As companies look to move into larger disease indications, what do you see as the critical challenges around effective scalability?

The key issue around scalability of autologous therapies is that most manufacturing processes still require a significant amount of manual intervention. This has two major implications: Firstly, manual intervention requires a highly-trained workforce; and secondly, while individual unit operations tend to be automated, or at least semi-automated, transfer from one piece of equipment to another is manual, and thus dependent on personnel availability and, critically, consistent techniques being employed by different personnel. Furthermore, manual and partly open

processes come with a range of regulatory and quality restrictions around facility sharing. To avoid cross contamination between individual patients' therapies, strict change-over regimes are necessary, which often results in a large, capital-intensive overall footprint. This reliance on skilled labor and space to implement effective scalability are the key factors that need to be addressed if we are to achieve consistent reproducibility and optimize cost of goods.

Q The consensus of when to implement automation in your manufacturing process is 'the earlier the better' – in your experience, is that a realistic for earlier stage companies and what approaches can they take to determine the potential value to their business?

I agree with the statement "the earlier the better" from a technical implementation, regulatory and clinical development perspective. Ideally you should design your manufacturing process with the end goal in mind, which is to optimize the transition towards commercial-scale manufacture. Unless your therapy is for an orphan indication with a small number of doses per year and a potentially high reimbursement price, then automation will be a key approach to reduce cost and enable scale-out, both of which will define your long-term commercial viability. The later automation is implemented, the more significant the impact will be on timelines and cost due to comparability studies, additional process development, or changes to facility design.

That said, I also agree with the question mark you put behind that statement. The cell therapy industry is primarily made up of small, early-stage companies, some exceptions notwithstanding. Their financial runway tends to depend on the achievement of technical and, more importantly, clinical milestones. As a consequence, treating the first patient often takes priority over implementing optimal manufacturing processes and automation technologies. Most early-stage companies therefore must perform a balancing act between developing a long-term viable process for commercial-scale manufacture and a "good enough for now" manufacturing approach.

One approach that can help identify the tipping point in terms of when to implement automation within your manufacturing process is to model patient numbers in relation to cost, space, and labor demands. We encourage our clients to work in parallel – to perform Phase I studies with a more basic, semi-automated process, while continuing development and automation implementation, ready for Phase II and beyond. From a Contract Manufacturing perspective, this requires the willingness to enter into flexible or "alternative" business models, with risk sharing and/or milestone-based payment schedules.

Q What are the key considerations when deciding to automate a complex biomanufacturing process such as autologous cell therapy manufacture?

The dose numbers per year, and manufacturing consistency and reproducibility will determine the inflection point. The more

DOI: 10.18609/cgti.2017.071

complex a process, the more difficult it is to train enough operators to perform at consistent quality for the required dose number. Automation can provide a strong risk mitigation argument by ensuring robustness, as well as simplifying the process. Equally, the footprint and personnel required for a commercial manufacturing operation can quickly become a limiting factor impacting product availability for larger indications. Automation platforms have the potential to deliver space efficiencies, in particular compact, 'GMP-in-a-box' technologies such as the Cocoon™, which can be arranged in a three dimensional space.

On a more granular level, certain unit operations are more easily automated than others. Most therapy developers already employ tools for cell selection, and harvesting, for example. Feeding regimens can be maintained in a range of bioreactors equipped with sensors to determine nutrient levels, gas contents, and cell density. While this represents a step towards efficiency, these tools don't overcome the need for experienced personnel, and will not immediately address the space constraints. This modular approach would therefore require robotics for the transition steps and a conveyor belt concept.

Q Do you feel that an end-to-end automated manufacturing process is ultimately going to become the gold standard for autologous cell therapy manufacture?

Considering the aspects I mentioned earlier, I believe that well developed processes can be automated using all-in-one platforms. The constraints that are sometimes raised in the context of these automation options are that they are inflexible and cannot be changed easily. While this is a correct statement, CMC experts would argue that a manufacturing process should not, as a rule, be changeable. Such platform technologies should, therefore, be considered from a commercial product delivery perspective, rather than from a process development perspective.

The key is to develop your individual unit operations using conventional or manual approaches, thus gaining detailed insight into your critical process parameters, and creating a baseline. We have been doing this in a way that allows for seamless translation into the CocoonTM, and have generated some very positive data and outcomes.

All in all, though, patient-to-patient variability remains a critical factor that requires adaptability of the process. If well understood, an automated system can adjust expansion phases and feeding frequency, while maintaining overall process characteristics and thus ensuring output quality.

From what we have seen in modular automation approaches, while more flexible, you are dealing with a range of manufacturers. Often they are not aligned on their individual product life cycles, and a change in one technology may have unexpected impacts on the entire process. Therefore, the technical support of such a setup can be exceedingly challenging.

Overall, automation should pay for itself: the potential upfront cost for the infrastructure should be compensated for by reduced footprint, reduced facility running costs, reduced personnel, and quite possibly improved process cost of goods. In the mid-term, these aspects should impact

on overall product pricing, thus ensuring commercial success through robust reimbursement options and prescription uptake by doctors. Therefore, I strongly believe that all-in-one concepts have the potential to become the gold standard in autologous cell therapy manufacture and will support the successful commercialization of these exciting new therapies.

Q One criticism is that we are not seeing sufficient genuine innovation in the manufacturing tools and solutions for cell and gene therapies – do you feel this is a fair assessment?

Whilst I can understand the criticism, I don't think it's a fair reflection of the approach the industry has taken to developing new tools and solutions. Overall, the industry has been building upon existing technologies from biologics manufacturing, as well as blood and bone marrow processing. We have seen stepwise innovation, but maybe not game changers. We now need to bridge the gap from using cells as mini-factories, producing proteins, which only requires basic monitoring, and move towards an understanding of cells as the active ingredient. I think we are still missing a fully detailed biological description of our cell therapy products, and are, thus, still lacking in biotech innovation that would allow for appropriate in-process controls. Ultimately, the industry hopes for a fully automated manufacturing system that provides a "green light" at the end of the process that would enable immediate product release. For this we would need to know the critical process parameters and how to measure them.

At a recent conference I was encouraged to see a range of new technologies that have the potential to be real game changers for cell therapy manufacturing. It's fantastic to see the enthusiasm our industry generates - the clinical success is now attracting engineers and technical individuals to the space and they look at our bottlenecks with fresh eyes. As such, I think we will start to see a host of new platform solutions that will enable the success of our therapies over the next few years, in a similar fashion to the evolution we saw with monoclonal antibodies.

Q You mention the Cocoon™ platform – what have some of the challenges been in moving this product towards implementation as part of the Lonza manufacturing approach?

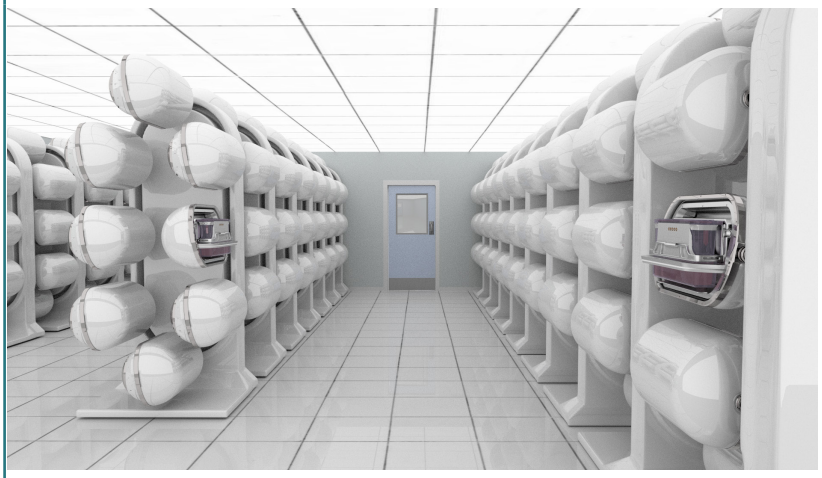
Although we would advocate that people adopt automation as early as possible, the earlier a process is translated to the Cocoon™ technology, the more upfront development work may be needed. You need to have your process parameters very well developed before you automate, so that you can compare your feasibility data and adjust the different levers to match output quality.

During our initial CAR-T process translation into the Cocoon™, we selected the most challenging case for the development program: We chose

 DOI: 10.18609/cgti.2017.071

FIGURE 1

Digital rendering of a Cocoon™ facility, Orchard.



a protocol from an academic lab, which only existed at a 96-well-plate scale and was fully manual and without any defined in-process controls. During the feasibility phase, the technical teams at Lonza and at our partner company, Octane, first expanded this process by 50x, and moved it into a semi-automated bioreactor. Subsequently, Octane's engineers designed and built a single-use Cocoon™ cassette, representing the key unit operations and thus demonstrating full automation. During the optimization stage, the team identified and assessed the relevant process parameters for comparability, and further adapted the system to accommodate clinical and market requirements such as cell numbers and overall quality factors.

We are now applying the exact same approach to our first beta customers, early adopters who see the benefits of automation, and who are keen to evaluate the technology for their individual processes.

Overall, while it is more difficult for us to perform the translation without clearly defined in-process controls, we have built our Cocoon™ translational team around the need to efficiently support and accelerate the customization, and build on the experience we have gained from our in-house work. Every process we translate is different, depending on process duration and specifications, cell type and potential gene modification options, and our customers need to rely on an accurate representation of their process parameters in the newly automated approach – think "the process is the product". Sometimes, the differences are relatively minor compared to our baseline process, while in others the process requires additional unit operations. Ultimately, a tailor-made cassette that captures the unique aspects specific to the clients' process, in combination with bespoke software programming, can provide a way to obtain and protect valuable process Intellectual Property.

Q Have you engaged in discussions with regulatory bodies throughout the development of this platform to determine how it might impact a product's path to marketing approval?

A lthough many existing regulatory guidances are applicable to cell therapy products, there is still a need for these to evolve to meet the specific needs of the cell therapy industry. Generally speaking, automation is a means to an end, not the 'end' itself. As with

a fully manual process, end-to-end automation must be proven, to both customers and regulators, to provide outputs that are reliable, consistent and repeatable, meeting the required safety and quality standards and providing reliable records.

In this context, we are excited to now be working with customers who are looking to enter the clinical approval path with the Cocoon™. We have also recently been invited to give a technical seminar at the FDA, and a few European agencies, where we presented the technology and the manufacturing concepts behind it. Overall, the feedback has been very positive, and the need for such a platform is well understood: It is anticipated that a closed system streamlines the overall manufacturing process, reduces risk and therefore increases supply chain security for cell therapy products once they enter the commercialization stage.

Q Do you feel that the industry will need to migrate towards a GMP-in-a-box approach to effectively scale cell and gene therapies?

For the autologous cell therapy industry, where scale-out is the only option to supply a commercial-scale product to the market, GMP-in-a-box provides an opportunity to overcome bottlenecks. If you then consider future developments, where near-patient manufacturing might become the new "normal", a GMP-in-a-box approach provides the robustness required to ensure replicability between different sites. This is also associated with the closed system aspect, which enables a reduction in clean room classification, thus making such a decentralized concept more easily imaginable.

Finally, having all unit operations in one machine enables straight forward integration into data management systems. If you imagine having to manufacture therapies for thousands of patients, you must have a software backbone that integrates the manufacturing aspects into patient scheduling systems, manufacturing management systems, and overall traceability and chain of custody and identity monitoring. That's not an insignificant challenge, but one that we feel will be underpinned by creating a GMP-in-a-box solution.

AFFILIATION

Dr Nina Bauer, Associate Director, Commercial Development, Lonza, Switzerland

DOI: 10.18609/cgti.2017.071


Lonza
Pharma & Biotech
the next milestone in cell and gene therapy...
We'll achieve it together.
We want to be your partner and add value to your therapy development process. We invest in enabling technologies and build expertise to support the development and commercialization of new innovative therapies.
Our scientists and engineers bring decade-long development experience across a broad spectrum of cell types and technologies. This builds the backbone of an extensive service offering, providing you with tailored process and analytical development, manufacturing and regulatory services.
Contact us
North America +1 301 898 7025
Europe & rest of world +41 61 316 81 11
Email celltherapy@lonza.com
pharma.lonza.com