INTERVIEW

Key considerations in expanding global manufacture of a commercialized CAR-T cell therapy

Following the successful commercial launch of CARVYKTI®, partners Legend Biotech and Johnson & Johnson are busy expanding global production capabilities. Sarah Snykers, Head of Operations, Legend Biotech, took time out to talk to David McCall, Cell & Gene Therapy Insights about the ins and outs of setting up commercial CAR-T manufacturing facilities in Europe.

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Q What are you working on right now?

SS: Legend Biotech is creating a global manufacturing footprint to produce cell therapy products. Currently, in collaboration with Johnson & Johnson, the company manufactures its CAR-T cell therapy, CARVYKTI® (cilta-cel), in the US. Two additional facilities based in Ghent, Belgium are anticipated to come online over the next two years to add to global supply.
CARVYKTI® is a B-cell maturation antigen (BCMA)-directed, genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory multiple myeloma, after four or more prior lines of therapy including a proteasome inhibitor, an immuno-modulatory agent, and an anti-CD38 monoclonal antibody. The therapy is being evaluated in a comprehensive clinical development program across multiple settings.

In a nutshell, the patient’s T cells are encoded with a CAR that can find and destroy BCMA-expressing cells. BCMA is highly expressed on the surface of malignant multiple myeloma B-lineage cells; it is also expressed on the surface of late-stage B-cells and plasma cells.

I lead the CAR-T production operations of CARVYKTI® at the two production hubs at Ghent: the brownfield facility, Obelisc, and the greenfield facility, Techlane. I support the commission and certification of the buildings and the tech transfer from the US to Belgium, including the execution of the preclinical package, such as engineering runs, comparability and stability runs, and the Process Performance Qualification. In particular, I focus on building up an agile and flexible organization that consists of people with the right mindset and a passion for healthcare.

**Q** What are some of the key high-level challenges and considerations in establishing commercial CAR-T cell therapy manufacturing operations in Europe?

**SS:** In the European Union, and even more specifically in Belgium, there is a noticeable scarcity of CAR-T companies, especially when compared to the United States. This situation impacts the availability of resources and the acquisition of talent in the region.

The production process for CAR-T is distinct when compared to small molecule drugs. It is a personalized and innovative technology that involves many open manipulations. These manipulations necessitate individuals to possess specific skills and the right mindset, which includes being aseptic, precise, agile, and having a problem-solving capability.

Specifically, for autologous cell and gene therapies/CAR-T treatments, deviation management requires quick resolution. While the process is robust, there is intrinsic variability due to the biological nature of the product. Achieving a fast or timely closure of investigations is crucial for the prompt release of the product, ensuring it’s made available to patients without delay. This process demands a unique set of skills and needs experienced investigators.

For commercial production, the focus is primarily on maximizing production. To achieve this, there is a significant need for many new hires, along with timely training and requalification. Furthermore, according to Annex 1 regulation in the EU, operators must undergo aseptic requalification every six months, which takes up a considerable amount of production slots.

When it comes to commercial production and operations, maximizing the production process is key. However, a manual process has limitations when it comes to scaling up, particularly in terms of space, capacity, and resources.

Therefore, it’s highly recommended that companies choose production or process technologies that are easily scalable. Additionally, when designing facilities, it’s essential to anticipate potential future changes.
What for you are some key recent breakthroughs and opportunities in terms of reducing manufacturing timeframes?

**SS:** For optimal operations, it is essential to organize and train teams so that we can function like a well-oiled machine with reduced idle time. Adjustments to the production process, such as closing off certain steps or implementing closed automation, allowing us to facilitate grade C environments based on regulations. This would result in less intensive gowning, cleaning, and environmental monitoring sampling. Furthermore, efficient flows of materials and personnel are crucial for smooth operations.

...and regarding reduced Cost of Goods (COGs)?

**SS:** Again, resources, materials, and maintaining a facility up to the required grade are the main cost drivers. One way to improve efficiency is by adjusting the production process, such as making changes that can lead to reduced environmental monitoring and facility costs. Reducing the number of required resources can be achieved by building an efficient, well-trained organization and eliminating open manipulations in the process. As a longer-term strategy, expanding the recycling of plastic consumables can be an environmentally friendly and cost-effective measure.

...and lastly, in terms of enhancing process control?

**SS:** Enhancing process control can be achieved through predictive data modeling and data analytics.

How to optimize cell therapy fill-finish—what are the key innovation gaps there?

**SS:** Whilst several technologies exist to fill and finish in closed vials, the opposite is true for bags. For autologous CAR-T therapy, the number of bags per production is very limited.

How can we move further towards the automation of data analysis in cell therapy manufacture?

**SS:** It is crucial to embrace the full potential of digitalization technologies. The reliance on manual data handling methods not only introduces a risk of human error but also presents scalability challenges as the volume and complexity of data grow.

The path to automation includes the adoption of integrated digital systems, such as electronic batch records or manufacturing execution systems, which automatically capture data...
in real-time across various stages of the manufacturing process. These systems facilitate end-to-end traceability and provide a robust framework for ensuring the consistency and reliability of data, which is vital for meeting the regulatory requirements in the pharma industry.

Advanced analytical techniques can be leveraged to explore and go through the extensive datasets involved, identifying anomalies and optimizing processes. Predictive modelling can become a powerful tool here, enabling anticipation and adjustment of production parameters for better outcomes.

Cloud-based solutions can significantly help in this automation journey by offering real-time data access and analysis capabilities. This ensures that decision-making is timely, informed, and can even be conducted from remote locations, enhancing monitoring and control flexibility.

However, as we integrate these digital systems, we must ensure they meet regulatory standards, such as the US FDA’s 21 CFR Part 11 and the EMA’s Annex 11. It is also crucial to consider the related costs and challenges, such as integrating new technologies with existing infrastructures and ensuring there is personnel skilled enough to maintain and manage these advanced systems.

In conclusion, it is important to bear in mind that while automation is key, the expertise and insights of scientists, engineers, and analysts remain indispensable. The aim of automation is not to replace the human element but to support it by freeing up time to focus on more strategic, creative, and complex tasks, driving innovation and efficiency in cell therapy production.

Q Finally, can you sum up one or two key goals or priorities, both for you in your own role and for Legend Biotech as a whole, over the next 12–24 months?

SS: In my role, I aim to achieve successful clinical and commercial production of CARVYKTI® at both production hubs. As for Legend Biotech, one of the company’s goals is to establish a global clinical and commercial CAR-T production footprint to meet the increasing demand.

BIOGRAPHY

SARAH SNYKERS is Senior Director of Operations at Legend Biotech, Ghent Europe. She has 20 years of experience in cell and gene therapy. She has headed several departments in biotech companies, including manufacturing, QC, R&D and manufacturing, science, and technology; all focused on clinical or commercial production of autologous and allogeneic cell and gene therapeutic products. Over the last 15 years, she was involved in three greenfield production hubs, and in several global tech transfer projects for clinical and commercial production of cell and gene therapy.

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