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

SPOTLIGHT

INTERVIEW

Automation in the translation of an autologous cell therapy from lab to commercial scale

Dr. Rodney Rietze is a Senior Research Investigator in the Exploratory Immuno-Oncology group at the Novartis Institutes for Biomedical Research (Cambridge, MA), developing novel bioprocesses and enabling technologies for the manufacture of next generation CAR-T therapeutics. This work is a continuation of his role at Novartis Pharmaceutical's Cell and Gene Therapy Unit, where he led the Automation Network that supported the manufacturing process and analytics for Kymriah™, the first FDA-approved personalized CAR-T cell therapy. Before joining Novartis, Dr. Rietze was a Senior Director at TxCell S.A., where he developed the process/analytics for Ovasave™, an antigen-specific type 1 regulatory T cell-based autologous drug product in clinical trials for the treatment of inflammatory bowel disease. Prior to TxCell, he was a Senior Principal Scientist at Pfizer Regenerative Medicine where he led teams in discovery and early clinical development of small both molecule and cell-based therapeutics for neural, cardiovascular and auto-immune indications. Preceding his transition to industry, Dr. Rietze was a founding member of the Queensland Brain Institute (Brisbane, Australia) and Head of the Neural Stem Cell and Aging Laboratory. His work on the purification of an adult mammalian NSC, and subsequent discovery of the pathway that activates endogenous NSCs spurred the development of several compounds that are currently in clinical trials.

Q What are the major challenges in the effective translation of an autologous cell therapy from laboratory to commercial scale?

One of the major challenges in translating an autologous cell therapy from laboratory to commercial scale is the unintentional loss of the active pharmaceutical ingredient (API) or drug product. Whether

it be a lack of expansion, altered potency, phenotype or another attribute, the API is altered as compared to what you have previously produced in the lab. While a number of factors may account for this, it is typically owing to an unstable or poorly controlled/understood manufacturing process.

The next challenge is dealing with the variability of the incoming materials. This is not only related to the stability and quality of starting materials, but also your supply chain. Due to the scale of your process, one is not typically exposed to the impact of lot-to-lot variations on the quality and consistency of materials in your supply chain when you're in an academic setting or at the early clinical trial phase with an evolving and small-scale manufacturing process. However, as you progress through clinical trials and transfer the process out of the lab it was created in, you're going to need to address questions related to quality, stability and consistency of all materials. This is especially true of apheresis material and serum.

Another important challenge is associated with changes in analytical devices. Analytical devices and methodologies are not typically identical between two centers, so this can cause immense difficulties.

One additional challenge that is often overlooked is related to the incomplete transfer of the process, often owing to either poorly written or transcribed protocols, or they're just not reflective of what is actually being done. If you don't capture what you're doing, it's hard to tell someone else what you've done.

Q How will automating CAR-T manufacturing help overcome the limitations currently posed by the manual biomanufacturing processes?

One of the key benefits of automation is that it minimizes operator-to-operator variability and manual handling biases that increase risk. Removing or controlling these variations increases one's insight into the process and helps to ensure a safe and efficacious product. It has to be remembered that these are lifesaving therapies that are being manufactured and therefore every product counts; if you can't robustly and reliably produce a safe and efficacious product, you are impacting a patient's life.

Secondly, automation reduces the cost of manufacturing process. It does so in a number of ways; one way is by reducing costs related to your infrastructure. For instance, automating and closing your process so that you no longer need to manufacture within a clean room will significantly reduce overhead. Another way is by reducing the number and volume of reagents you use. Automated, reagent-free technologies are now available for a number of unit operations. Tried and trusted technologies such as liquid handlers further represent low-risk devices that save both time and money by rapidly and accurately performing widely used assays. Flow cytometric panels can be performed with greatly reduced volumes of antibodies as compared to those performed by manually aliquoting and transferring cells and antibodies.

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Automation is the key to rapidly scaling a therapy in a cost-effective manner. It's also the key to reducing the risk and complexity of process transfer. Transferring a unit operation via a device is straightforward and unambiguous by design, as opposed to having to demonstrate how to perform the operation manually, or trying to interpret or reproduce these complex manipulations by hand.

Automation also enables the seamless implementation of an electronic batch record. Transcription errors are common for a manual manufacturing process and having an accurate and prescriptive batch record that's faithful to what actually happened lowers risk and allows one to consistently produce safe and potent products.

And finally, in terms of regulation, automation reduces regulatory burdens. Automated closed systems reduce the risk of unintended loss or sterility issues. The more automated steps in the manufacturing process, typically the more regulatory compliant it is and you have much more confidence in the reproducibility and safety of your product.

Q What are the key considerations for automation of a complex biomanufacturing process such as CAR-T cell production?

The most important consideration is ensuring that you have a sufficient degree of product and process knowledge before you start considering automation strategies. How is the product defined, how is it produced, and how is it controlled? Unless you have a deep understanding of product attributes, you cannot modify your process without significant risk of altering your final product. You should also consider factors outside of the process. Is the final product in a bag? Is it in a bottle? How will it be shipped? You need to consider these factors and the science around your product before attempting any alterations to the product, as these alterations will impact the safety and efficacy of your product.

Once you have a sufficient degree of knowledge, the second consideration is deciding where to start automating. For this, an understanding of where the high-risk unit operations are in your process and associated analytics, is required. Typically, the areas that represent the greatest risk are the most labor-intensive unit operations.

The next consideration is when to automate in the clinical trial process. As you proceed to later phase trials where efficacy is more clearly demonstrated, the probability of success for that product increases, which in turn increases the net present value of the product, which provides a better cost/benefit ratio for any device expenditures you may be contemplating. But as the probability of success increases, so does the cost and comparability demands of introducing any new technologies. Therefore, we like others, use a formula to determine the cost/benefit ratio of any proposed change. It's about getting that balance just right.

And the final consideration is what platform will be best for you? For smaller companies that have less funds or smaller pipelines, an off-the-shelf device is often the best solution. If you have a greater depth of

funding or a pipeline of similar products, you have the option of developing an emerging technology that might take longer to integrate into your process, but it could provide you with a valuable competitive advantage in the long run.

Q What are the barriers to effective cell therapy automation?

Lack of understanding and data concerning the scientific foundation of your process, product and analytics is the first barrier to effective cell therapy automation. You need to know what your critical quality attributes and critical process parameters are before you can even contemplate beginning this journey.

Another barrier is the lack of robust clinical readout or feedback to tell you what the impact of any process change has on your final product. What you don't know is dangerous. What you've done, if and how it impacts your product, and how this change ultimately impacts your patient are critical questions that must be answered.

And finally, the lack of a well-defined and, I would say, properly vetted strategy. Automation is a team effort. It is not a one and done solution. Automation is a continuous and evolving strategy that is rolled out over time. It evolves as your product portfolio evolves. If you have not shared and vetted your strategy with key stakeholders, or failed to gain endorsement from your senior management, they're not going to provide you with the long-term support that is critical for your success. If you get halfway through rolling out your strategy and your funding dries up, you're sunk.

Q With such potential variability in the quality of starting materials for CAR-T therapies, how can automation be utilized to help to standardize the end product quality and potency?

I think a great example of standardizing end product quality through automation is found in the apheresis and blood collection centres. In the past, there were operators, nurses or technicians, who were trained to subjectively tune an apheresis device based on visual appearance and they did this to optimize the collection procedure. This was as much an art as a science. Now the company supplying the device has automated the monitoring and collection procedure in the next-generation device. This effectively removes the subjective nature of a collection and in doing so, standardizes the composition of the final product regardless of the operator or geographical location where the procedure is taking place.

Equally important, these devices capture and transmit data on the performance of the device and the collection procedure. You're no longer relying on a person to assure the procedure went well. Indeed, the device will alert you of an unexpected change mid-run, enabling an automated adjustment, or the choice to pause the procedure. At the conclusion of the procedure, metrics for the run are displayed in relation to other procedures,

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so you can know if it was an out of spec run. This gives the confidence that the procedure has been run well, the protocol has been followed, and you have the best possible product. That sort of standardization is happening across the field in apheresis centers. And it's really this type of flexible, intelligent approach that positively impacts end product quality and potency. I have coined the term 'reactive automation' to describe this approach.

Incorporation of like-devices in CAR-T manufacturing would similarly reduce operator variability and positively impact product quality and safety. The global use of such devices would of course enable us to standardize end product quality and potency to a much greater extent than we are currently able to do.

Q What progress has been made in automating the CAR-T manufacturing process?

I am really encouraged by the progress in the field. Decades old, yet cost-effective technologies are beginning to be replaced with 21st century, digitally connected, smart platforms that promise to be equally cost effective. Smaller and more cost-effective platforms are being developed specifically for the cell therapy space, rather than borrowing existing technology from a related field.

Manufacturing can now be accomplished with a single device, or we can elect to connect a number of devices in a functionally closed system. There are more choices available now and that's great progress for both centralized or distributed manufacturing models.

We started our automation journey for CAR-T manufacturing around 2 years ago and had to really think outside the box to meet all of our needs, as the number of commercially available devices was more limited at that time. One approach we took to overcome this hurdle in the arena of analytics was to 'build' a novel device by assembling a number of off-the-shelf devices together to make an end-to-end automated platform called FlowSPA[3] (Flow Sample Prep Automation, Acquisition and Analysis). It was the product of some very talented individuals and it is working very well, which is a testament to the innovative thinking and outstanding work that went into developing this novel device.

Q What developments do you hope to see in CAR-T manufacturing automation in the next 5 years?

I hope to see truly transformative and cost-effective technologies in gene editing, analytics and data management platforms. I coined the term 'responsive automation' to describe what these devices would look like in the arena of the manufacturing process, but the term can equally apply to other areas as well. These next-generation devices will have non-destructive, in-line analytics that will sense and respond to the incoming material. They will automatically report and respond to information about the product, the device's progress in completing the unit operation, and inform how this batch compares to end-users. Data silos will be gone. Data will be shared with other devices and the entire process

will be reported to manufacturing, quality and clinical specialists alike. The treating physician will be able to follow their patients' product in real time.

The devices will be smaller and will use fewer reagents, if any. They will produce only those materials that are necessary for the drug product to be efficacious. The devices will redefine what we currently call a drug product.

The solutions will be functionally closed, and that's important because the closure of a device and these other advances will enable the devices to be used in countries whose infrastructure does not support our current technology. The coming years will see a truly global solution that's enabled by a technology or a series of technologies, to bring these life-saving therapies to the world.

AFFILIATION

Rodney Rietze, Senior Research Investigator, NIBR Exploratory Immuno-Oncology, Novartis

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