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

SPOTLIGHT

INTERVIEW

The Evolving Role of Automation in CAR-T Cell Commercialization

Andrew Kaiser joined Miltenyi Biotec's R&D in 2012, where he heads a team that focuses on developing tools and technologies for clinical applications of adoptive cell therapy and more specifically the automation of gene-modified T cell manufacturing. During his PhD, he focused on translational research of dendritic cell maturation for vaccines at IDM Pharma and at the Cochin Institute in Paris, France. As post-doc, he aimed to further cancer immunotherapy using gene-modified T cells at the Surgery Branch of the NCL, Bethesda, USA and later at the Netherlands Cancer Institute in Amsterdam. Dr. Kaiser is also the scientific coordinator of a Horizon 2020 European consortium called CARAT, that aims to integrate innovative cell manufacturing tools and enabling technologies into a new comprehensive platform that will facilitate the safe, automated, and cost-effective manufacture of gene-engineered T-cells.

Q As a company moves towards commercialization how does the approach to automation evolve?

We have seen in many cases that the process comes from early R&D - often academic labs - that naturally focus on the required scientific and biological aspects rather than the development of a clinical product and therefore automation is not really a high priority topic at that stage.

But that means that in order to prepare for commercialization a large development effort is required. Stephen Ward from the Cell and Gene Therapy Catapult in the UK puts it very clearly: It's a 4-step transition that moves from manual, to modular automation to integrated automation and step change of automation. Along the way, cost of goods (COGs) should reduce and industrialization potential should increase.

In most cases, it seems that the implementation of automation is done step-wise: get a device to wash the cells, a device to enrich the cells of interest, another to expand the cells, one to concentrate and so on. This multitude of devices and the automation of certain steps is appreciated because it gives an impression of being flexible during development and it seems to be easy to make changes; however this approach means results in a lot of liquid handling and thus high potential for failure, as well as disruption of the temperature control, which is far from ideal from the cells perspective. In addition, the remaining open steps dictate the infrastructure the cell products must be made in.

As the field is currently racing forward, compromises are made early. Material from healthy donors is too heavily used instead of actual patient material. For instance, we have seen many companies 'settle' for the use of peripheral blood mononuclear cells as a starting material because it removes complexity on the process side if an enrichment step is discarded; but then patient material is so variable that consequently it means less control on the outcome of the run. This is a classic example of where biological complexity may be preferable to control over process complexity.

This trade-off ultimately means that products may end up being made in a relatively complex manner, with companies knowing they will have to "switch" to a better process at "some point" down the line, or maybe with their next drug, which of course presents added difficulties and time requirements.

In my opinion, this modular automation approach taken to commercialization seems to be the mainstream thinking, in part because of the limited current understanding on the available tools at hand. In the case of allogeneic products, we are talking about campaign manufacturing. The idea being large batches not produced all the time. But for autologous cell products, it's a continuous repetition of the manufacturing process for each patient.

Here, the level of automation required should allow for the integration of all the modules mentioned earlier. For this, companies may need to come up with new devices that bridge all the other devices or simply use platforms that are not dedicated to a few process steps but cover the entire manufacturing process.

Q Do you feel there is sufficient clarity and understanding when it comes to discussions around automation?

Unfortunately, no. The word automation is highly abused and easy leads to misinterpretations and confusion around the terms and what automation means to different people i.e., integration, end-to-end, closed systems.

A lot of companies take advantage of this lack of clarity to push forward suboptimal solutions. For instance, we have recently seen posters at large conferences with claims of "improving the manufacturing of CAR T cells through automation". However, when you actually look into the specific details of process, the automation to which they refer is an improvement on the formulation step which instead of requiring six operational steps has now become two steps, thanks to a device meant to perform a specific

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task. Whereas in fact the rest of the manufacturing process still requires an incredible amount of operational step and therefore the true gain of implementing automation there seems very marginal.

When we talk about automation we mean end-to end in a closed system with maximally reduced user interactions: connect the starting material, and all reagents, start program, interact as little as possible – to bring the viral vector for instance – and collect the bag containing the drug product.

Q How do you envisage technology evolving over the coming years in response to a more flexible approach to automation?

The technological effort should be towards creating devices that are fit for purpose, with that purpose being the manufacture CAR-T cells from end to end: an all-in-one type of automated platform. The trick here is that the devices/tools that allow flexible development and fixed commercial manufacturing should be the same.

This has several advantages besides the obvious reduction of hands-on time and reduction in handling errors. For instance, as we developed the T-cell transduction process (TCT) on the ClinicMACS Prodigy platform we knew we had to test many parameters such as temperature, gassing, cell density, time of transduction, feeding conditions for example. Therefore we built in the program and the tubing sets the means and ability to change and test these variables. We were surprised to see that we often obtained better results – in terms of phenotype and viability for instance – in the Prodigy compared to the small-scale control experiments. We could attribute some of these differences to the fact that in the Prodigy, the T cells were constantly kept at 37°C whereas cells in plates had to be taken out of the incubator often and were submitted to large variations in temperature.

We now can make recommendations but customers can adapt these parameters to there preferences of course. After all-the-one Prodigy platform is already used clinically to prepare stem cells for graft engineering, dendritic cells for therapeutic vaccines, pathogen-reactive T cells for infectious diseases and CAR-T cells, which is a testament to how flexible and versatile all-in-one platforms can be.

With this in mind, one can move away from the conventional manufacturing line to more device-based manufacturing. Of course this means investing differently in the instrumentation but it means having more flexibility to react to the doctors requested drug. For instance making a CD19 CAR-T product of the one device for patient X and a CD20 CAR-T product for patient Y on another device at the same time.

Another aspect to consider is quality control (QC): there is no product without some form of release control. The technologies, along with our understanding on critical quality attributes will need to evolve to offer full automation of the QC analysis and potentially, at some point, even automated release of the product. Therefore, we need to find a perfect marriage between manufacturing and analytical tools.

Q The recent approval of the first CAR-T therapies is undoubtedly a milestone for the field, but thus far these approved 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 scaleability?

Indeed, this is a fantastic and historical achievement that is demonstrating how complex individualized cellular drugs can be a means of therapy for the greater public. Upon success, the number of patients requesting these therapies is going to rise dramatically and meeting the demand is inevitably going to become a real challenge.

Conventional pharma manufacturing is about upscaling batch size: how to make a lot of the one product. But here, in autologous cell therapy manufacture, upscaling is about making many batches - enough for the one patient but reproducibly for all the patients requesting it. And now the clock is ticking as the needle-to needle time is critical for the patient whose disease does not wait for the cells to be made successfully.

With such a drastic shift, it makes sense to look for new manufacturing models, and here again we believe the device-based approach is key.

Challenges around this type of upscaling are a plenty. For starters, how to implement failure handling and risk reduction measures to avoid compromising the time-sensitive drug delivery. The process must be very robust and reproducible and this can be achieved using programs – dedicated software that controls the manufacturing run.

Of course, logistics will be critical: control of goods, stocks, chain of supply, track-and trace, managing barcoding of intermediates, scheduling, data management. For all these, solutions do exist and more will be developed. What will be interesting is how the solutions/tools for each one of these steps will come together and lead to an essential simplification of the entire commercialization pathway.

One can easily envisage that in the near future, CAR-T cell therapies being offered in several centers of excellence across many different countries. In order to reduce the needle-to-needle time and complex logistics, it makes sense that the manufacturing will be very close to the centers of excellence, meaning the cell preparation is likely to become decentralized. Another challenge then will be to ensure that every site is manufacturing the products in exactly the same way. There again, all-in-one technology controlled by a robust program will be key.

Q What issues need to be addressed to facilitate the adoption of point of care manufacturing?

I would tend to say all the above discussion points. But going more into the specifics, the manufacturing process needs to fit the infrastructure of the point of care. It is likely that not all centers of excellence will have a multimillion dollar class B facility accredited for the manufacturing of gene-modified T cells. And it is likely that several centers will not be able to implement such complex

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infrastructure. In this regard, there is a lot to be learned from the blood centers and the blood collection units that prepare blood products routinely.

First it will be necessary to prove that the complex cell manufacturing process can be reliable and safe (for the users and for the environment as well) that the authorities would accept that it can be carried out in facilities of lower grade. A light QC will be necessary and the logistics adapted to such an environment.

Everywhere the manufacturing should be the same. It should be clear that a patient in hospital X should be able to receive the same quality drug as another patient in hospital Y. This is no small challenge but similarly to the decentralized facilities, an all-in-one device-based manufacturing approach makes most sense, with the platform and program ensuring reproducibility of manufacturing on all sites

Ensuring control of goods for the runs across the board will be a challenge that will require the distributors to get more involved. And of course, simple things such as processes that complete within standard hospital working hours, and manual steps being simple and not requiring highly trained personnel.

Q Beyond the core manufacturing processes, to what extent do you think the entire vein-to-vein pathway can be automated?

I believe the entire manufacturing process, the QC, the logistics, the data management and even the release can be automated. For instance, we are now working on a fill-and-finish device that works with the CliniMACS Prodigy that will prepare the desired dose of cells in bags ready for QC, infusion and cryopreservation. But there are many steps to work on to optimize vein-to vein automation: for instance there are still some open steps that need to be closed upstream and downstream of the actual run. They aren't the kind of products that tool providers will necessarily rush in to develop, such as medium preparation outside of a safety cabinet.

Another aspect is interconnectivity. Imagine that your flow cytometer can give your all-in-one manufacturing device the information it requires for the next steps. These are key features that we are working on that I believe will make a big difference.

On the other hand, beyond automation itself and its optimization, there are a lot of ongoing efforts to improve cell quality, CAR design, gene delivery for example and these are aspects that we are tackling in the context of a European grant called CARAT.

To conclude, these are exciting times and it is clear that the needs that arise from developers, commercial manufacturers and regulators will continue to shape technological advances, so that the patients and the therapeutic field can be served appropriately.

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