CRITICAL ROLE OF AUTOMATION IN THE MANUFACTURE OF CELL & GENE THERAPIES

SPOTLIGHT

INTERVIEW

Automation: the key enabler of point-of-care cell & gene therapy manufacturing

LUTZ UHAREK is professor and senior physician at the Charité. As a haematooncologist he has a long experience in caring for patients with difficult-to-treat hematological disorders, in particular leukemias and lymphomas. Since his doctoral thesis, he has the vision to cure diseases with cells filled in bottles.

Working in the field of stem cell transplantation and clinical cell therapy for many years, he gathered experience both in experimental research and clinical trials. Responsibility as Principal Investigator for Phase I and II trials and as Qualified Person for cellular products made him familiar with Quality Assurance Systems for GMP-compliant manufacturing and GCP-compliant clinical research.

Under his responsibility, Charité became one of the largest manufacturing organisations in Europe for autologous and allogeneic stem cells and cellular products. Confronted with the administration of high-throughput pharmaceutical manufacturing of cell products during the last years, he has actively expanded his expertise in process, change and lean management. The current focus of his work is the production, clinical testing and application of genetically modified immune and stem cells. As part of partnerships with industrial companies, he is involved in the development of innovative biotechnology systems for personalized medicine.

Q How does manufacturing automation play into your activities at Charite Berlin?

LU: From a manufacturing perspective, Charite provides services and products in two main fields: firstly, conventional cellular products – meaning minimally manipulated stem cell and immune

"...we need new molecular technologies ... for rapid viral and microbiological safety testing."

cell products – and secondly, we manufacture ATMPs such as genetically modified T cells. In the future, we will also manufacture stem cells and other cell types that have been genetically modified, but today, we are already producing more than a thousand autologous and allogeneic cell preparations for clinical use worldwide.

Regarding automation, I think it's clear that conventional batch manufacturing practices cannot be employed with these cell therapies for two main reasons.

Firstly, individual apheresis products exert a substantial influence on cell bioprocessing, as well as on clinical delivery and logistics models – they are very personalized, of course. And secondly, starting material variability is of critical importance within the complex production processes of ATMPS.

So automating ATMP manufacture is a vital step, but also a very demanding one. However, the role of Charite is to develop new approaches to patient care, and that also means developing technologies for the future – and that future happens to be right now for us when it comes to cell and gene therapy.

We believe automation is essential for translation from bench to bedside, because it finally ensures safety and cost–effectiveness. At the end of the day, given the requirement for well-defined, robust and increasingly complex production processes, standardization and automation will be the keys to enhancing clinical and economic effectiveness while facilitating regulatory compliance.

Q Decentralized manufacturing, including at the point of care itself, is a red-hot topic right now – what for you are the key obstacles that remain in its path, though?

LU: We also believe automation and a decentralized or point of care model for cell therapy collection, manufacturing, storage and delivery are absolutely key for bringing personalized therapeutics to a large number of patients.

It is critical to achieve what I would call a 'status of mass personalization'. This can be compared with the development of smartphones: everyone now uses a highly personalized system for an individualized collection of tasks. Of course, personalized smartphones are available at a moderate price today and I think that we have to achieve the same for ATMP production. In order

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to achieve this status of mass personalization, which is a prerequisite for industrial manufacturing, we will have to develop and guarantee two things.

Firstly, an open technical standard – both for quality control and manufacturing. And secondly, we have to employ smart information technology – Industry 4.0 or the equivalent – in order to connect our systems under one roof, so to speak. And again, this should include both quality assurance and manufacturing.

Q Can you elaborate on how you seek to enable management of quality monitoring and testing, and of regulatory compliance in general, at the point of care?

LU: In order to effectively automate and standardize, it is necessary to collaborate – for one thing, we need to establish collaborative efforts to document and qualify routine processes such as immune cell characterization. So we work together with companies and other academic and non-academic institutions to develop such standards. These joint efforts aim to qualify QC methods and technologies so that they can be used in multicenter trials, for example.

Of course, to guarantee a standard for quality control across multiple locations, you need a form of automation – it's not possible to harmonize based on manual procedures. I think this is a very important point.

At Charite, we have successfully established such collaborations with industrial partners for cell characterization, and we are now aiming to achieve something similar for viral and microbiological safety testing.

Q There is an increasing focus on accelerating product release testing in particular, given the time-sensitive nature of many autologous cell and gene therapies – what are your thoughts on how to speed up this particular aspect?

LU: First and foremost, we need to leverage new digital technologies to connect manufacturing and quality control – and with decentralized manufacturing in mind, to connect different sites of manufacturing/QC: to collate this QC data and thus enable instant centralized release.

We also need novel technological approaches for cell characterization, which are easy to standardize. And finally, we need new molecular

technologies – in particular, for rapid viral and microbiological safety testing. I think these three items are essential to further improve QC and release testing.

Q So can you paint me a picture of what hospital-based cell and gene therapy manufacturing could – or should – look like in 10 years' time?

LU: Last year, I saw the film 'The Founder' and I was fascinated by the concept of Ray Kroc's McDonald's franchise model. For me, this can be regarded as the preeminent form of decentralized manufacturing.

Kroc recognized that consistency and automation were key to the success of the franchise model, and my vision is that personalized therapies will follow a similar path: they will be based on active substances which are produced at the point of care with the help of standardized machines – perhaps let me call them 'bioprinters'. These bioprinters will work with the help of programmes that are developed for particular purposes – for cancer treatment, for instance – so that they can produce more required molecules or genes at the point of care. And the information for the molecular structure and construction of such a drug – for example, a DNA vaccine for a very rare tumor mutation, or for a patient with a rare genetic tissue type – will be shared and sold as IP worldwide. A somewhat similar model to smartphone apps.

Based on these developments, I am convinced the future will also bring us completely new types of companies: the distinctions between pharmaceutical manufacturer and hospital or healthcare provider will disappear within the next 10–20 years, I believe. We will see more hybrids between hospitals, pharmaceutical companies and technology providers emerging in the fairly near future.

Q What particular automated technical innovations excite you at the moment?

LU: We're currently developing isolator-based automated production systems. I'm fascinated by this approach because it provides a modular and open structure.

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I do also see a role for closed systems like the Miltenyi Prodigy – they don't have an open standard, but they can enable point of care

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manufacturing for hospitals at the moment, so I think they are an important bridge to large scale point of care manufacturing. Closed systems are a very innovative and helpful approach because they avoid contamination and can be operated outside of a class 1 cleanroom environment.

But for me, as someone who has his roots in research and academic development, I think the most important point is to collaborate with companies and technology partners to develop these open standard, modular production systems. I believe this will be the future.

Q Finally, if you could wave a magic wand and conjure up three automated bioprocess and supply chain-related solutions that don't currently exist, what would they be?

LU: Number one, the bioprinter I mentioned earlier – let me call it 'point of care vector bioprinting'. This would be very valuable! Second, a fast, no-touch cell selection system. And third, an on-the-fly microbiological testing system.

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