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Point-Of-Care Manufacturing Successfully Treats B-Cell Cancers; How Will FDA Regulate It?

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Executive Summary

In Cleveland and Moscow, researchers found freshly-manufactured T-cells showed faster reduction of tumor burden than cryopreserved cells, but uncertainty remains about what the clearance process for the technology will be at the US FDA.

POINT-OF-CARE MANUFACTURING SUCCESSFULLY USED TO MANUFACTURE T-CELLS FOR CANCER TREATMENT *Source: Alamy*

In what the authors call the first study of its kind, a team of researchers at the non-profit Caring Cross have successfully used point-of-care manufacturing technology to create T-cells to treat patients with B-cell malignancies – specifically, children with acute lymphocytic leukemia and adults with non-Hodgkin lymphoma.

The study, published on 10 December in *Nature Communications*, describes how researchers were able to manufacture CAR19 T-cells in as little as eight days using the CliniMACS Prodigy closed-cell manufacturing

system from Miltenyi Biotec B.V. & Co. KG. Turnaround times for typical manufacturing, by contrast, range from 21 to 60 days, as traditional manufacturing involves cryopreserving and transporting cells to a separate location.

The study authors also found that freshly-manufactured cells reduced tumor burden more quickly than cryopreserved cells. Fresh cells reduced the tumor burden eight days sooner than frozen cells, while tumors showed some growth before eventual control by the frozen cells.

For several years, the US Food and Drug Administration has encouraged the use of advanced manufacturing technologies in an effort to refocus pharmaceutical production in the United States, as well as to provide more agility to the industry in case of future health emergencies.

One such method is point-of-care manufacturing, which involves a mobile manufacturing platform that can be deployed to various sites of patient care, such as hospitals and pharmacies. (Also see "US FDA 'Quietly Working Hard' To Develop Advanced Manufacturing Framework" - Pink Sheet, 23 Nov, 2021.)

The study's findings seem to indicate another step has been taken toward successful use of this technology in the real world, but the FDA has not yet indicated how it will manage oversight for the novel method.

How The Treatment Worked

Researchers harvested lymphocytes, or T-cells, from patients and used the CliniMACS system to engineer the cells to target CD19, a protein found on the surface of B cells which is commonly used as a target for anticancer treatments. The cells were then infused back into patients, who were located at two sites in Cleveland, Ohio and Moscow, Russia.

Many patients enrolled in the study had cancer that had relapsed or not responded to previous treatments.

The median apheresis to infusion time was 13 days in patients with both types of cancer, but seven patients in the non-Hodgkin lymphoma cohort had cells manufactured in eight days.

The treatment resulted complete response rates of 73% in adult patients with non-Hodgkin lymphoma and 89% in pediatric patients with acute lymphocytic leukemia, leading researchers to conclude that "use of place-of-care manufactured CAR-T cell products results in clinical outcomes that are effective in the treatment of patients with B-cell malignancies."

"The clinical outcomes for patients were especially remarkable considering that almost all the patients enrolled were treated, even patients that otherwise would not be eligible due to their advanced disease, demonstrating the enormous value of this approach," Boro Dropulić, Executive Director of Caring Cross, said in a press release.

Advantages Of Point-Of-Care Technology

Point-of-care manufacturing, also known as distributed manufacturing or place-of-care manufacturing, provides several advantages over typical production of cell therapy products.

Researchers noted that the system created cells in two far-flung locations that had "similar cellular composition," resulting in a consistent treatment standard. Because they did not need to be transported to a central location, patients received the engineered lymphocytes more rapidly and the fresh cells achieved a better treatment response.

Receiving the therapy sooner is "very important for patients with rapidly progressing disease," Marcos de Lima, director of Stem Cell Transplantation and Cellular Therapy at The Ohio State University Medical Center and one of the lead investigators on the clinical trial, said in the press release.

Dropulić said, "Place-of-care manufacturing also offers the potential to dramatically reduce the cost of these transformational therapies to a fraction of their current cost due to obviating the need for transportation and the cost of multiple layers of quality and custodial assurance that are required for centralized manufactured CAR-T cell products. The next step will be to expand CAR-T cell clinical trials to include more clinical centers and support the development of regulatory pathways for the approval of CAR-T and other gene-modified cellular products that are manufactured at the place-of-care."

Point-of-care platforms could also be transported to the site of future disease outbreaks, thereby aiming to contain illnesses more promptly.

What Kind Of Inspections Will FDA Conduct?

From a regulatory perspective, mobile platforms offer an advantage in that they use the same technology and quality management system in multiple locations. However, the FDA has not yet indicated whether this will result in more lax inspection policies.

When asked about the topic at the recent US FDA/Product Quality Research Institute Joint Conference on 3 December, Larry Lee of the FDA's Office of Pharmaceutical Quality said that inspection procedures for advanced manufacturing technologies are something the FDA is currently working on.

Lee referenced the FRAME initiative, the FDA's initiative to develop a regulatory framework for advanced manufacturing, and said that this question is one FRAME is considering.

Lee additionally mentioned that mobile pods that can be moved anywhere may be more complex in terms of how they're manufactured than traditional manufacturing platforms and therefore might need more thorough inspections, so he couldn't say how inspections will proceed, but they "will not be the same as what we are doing right now," he confirmed.

International Harmonization

Also at the FDA/PQRI conference session, Christine Moore, Organon's head of global quality and compliance and the former acting director of FDA's Office of Process and Facilities, pointed out that the UK's Medicines and Healthcare products Regulatory Agency had recently launched a proposal for a point-of-care regulatory framework. (Also see "UK Claims World First With 'Point Of Care' Manufacturing Rules" - Pink Sheet, 12 Aug, 2021.)

In the MHRA framework, point-of-care manufacturing platforms would be distributed around a core control site. While all sites could potentially be examined, inspectors would start at the core facility. Moore also mentioned the possibility of "flexibility in how oversight is provided," meaning more use of remote methods developed during COVID-19.

However, FDA officials have previously said that remote methods would supplement but not replace on-site inspections. (Also see "How The US FDA's Inspectional Approach Is Shifting For The Post-Pandemic Era" - Pink Sheet, 14 Nov, 2021.)

Lee added that FDA is looking to collaborate with international agencies regarding an advanced manufacturing framework. He said that FDA had met with the Pharmaceutical and Medical Devices Agency of Japan, and had planned to meet with the European Medicines Agency and the Brazilian Health Regulatory Agency before COVID-19 complicated travel.

This is something we're "really thinking about," he said.