"The first step in the journey is to collect white blood cells by a process called leukapheresis"

Myeloma Patients Europe (MPE) has conducted a series of four written interviews on CAR-T manufacturing to better understand the manufacturing processes and challenges of various myeloma CAR-T therapies. Four different stakeholders have answered our questions, including two pharmaceutical companies, which each have a myeloma CAR-T product approved in the European Union, and two academic teams which have developed myeloma CAR-T products currently under clinical investigation. In this interview, we will learn about the manufacturing process at Janssen Pharmaceuticals.

What is the journey of patients' cells?
The important steps taken to manufacture personalised CAR T-cells start with the collection of white blood cells, followed by T-cell separation, T-cell reprogramming and CAR T-cell infusion. While some details of these steps will differ between manufacturers, the overall process will be similar. At the CAR-T centre: The first step in the journey is to collect white blood cells by a process called leukapheresis. The process of leukapheresis involves drawing the patient's blood into a machine, separating out the white blood cells and returning the other parts of the blood, such as red blood cells and platelets back to the patient. At the CAR-T centre, hospital or at an external specialised laboratory: The white blood cells are frozen in a process called cryopreservation which needs to happen within a very short time after leukapheresis. These cryopreserved cells are then transported to the manufacturing facility, which may involve air freight. At the manufacturing facility: The white blood cells arrive at the manufacturing centre and are stored in liquid nitrogen. The CAR T-cells are prepared (see next question for details) and packed. At the CAR-T centre: The CAR T-cells are then transported back to the centre for infusion.

More information is available **here.**

What happens to the cells?
In a specialised room at the manufacturing centre, the white blood cells are first thawed and then washed. Next, the T-cells are separated from other white blood cells using very small magnetic beads called microbeads that identify the T-cells. The microbeads and attached T-cells are held in place by magnets, and the other white blood cells are washed away, leaving only the T-cells. The selected T-cells are then activated with antibody coated beads.

The T-cells are reprogrammed, usually with non-infectious viruses, so they can now make a special type of protein called chimeric antigen receptor or CAR proteins. CAR proteins have been specially designed to target the patient's cancer cells. This means that the patient's own immune system can identify the cancer cells and attack them. The CAR proteins can be found on the surface of the T- cells, so they can stick to the cancer cells. The newly programmed CAR T-cells are then multiplied until there are enough to provide the correct dose for the treatment. Once the cells have multiplied for several days to the appropriate number of cells needed for treatment, the CAR T-cells are prepared and frozen.

Who is involved in the process?
At the CAR-T centre: the leukapheresis staff, who may be part of the hospital, or a blood bank (doctors and nurses who perform the leukapheresis process). In the cell lab, a pharmacist, or a cell lab specialist (depending on the country) prepares the cells for shipment. At the manufacturing centre: several team members are always present to ensure maximum quality control. Additionally, the process's progress is monitored within process controls and sampling by the manufacturing, quality, warehouse, planning and logistics teams. Third parties may be involved: a Cryopreservation centre (if applicable), a Lentivirus manufacturer (if applicable) and manufacturing partners (if applicable). The services of materials suppliers and transportation couriers may also be used.

How is the quality of the product ensured?
When the white blood cells are collected (leukapheresis step), they are assigned a unique identifier and linked to the patient through several identifying factors, including their name, date of birth and a unique identification code. This identifier will be tracked throughout the CAR-T manufacturing process in order to maintain the 'chain of identity'. The date, time, location and responsible person for the cells is also recorded from the leukapheresis step. This information continues to be recorded at every step of the CAR-T manufacturing process.

"At the manufacturing centre: several team members are always present to ensure maximum quality control"

Janssen is a pharmaceutical company owned by Johnson & Johnson.

Janssen received the authorisation to market Ciltacabtagene autoleucel (also known as cilta-cel, Carvykti®) in the European Union in May 2022, after several years of clinical investigation to evaluate safety and efficacy of the product. This BCMA-targeted CAR T-cell therapy is indicated for treating adults with multiple myeloma whose cancer has returned (relapsed) or has not responded to treatment (refractory).

Cilta-cel is commercially used when patients' disease worsens despite receiving at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody. The product is currently under investigation to evaluate efficacy at earlier lines of therapies and benefits over other standards of care.

This is referred to as a 'chain of custody'. The chain of identity and chain of custody ensure that the correct product is delivered to the correct patient.

Prior to infusion of the CAR T-cells, the product's chain of identity document will be checked again to ensure the patient receives the correct cells. Quality compliance is ensured through multiple in-process tests and extensive testing after manufacture.

What could go wrong?
Commercial CAR-Ts have undergone clinical trials to quantify their safety-to-efficacy trade-offs, providing a level of confidence in outcomes. They have also undergone extensive product characterisation and process validation, with qualification of the premises and equipment etc., to ensure consistent and reliable quality medicine.

Only after a thorough inspection by healthcare authorities and obtaining the necessary approvals, can commercial CAR-T manufacturers safely ensure that all infrastructure, processes and capabilities are in place to manufacture such a complex product. We believe this is a very important requirement for patient safety. Hence, we have put in place extensive training, preparation and certification to maintain the highest quality product and experience for patients:

- All centres prescribing CAR-T need to enter first into a certification process to confirm all training is in place, but also that they have the infrastructure allowing to treat patients efficiently and safely with a specific CAR-T therapy - and according to regulations in place - which is also an important step in safeguarding patient wellbeing.
- All healthcare professionals who administer CAR-T products are trained to ensure eligibility and minimise risks.
- The chain of identity and chain of custody are maintained throughout the process to ensure traceability.

"If an issue happens during the manufacturing process, the company involves all key stakeholders, including the physician, to decide on the way forward"

- Commercial CAR-Ts are cryopreserved (i.e., frozen) so that they are available at the right time for patient infusion.
- Our starting material to make CAR-T is living cells, so their quality is very variable.
- This may impact the final product and ability to meet the specifications according to manufacturing regulations. CAR-T centres are also trained and experienced in collecting cells in conditions that make them suitable for manufacturing. In addition, most of the time, there are enough cells collected to allow remanufacturing, if needed.

If an issue happens during the manufacturing process, the company involves all key stakeholders, including the physician, to decide on the way forward. This may include remanufacturing to have an approved product according to regulations.
As a result of these numerous commercial control processes, there is a high degree of consistency in quality across all patients treated, regardless of where the patient is treated.

How many samples can you process and how will this evolve in the future?
Through a phased approach, the company will work diligently to activate a limited network of certified treatment centres in Europe and will aim to increase availability of our CAR-T therapy in an effort to provide oncologists and patients with treatment in a reliable manner.
As a leading multiple myeloma company our top priority remains our patients, customers and employees.
We are partnering with global and local health authorities to collaborate in addressing the need to ensure a sustainable supply of our critical medicines, and remain excited about the potential of our CAR-T therapy.
We value our close partnership with the multiple myeloma community and are doing all we can to ensure availability in a reliable manner following any potential approval.

"We continue to explore multiple options to enable the maximum number of patients to benefit from CAR-T in the future. For patients, it would also be good to reduce the waiting time for the manufacturing process of CAR-T"

What could change in the manufacturing process to improve a patient's experience?
As a pharmaceutical company, producing these medicines at scale, we believe in the value of the stringent processes described above to validate, monitor and, ultimately, enhance the quality of our CAR-T.
We continue to explore multiple options to enable the maximum number of patients to benefit from this in the future. For patients, it would also be good to reduce the waiting time for manufacturing. It could improve their experience but also their outcomes. We are taking various measures to shorten the time while maintaining very high standards of quality. We are working on increasing the capacity of existing manufacturing sites, adding new manufacturing sites in different parts of the world and expanding our cryopreservation network. This will help to increase flexibility in planning and manufacture closer to patients.

CAR-T Interview Series

The CAR-T Interview Series is composed of four different interviews about CAR-T manufacturing, from cell collection to cell infusion. Click on the links below to read the interviews responded by:

- Hadassah Hebrew University Medical Centre
- Bristol Myers Squibb (BMS)
- Dr. Halvard Bönig, Translational Development of Cellular Therapeutics, Goethe University

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 754658. Myeloma Patients Europe chose the interview questions, the stakeholders to be interviewed, and edited and published the interviews. Neither interviewee nor funders took part in this process. Interviewees sent their answers in writing and reviewed the final draft of their respective interviews before publication.

CONTACT US

info@mpeurope.org

www.mpeurope.org

@mpeurope

@MyelomaEurope

Myeloma Patients Europe

Myeloma Patients Europe