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# A place-of-care approach to CAR-T cell manufacturing


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## Introduction to the commercial CAR-T landscape

CAR-T is a multi-step, gene-modified cell therapy process used to treat refractory hematologic malignancies. Since the historic FDA approval of Kymriah for the treatment of B-cell leukemia, CAR-T has provided a durable treatment option for heavily pre-treated leukemia, lymphoma and multiple myeloma patients. This therapy is unique among other drug types in that the final product is a manipulated version of the patients' own T-cells. Blood is collected from patients, T-cells are isolated and genetically engineered with a synthetic CAR gene. Once modified, the T-cells are infused back into the patient's bloodstream and the CAR protein enables the T-cells to bind and kill cancer cells. In this sense, CAR-T is a living drug that delivers the potential for long-term remission after a single treatment.

Following the 2017 Kymriah approval, CAR-T usage has expanded considerably as more therapies have been approved. Six total CAR-T products are now commercially available. Kymriah, Yescarta and Breyanzi are used for various forms of relapsed/ refractory (r/r) lymphoma. In July 2020, Tecartus became the first approved product for (r/r) mantle cell lymphoma. Abecma made history in March 2021, as the first BCMA targeting CAR-T therapy approved for (r/r) multiple myeloma. In February 2022, the FDA also approved Carvykti for (r/r) multiple myeloma based on the CARTITUDE-1 trial, which produced an impressive 98% ORR and 21.8 month median duration of response.

## Anticipating increase in future demand

CAR-T usage is poised to dramatically increase in the next decade. The approved therapies mentioned above are indicated for heavily pre-treated cancer patients whose disease has already progressed after multiple lines of therapy. Recent studies from both Bristol Myers-Squibb and Gilead Sciences demonstrate patients also benefit from CAR-T when it is administered as an earlier, second-line treatment. In the ZUMA-7 trial, Gilead compared their Yescarta CAR-T product against the standard of care for second line B-cell lymphoma. Yescarta treatment improved event-free-survival by 60% over chemotherapy plus stem cell transplant. Bristol Meyers Squib reported similar positive CAR-T results in their TRANSFORM trial. In response to these trial results, the FDA recently approved Breyanzi and Yescarta as a second-line therapy, thereby allowing the use of CAR-T after just one prior treatment (usually chemotherapy). This second-line approval should greatly increase the number of cancer patients using CAR-T. Gilead stated that expanding Yescarta use to second-line would add approximately 14,000 eligible patients, up from 8,000 patients currently.

The extent of CAR-T expansion in the future can also be approximated by assessing the volume of CAR-T therapies currently in clinical development. Between 2010-2020, within the oncology sector, the number of cell and gene therapy drugs entering into clinical development has increased more than another other drug category (e.g., proteins, peptides, small molecules). Cell and gene therapies targeting cancer are entering into clinical development at a rate of 14% year over year growth (CAGR). In 2021, the Cancer Research Institute reported a global count of 1,041 total CAR-T cell therapies in some stage of clinical trial. If only a small fraction of these CAR-T trials receive approval, the treatable patient size will increase considerably. A recent statistical analysis, based on clinical trial volume and targeted disease incidence and prevalence data, predicted that by 2030, the field

of hematological cancer will see 23 total approved cell therapies in the U.S., with over 130,000 patients treated[1].

As new CAR-T therapies come online, there is an urgent need for healthcare communities to expand manufacturing capacity and streamline the CAR-T production process in order to keep pace with patient demand.

## Centralized vs. distributive model of manufacturing

The commercial CAR-T industry is based on a traditional, centralized model of drug manufacturing. After the FDA approves a CAR-T therapy, a biologic license agreement (BLA) is granted for patients' cells to be manufactured at a small number of locations. Since the beginning of commercial CAR-T production in 2017, this centralized approach has struggled to keep pace with patient demand. Patients routinely wait three to five weeks from the point of registering for a product until the moment the drug is infused. These long manufacturing wait periods can have dire consequences for late-stage cancer patients. An alternative approach relies on a hybrid model of CAR-T production. The output of centralized, commercial CAR-T could be complimented with a distributive manufacturing channel. Medium and large medical centers across the U.S. can develop their own cell manufacturing facilities to allow local CAR-T production for their regional patients. This distributive model is often referred to as place-of-care manufacturing[2]. Once established, a place-of-care system would introduce efficiencies in production times, allow flexibility to address patient specific criteria and may offer a substantial reduction in product price (Fig. 1.) In the sections below, current challenges with commercial CAR-T production are described as well as how a place-of-care approach could relieve strains on the current system are presented.

## Patients currently experience long manufacturing wait times

Centralized CAR-T production requires a complex cold chain transportation and manufacturing process for each patient treated. Multiple steps (apheresis, shipping out cells, receiving engineered cells, etc.) must be coordinated between the manufacturer, patient and health care providers. In the (r/r) B-cell lymphoma setting, patients often wait two to three weeks for an available manufacturing timeslot at a centralized facility. Once the timeslot is confirmed, the healthcare staff performs apheresis to collect the patient's blood. This step initiates the next waiting period known as vein-to-vein, which includes shipping times, the manufacturing process and time until engineered cells are re-infused into the patient's bloodstream. In clinical trials, the average vein-to-vein time varied according to the specific product. The median vein to vein time from Yescarta clinical trials was 24 days. In the real-world setting, administrative delays and manufacturing bottlenecks also add delays to this time period. When taken together, the combined wait for a scheduled timeslot and the vein-to-vein time often demands that a patient wait four to six weeks before receiving their drug. This wait period is often too long for cancer patients with advanced disease.

A place-of-care approach can dramatically reduce patient wait time for infused product. Time and costs associated with cold chain transportation are eliminated since the patients' cells never leave the hospital. Additionally, the initial wait period for a manufacturing time slot can be dramatically reduced once the medical center's infrastructure is properly scaled for regional patient demand. Hospitals that currently manufacture cells on-site in the context of clinical trials often experience a

combined wait time of less than two weeks. The Medical College of Wisconsin (MCW) performs place-of-care CAR-T and reports a 2-3X reduction in total patient wait time compared to centralized, commercial CAR-T. Nirav Shah, MD at MCW emphasized that his 'clinic's point-of-care manufacturing can produce an autologous therapy within 8 to 10 days, compared with an average of three to four weeks for commercial CAR-T.'

## Product costs can be reduced with a place-of-care approach

While CAR-T represents a breakthrough medical advance, the high, total cost of delivering this therapy places significant strain on payors, providers and patients. Drug acquisition is the largest component of the total cost of CAR T therapy. The wholesale acquisition costs for commercial product ranges from $373,000 (Kymriah for B-cell lymphoma) up to $465,500 (Carvykti for multiple myeloma). Place-of-care manufacturing introduces the possibility of a dramatic reduction in the cost of manufactured cells. In 2020, Ran et al. published a place-of-care, cost analysis in a German, non-profit, medical setting[3]. The authors tabulated fixed annual costs and variable costs per patient to arrive at a total cost per patient of $78,849. Variable costs include expenditures on cell media, cytokines, plasticware, and lentiviral vector. Fixed annual costs include salaries for trained personnel, a closed cell manufacturing system, liquid nitrogen tanks, clean room costs, etc. The total cost per patient moves lower as more patients are treated annually with the same equipment and staff. It should also be noted that much of the equipment and space necessary for CAR-T already exists in hospitals that perform stem cell transplants. The authors conclude that decentralized CAR-T can be performed in a cost-effective manner, however, the analysis is limited in that it does not include any clinical and research costs associated with the development of an infused CAR-T product.

## Place-of-care is adaptive to individual patient criteria

CAR-T is a highly customized and patient-centric process. Each therapy is produced one batch at a time for each individual patient. A place-of-care approach allows medical staff and physicians greater process control when planning and administering the therapy for their patients. Local manufacturing allows more precision and flexibility with regiment scheduling, apheresis and final cell product infusion. For example, if a patient's clinical condition rapidly deteriorates, the process of adjusting bridging therapy and re-scheduling apheresis and manufacturing is much more streamlined with a place-of-care approach.

## Local manufacturing is already established in some medical centers

As patient demand for CAR-T continues to build in the next decade, the medical community would benefit from multiple channels capable of delivering effective CAR-T therapies. A hybrid model would complement the traditional, centralized CAR-T channel with a local, place-of-care channel.

The hybrid model already exists for a handful of large hospitals, such as Stanford, Memorial Sloan Kettering and Case Western Reserve University. These medical centers produce CAR-T cells in-house and treat patients within the context of clinical trial protocols. Small studies based on place-of-care CAR-T demonstrate that health outcomes are comparable to pivotal trial data for commercial product. Case Western Reserve University performed a place-of-care study with an anti-CD19 CAR-T on 17 adult patients with B-cell lymphoma. The treatment resulted in 82% overall response rate (ORR). FDA approval for Breyanzi was based on the pivotal TRANSCEND trial, which produced 73% ORR among 192 patients in their main efficacy population. Further studies and analysis of

real-world evidence will be necessary to assure that a place-of-care approach does not introduce any reduction in safety and efficacy as compared to commercial product.

## Regulatory updates would facilitate the place-of-care approach

Scaling up decentralized manufacturing across the US would require a shift in the current regulatory framework. One possibility centers on the issuance of site specific BLAs. The FDA could issue BLAs that allow multiple, medical institutions to manufacture cell product under guidance and master file protocols provided by the approved BLA holder. In this scenario, the BLA holder could be a company, hospital or non-profit organization. This alternative licensing procedure is being considered by the FDA. In a 2018 article in The New England Journal of Medicine, Scott Gottlieb, the former FDA Commissioner, and Peter Marks, the current director of CBER (Center for Biologics Evaluation and Research) describe such a place-of-care framework[4].

'The current biologics licensing involves manufacturing a product at a single facility that is then used at one or more clinical trial sites. Approved products then receive a biologics license for a single product. The proposed alternate licensing procedure would involve multiple manufacturers using the same protocol to make a CAR-T product at the point of care and, if approved, site-specific biologics licenses would be issued.'

On a global level, other nations are also considering regulatory landscapes that facilitate the decentralized distribution of innovative products. In August 2021, the United Kingdom published a consultation document seeking feedback on the development of a framework that allows place-of-care, blood cell therapy products.

A new regulatory framework is being considered to enable the safe development of POC [point-of-care] products for supply to patients through clinical trial studies and then on to licensing.

## Summary

In the next decade, patient demand for CAR-T therapy is set to significantly increase, as indicated by the proliferation of regulatory approvals combined with a robust developmental pipeline. The current manufacturing method relies on a centralized model. This approach has been hindered by long patient wait periods and a high cost for drug acquisition. A new, hybrid model would complement the centralized approach with a distributive, place-of-care option. The place-of-care approach allows medical centers to manufacture customized CAR-T therapies for regional patients with minimal wait periods, at a lower cost per product and with a high level of process control.

## References


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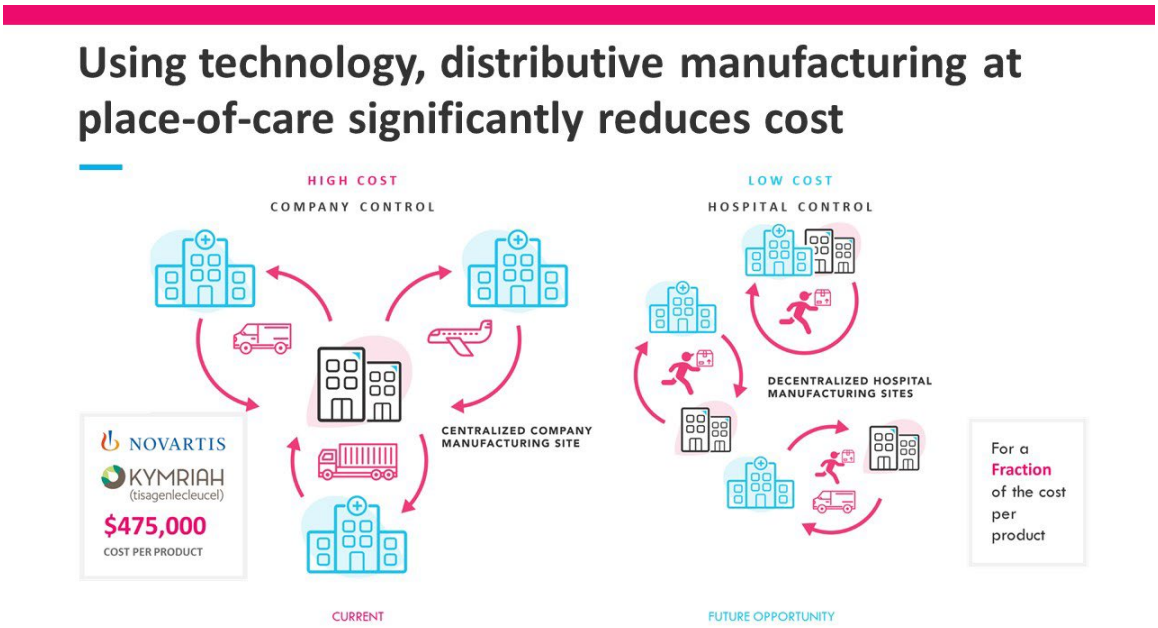


**Figure 1.** Place-of-care provides an alternative CAR-T manufacturing model. Centralized (left panel) versus low-cost place-of-care (right panel) CAR-T manufacture is illustrated.