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Centralized vs Decentralized Manufacturing of Personalized Cell Therapies: CAR-T cell Product Manufacture, Quality and Release

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Gene modified cellular products, such as CAR-T cells, are increasingly becoming critical medicines in the arsenal used for the treatment of serious diseases. Several curative therapies have been approved by the FDA for the treatment of Leukemia and Lymphoma, including Kymriah®, Yescarta®, Tecartus®, and recently Breyanzi® with many in the pipeline. One of the most important aspects for successful implementation of CAR-T cell therapy is product quality and release. While the types of quality attributes are similar for all CAR-T cell products, their mode of manufacturing and release differs when comparing centralized and decentralized manufacturing paradigms.

In centralized manufacturing, blood apheresis products are collected and shipped from hospitals to a centralized facility, either frozen or fresh, to be manufactured in clean rooms at the central site. The logistical burden to ship and ensure chain-of-custody integrity during the manufacturing cycle is high, which invariably drives up the cost. One potential advantage of centralized manufacturing is the use of centralized testing facilities for assessing product quality and release, which would reduce assay variability since the same instrumentation, reagents and operators are used to perform the testing and release of all final products. At centralized facilities, the final CAR-T cell product is invariably frozen before being shipped back to the hospital, thawed at the patient's bedside for infusion. This is a second potential advantage, as cryopreserved product is thought to be more standardized than freshly-made non-frozen cellular product.

Decentralized or place-of-care manufacturing (POC) of CAR-T cell products are made generally within the hospital's own facilities, such as a transplantation center. Automation is a key aspect place-of-care manufacturing (Figure 1), where closed-system devices are able to use blood cell products collected after apheresis and then after isolation of specific cell types, such as T cells, genetically modified with, for example, a Lentiviral vector expressing a tumor-targeting CAR gene. The gene-modified cells are cultured and expand to sufficient numbers needed for an effective dose, and finally formulated as the final CAR-T cell product, ready for infusion. In contrast to centralized manufacturing, place-of-care manufacturing has a much lower logistical burden, due to the manageable number of patients being treated in any one hospital at any given time. This lower logistical burden, coupled with leveraging existing cell manufacturing personnel resident at hospital transplantation centers, significantly reduces the cost while maintaining product quality. Instead of having multiple layers of oversight to ensure chain-of-custody, hospital manufacturing sites are generally producing few products at one time, significantly reducing the need for multiple layers of oversight to ensure proper chain-of-custody.

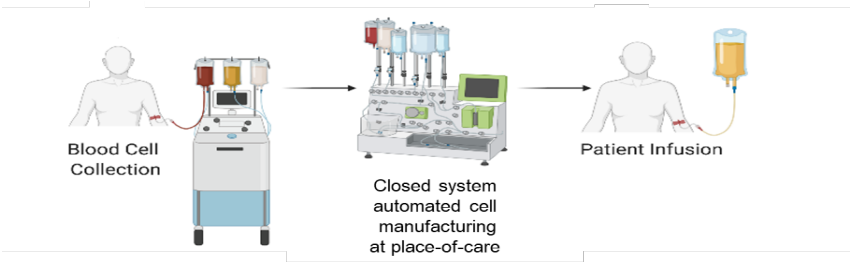

Figure 1. Closed system automated cell manufacturing performed at hospital-based place-of-care facilities

As manufacturing methods and quality systems have improved over time, so has the product failure rate decreased. This is true for both centralized and decentralized manufacturing of CAR-T cell products. Interestingly, place-of-care manufactured products have a very low failure rate, despite differences in location and personnel used to make the product. Automated devices located at place-of-care facilities reduce product variability and failure rates to very low levels making it feasible to robustly produce product locally.

One criticism of decentralized manufacturing models is their purported inability to perform reproducible testing of the final product for its release for infusion into patients. For this we should examine the types of assays that need for testing and release of CAR-T cell products.

There are three types of assays that need to be performed in order to release CAR-T cell products: (1) sterility of the product; (2) cell product composition and; (3) molecular analysis[1]. A number of assays are performed to assess the sterility of the product including bacterial sterility, mycoplasma and endotoxin (21 CFR part 600-680). These assays are standard practice and performed routinely at hospitals that perform transplantation which are presently the only sites that conduct place-of-care manufacturing of gene modified cell products such as CAR-T cells. Therefore, such assays assessing sterility are robust at hospital-based place-of-care manufacturing sites. The second type of assays characterize their cell composition, which are performed by flow cytometry. Parameters such as the number of CD4, CD8, CAR-T final product cells are assessed, but also the numbers of other cells that are not a component of the therapeutic product, such as CD14 monocytes. While the results of these assays can vary from site to site depending upon the instrumentation and reagents used, the range of values are not highly disparate, and useful comparisons can be made between hospital sites[2]. A decentralized model that links multiple sites for an approved gene-modified cellular product would require harmonization of the instrumentation and reagents used to assay cell composition by flow cytometry. Finally, there is molecular testing, using two PCR assays, one that determines the genetic dose, or vector copy number, and the second is a safety test for a recombinant virus or RCL. These assays can be routinely performed at hospital sites when provided with harmoniously provided DNA primers and probes with control DNA and standard real-time PCR instrumentation.

One of the key advantages of place-of-care manufacturing is the ability to manufacture gene-modified cell products from fresh apheresis material and to infuse freshly manufactured product to the patients that are desperately awaiting them. This has the advantage of reducing the vein-to-vein time to manufacture and administer CAR-T cell products. Also, fresh products have been shown to be active immediately after infusion, rather than having a delayed activity seen with cryopreserved product[2]. This improved vein-to-vein time and immediate activity of the product may be important for patients that are in advanced stages of disease and need therapy immediately. In one study, 100% of patients treated with bi-specific CAR-T cells had a response with freshly manufactured and infused product, with 92% of these patients showing a complete response[3]. This study demonstrates the importance of using fresh product when available.

The quality of gene-modified cell products and their testing is key to their success as therapies for disease like leukemia and lymphoma. Centralized manufacturing aims to bring cell manufacturing and testing under one roof in order to avoid product variability that is thought to occur at hospital place-of-care CAR-T cell manufacturing sites. However, highly robust CAR-T cell manufacturing has been demonstrated at hospital sites, building upon a tradition of cell processing excellence already resident at hospital transplantation facilities. The data to date indicates that place-of-care manufactured products are made robustly when automation, materials and reagents are

harmonized, with a very high percentage of products passing release testing, certainly no less than that what is seen at centralized manufacturing facilities. While presently no FDA approval for place-of-care manufacturing exists, the growing clinical manufacturing experience indicates that such manufacturing will be possible and needed in the future. Place-of-care manufacturing offers the advantage of manufacturing fresh in, fresh out, CAR-T cell product with shorter vein-to-vein times and a product that is active immediately, which will likely be important for patients with advanced disease. It also provides physicians with options to use the whole dose, or part of the dose, as is sometimes needed with bulky disease to avoid adverse events such as Cytokine Release Syndrome. Building a regulatory pathway for place-of-care CAR-T cell manufacturing will provide options for physicians treating patients needing expeditious care due to advanced disease.

Regulatory authorities are seeing a need for decentralized modes for the manufacture of biological products such as gene-modified cellular therapies. In a recent address to manufacturers of biologic and gene therapy products, Dr Janet Woodcock, the acting commissioner of the FDA, and Dr Peter Marks, the Director of CBER, both commented on the need to develop regulatory pathways for distributive manufacturing of biological products [4]. Also, the Medicines and Healthcare products Regulatory Agency (MHRA), which regulates drug approvals in the United Kingdom announced that it wants to build a regulatory framework that would enable point- of-care decentralized manufacturing[5]. A point-of-care (i.e. place-of-care; at or near the clinical treatment center) regulatory framework would balance regulatory requirements for the control of these products to ensure levels of safety equivalent to current products, which are manufactured using the centralized paradigm, while avoiding unnecessary regulatory barriers and enabling broader access to patients. With respect to quality control testing of the final product, the MHRA acknowledges that in a decentralized manufacturing approach "there is likely be no time at the end of manufacture for Quality Control testing and Qualified Person certification prior to supply." The MHRA is looking for new Quality Control testing measures that can "provide assurance of the quality of products followed by a rapid decision to either supply and administer or to reject the product." This type of creative regulatory policy will enable broader rollout of the decentralized manufacturing paradigm. Closed system automated devices will play a key role in the robust manufacture and release testing of gene-modified cell products at the place-of-care.

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[3]Shah, N. N., Johnson, B. D., Schneider, D., Zhu, F.,et. al. (2020). Bispecific anti-CD20, anti-CD19 CAR T cells for relapsed B cell malignancies: a phase 1 dose escalation and expansion trial. Nature medicine, 26(10), 1569–1575. https://doi.org/10.1038/s41591-020-1081-3

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[5] **Consultation on Point of Care manufacturing.**
https://www.gov.uk/government/consultations/point-of-care-consultation/consultation-on-point-of-care-manufacturing