The challenges of manufacturing and distributing CAR-T therapies

For decades, development of novel immunotherapies has largely been the remit of academic settings, which could afford to invest the time, focus and specialisation required to research and develop these highly personalised medicines. As significant and notable advances in progression-free survival and overall survival in relation to standard of care have occurred for cancer patients treated with such modalities, the need to increase the production, scale and reach of these treatments has assumed global importance. What has not changed, however, is the considerable effort and customisation required to yield these therapies in the first place. Herein, we discuss some of the challenges in the labour-intensive manufacturing and distribution of chimeric antigen receptor T cell (CAR-T) therapies for patients with cancer, and how scalability, logistics and quality control will require new solutions in the continued evolution of these medicines on a global stage.

Key challenges in CAR-T manufacturing

Viral vector selection, leukapheresis, gene transfer and cellular expansion in CAR-T manufacturing are critical initial steps to ensuring generation of successful patient products. Consistent generation of high-quality vector for predictable genetic modification of cells is the first and possibly most important consideration in this entire process, regardless of scale. From vector selection portends the need to understand the potential long-term safety concerns for this form of gene therapy, as well as how global regulators may (or may not) authorise such uses in a large scale setting with novel bioreactor culture systems.

Cell collection, being a manual, operator-dependant step, poses the risk of starting material variability. It is, of course, crucial to train operators in leukapheresis good practices, but the method of cell collection should be standardised in order to mitigate variability of apheresis products. Adapting singular institutional experience in leukapheresis best practices to a templated process in much larger, industrial environs requires considerable validation so as not to compromise patient product in terms of quality, yield and efficacy observed at the institution level. Thus, the 'scaling up' of this form of cellular manufacturing will likely require levels of optimisation and recalibration at the vector batch, cellular and qualified product (QP) release levels that may otherwise not be required (or as rigorously so) as occur in smaller manufacturing exercises.

As increased production scale is configured, it is also important to appreciate how quality, yield and efficacy are negotiated in terms of regulatory compliance regarding standards and reproducibility set forth for CAR-T manufacturing. Given the diverse regulatory landscape, there will likely remain significant uncertainty in the evaluation of patient product developments, resulting in subjective judgements by regulators. To be prepared for such uncertainties and subjectivities, manufacturers of scale must have readily available for submission and/or inspection documentation and validation all reagent origins, compositions, traceabilities, and certifications that are in use. Progress is being made in Europe as the European Medicine Agency is currently revising its guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells (EMA/CAT/GTWP/671639/2008) to specifically include consideration of CAR-T products. This initiative intends to harmonise regulatory reviews in Europe, and possibly beyond.

The Alliance for Regenerative Medicine has recently urged regulators to consider genetically modified organism (GMO) requirements in upcoming reforms, as advanced therapies utilising such require additional approvals prior to trial initiation. The GMO application and clinical trial approval processes in some European Union member states place a "significant burden" on gene therapy medicinal product clinical trials, ultimately delaying patient access to potentially transformative medicines.

Advanced planning may be particularly necessary in the EU as well as Asia, given that ~90% of all CAR-T trials to date have been operated in North America. Scaling up also implies comparability testing to ensure that the changes to production have no definitive clinical impact. CAR-T manufacturing has the additional challenge that variability between patient apheresis starting materials is likely to contribute to much greater differences than factors related to manufacturing. Thus, it is imperative to identify critical in-process parameters and controls in each step of the manufacturing processes so as to minimise overall variability related to the patient product for the purposes of analysis and standardisation.

> **"Shipping is a step that encompasses potential risks"**

In the final manufacturing steps, the patient product must meet the standards set for quality control testing, quality assurance batch review and QP release before cryogenic packaging and distribution to GMP processing facilities for patient infusion. These standards may invariably differ as CAR-T manufacturing penetrates new regulatory regions, and new protocols and requirements are set forth by competent authorities (CA) and GMO committees. As such, the need for unified standards and harmonisation of production requirements should not only make large-scale CAR-T manufacturing safe, efficient and reliable, but will expedite the opportunities to treat larger patient populations and potentially a wider range of indications.

The experience of the contract medical organisation within the manufacturing process is also a critical success factor to ensuring that the patient product can be manufactured consistently to required standards and specifications. However, one important aspect to consider is the occurrence of out of specification products and what steps to follow in order for whether a non-conforming product should be administered to patients, typically within a short time. Currently, no formal guidelines exist to address this matter; however, the draft EU guideline for ATMP currently under review by the European Commission should provide insight regarding future occurrences for this. In the meantime, it cannot be assumed that any CA will provide a general agreement/pre-approval for the use of out of specification products. In the absence of such guidelines, different regulatory authorities may take different approaches, so early dialogue with CAs to ensure expedited decision making is a must.

Key challenges in CAR-T distribution

Once a patient product has achieved QP release, the greatest risks in the process may just be beginning. Specifically, this form of therapy is solely applicable to the individual patient from which starting material is derived, and thus can only be used to treat that patient. To this end, chain of identity as well as chain of custody practices for CAR-T cells assume paramount importance due to the unique, individual endpoint of application. This can be particularly challenging outside of a single institution (with a limited number of personnel involved), where sample tracking, logistics and administrative documentation enter into scalable workflows and global commerce pathways that require rigor, validation and testing.

Another challenge is that CAR-T manufacturing and infusion require strict schedules. The clock starts with apheresis followed by conditioning lymphodepletion, and finally CAR-T infusion, all within a limited, clinically relevant timeframe. Additionally, due to the very short shelf life of CART-T cells, the medicinal product cannot be prepared in advance. This critical delivery time does not leave margins for logistical miscues, as any delay could result in product expiration. While it is complex on a small scale to precisely schedule leukapheresis and manufacturing deliveries, it becomes even more challenging for commercial practices. Manufacturers will have to assess how the uncertainties of starting material arrival and patient availability to receive the modified cells will impact planned manufacturing schedules and capacities, as well as to identify potential bottlenecks early on in order to avoid overall supply issues.

Shipping, whether it be leukapheresis material or final patient product, is a crucial step that encompasses potential risks. Transport conditions are subject to stringent controls and any environmental excursions will require careful, case-by-case assessment. It should also be noted that global distribution means longer distribution chains, which exponentially increase the complexities described earlier, and cumulatively the risks for patients. Different manufacturing models should be considered, from one centralised manufacturing site, which facilitates harmonisation of products, but would be difficult to manage if thousands of patients have to be treated simultaneously, to multiple local manufacturing sites, or even individual hospitals, which allow for shorter distribution chains and align with local practices, but raise the issue of comparability.

Conclusions

For any CAR-T patient product, quality data (clinical manufacturing and controls) are the keys to success. Such data will come under scrutiny by regulators during the assessment of clinical trial applications and marketing authorisation applications. Early dialogue with CAs is essential to get their advice and agreement on these important aspects. The manufacturer of these types of products raises some unique challenges, questions and debates. Furthermore, these answers are not necessarily published in guidelines; hence, the need for early dialogue with CAs, followed by early planning. In particular, it is highly recommended to discuss manufacturing and distribution aspects with regulators during initial clinical development strategy and planning to ensure that manufacturing and supply chains are robust enough to meet demand. It would be too late to change these critical paths after the product receives marketing authorisation. Thus, plan early and often.

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