Regulatory Challenges in Global CAR T Cell Therapy Development

When exploring the complex and rigorous regulatory landscape for CAR T cell therapies, sponsors may encounter challenges in their efforts to bring products to market

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Since the historic approval of Kymriah® (tisagenlecleucel) in 2017, research on chimeric antigen receptor (CAR) T cell therapy has accelerated. There are more than 230 regenerative medicine companies in Europe and Israel, of which more than 140 are focused on cell therapies. Around the world, there were 452 clinical trials of gene-modified and cell-based immuno-oncology therapies under way at the end of 2019 (1). Of these, 215 are in Phase II trials and 15 have progressed to Phase III trials.

Despite the bustle of research activity, only two CAR T cell therapies are on the market today, both targeting the CD19-expressing target cells, and clinical experience remains limited (2).

Regulations for Cell Therapy Products

In the EU, cell therapy products are subject to the EMA's guideline titled *Quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells*, which went into effect in November 2012 (3). A draft revision of this guideline was released in July 2018 to reflect the evolution of scientific and regulatory experience as well as current thinking on the requirements for non-clinical and clinical studies, including a focus on CAR T products. This draft was in public consultation until 31 July 2019, and the revision is still in progress.

Cell therapy products in the EU are also subject to the guidelines on Good Clinical Practice specific to advanced therapy medicine products (4). Additionally, CAR T cell therapies must conform to legislation for genetically modified organisms (GMOs), and sponsors are required to classify these therapies as either 'contained use' or 'deliberate release'. Contained use describes any activity in which specific measures are used to limit contact of the GMO with the environment. The deliberate release refers to any introduction of a GMO into the environment with no specific containment measures. In some EU member states, any use of a GMO – including in a clinical trial – is considered a deliberate release.

In the US, the FDA issued its first guidance on cell therapy in 1998 and has continued to publish new guidance documents as cell technologies advance. A list of cell therapy-related guidance documents can be found in **Table 1 (page 16)**.

Both the EU and the US offer regulatory pathways to facilitate and expedite review and approval for CAR T cell therapies, as seen in **Table 2 (page 16).**

Challenges and Opportunities

Some of the main considerations of CAR T cell therapies include:

Lack of Harmonised Regulatory Standards

Regulatory requirements for CAR T cell therapies differ from country to country, and this lack of harmonisation makes global CAR T clinical trials a significant challenge. In the EU, certain countries – and even individual sites within countries – may have their own CAR T-related requirements beyond standard regulatory and ethical review. Recently, the European Hematology Association (EHA) issued

Preclinical Assessment of Investigational Cellular and Gene Therapy Products (5)
Determining the Need for and Content of Environmental Assessments for Gene Therapies, Vectored Vaccines, and Related Recombinant Viral or Microbial Products
Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (6)
Evaluation of Devices Used with Regenerative Medicine Advanced Therapies (7)
Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use (8)
Expedited Programmes for Regenerative Medicine Therapies for Serious Conditions (9)

Table 1: FDA guidance on development of cell therapies

EU Priority medicine	US Fast track designation
Adaptive pathways	Breakthrough therapy designation
Accelerated assessment	Regenerative medicine advanced therapy designation
Conditional marketing authorisation	Priority review designation
Marketing authorisation under exceptional circumstances	Accelerated approval

Table 2: Expedited review and approval pathways available for CAR T cell therapies

a call to action for cross-border collaboration to develop harmonised processes for clinical trials and approvals across the EU, as well as a uniform framework for pricing and reimbursement to promote affordability and access (10).

Complex Manufacturing

Currently, the available CAR T cell therapies are individualised treatments, manufactured from a patient's T cells. To be used as commercial products in clinical practice, CAR T cell therapies must meet strict label specifications; this can be a significant challenge from a manufacturing perspective. For example, the initial launch of tisagenlecleucel was plagued with production issues, which resulted in the manufacturer having to deliver some CAR T treatments for free under investigational use. To mitigate the risk of production issues, sponsors should consider how their manufacturing platform will evolve from early-stage clinical testing to scalable, multi-site manufacturing.

One opportunity to simplify manufacturing may be 'off-the-shelf' CAR T cells developed from allogeneic T cells, which are an active area of research. The use of allogeneic T cells offers potential advantages, such as standardisation, immediate availability of cryopreserved batches, decreased cost, and opportunity for re-dosing or combining CAR T cells directed against different antigens. Allogeneic T cells, however, may also cause graft-versus-host disease or be eliminated by the host immune system, limiting their efficacy.

Complex Administration

Administration of CAR T cell therapies is a multi-step process that begins with harvesting cells from the patient and ends with delivering genetically engineered cells back into the patient. In between, the cells change hands numerous times, creating a complex chain of custody. All aspects of this chain must be tracked and managed in a highly controlled manner to ensure product integrity and patient safety. The administration is further complicated by the fact that CAR T cell therapies can only be administered at certified medical facilities, which can limit patient access. In the EU, the EHA is developing a harmonised curriculum, which includes recommendations on minimum levels of competence and knowledge required for all healthcare professionals involved in the administration of CAR T cell therapy.

Recently, the American Society for Transplantation and Cellular Therapy (ASTCT) published an expert panel opinion on the use of CAR T cell therapies for patients with relapsed or refractory aggressive B cell non-Hodgkin lymphoma (11). This document provides guidance for the use of both tisagenlecleucel and axicabtagene ciloleucel (Yescarta®) in clinical practice and covers ten key clinical questions, ranging from critical considerations for referring patients to CAR T therapy to strategies for monitoring toxicity, treatment response, and long-term effects. It also details specific requirements for the administration of CAR T cell therapies through the FDA's Risk Evaluation and Mitigation Strategies (REMS) programme.

Immunogenicity and Adverse Events

CAR T cell therapies are associated with significant treatment-related toxicities, including cytokine release syndrome (CRS) and immune effector-cell associated neurotoxicity syndrome (ICANS), which can be life-threatening. As such, both tisagenlecleucel and axicabtagene ciloleucel are approved with REMS, which include elements to assure safe use. Other adverse events include haematologic disturbances, serious infections, hypotension, hypoxia, and acute renal failure.

A number of groups, including the ASTCT and the CAR T cell-therapy-associated TOXicity Working Group, have developed guidelines on CAR T treatment-related toxicity assessments. In its expert panel opinion document, the ASTCT encourages use of its toxicity consensus grading system across all CAR T cell products and indications to facilitate consistent reporting and

	Tisagenlecleucel (Kymriah)	Axicabtagene ciloleucel (Yescarta)
EU	For acute lymphocytic leukaemia (ALL): • Post-authorisation efficacy study (PAES) based on a registry with a follow-up period of 20 years For diffuse large B cell lymphoma (DLBCL), three additional PAES studies: • A prospective observational study based on a registry with efficacy outcome measures in line with the clinical trial used to support approval (study C2201), including details on manufacturing turnaround time • 24-month follow-up for patients from study C2201 to further characterise long-term efficacy and safety, as well as submission of the final clinical study report, including five years of follow-up • Open-label, Phase III study of the product vs standard of care in adult patients For ALL and DLBCL: • Non-interventional post-authorisation safety study (PASS) to assess the safety and long-term safety based on a registry with a follow-up period of 20 years	• PASS based on a registry to assess the safety profile • Periodic safety update reports • Risk management plan • An educational programme which must be agreed with the National Competent Authority prior to launch in each member state
US	For ALL: • REMS • Multi-centre prospective observational safety study, including 1,000 subjects enrolled within three months of infusion over five years. All enrolled subjects will be followed for 15 years from the date of infusion, with a primary endpoint of evaluation for secondary malignancy For DLBCL: • Amendment of the protocol for the ALL safety study to include 1,500 subjects with DLBCL	• REMS • Multi-centre, prospective observational safety study, including 1,500 subjects enrolled within three months of infusion over five years. All enrolled subjects will be followed for 15 years from the date of infusion, with a primary endpoint of evaluation for secondary malignancy

Table 3: Post-marketing requirements for approved CAR T cell therapies

comparison among products. The ASTCT also recommends monitoring patients for signs of treatment-related toxicities for at least four weeks after infusion and provides specific management strategies for both CRS and ICANS.

Long-Term Follow-Up

As an *ex vivo* gene therapy, CAR T cell therapies may require long-term follow-up (LTFU) of up to 20 years in the EU and up to 15 years in the US to collect sufficient safety and efficacy data and to evaluate for secondary malignancy. Both tisagenlecleucel and axicabtagene ciloleucel are subject to post-marketing requirements in the EU as well as in the US, as shown in **Table 3**.

To help sponsors determine if a CAR T cell product requires LTFU, the FDA has provided guidelines on performing a risk assessment in their updated guidance on Long Term Follow-up After Administration of Human Gene Therapy Products, released in January 2020 (12). This document also includes recommendations on the design of LFTU studies for collecting data on delayed adverse events and long-term safety and efficacy following gene therapy administration. If LFTU is required, the FDA specifies that the observation should include a minimum of five years of annual examination followed by 10 years of annual patient queries, either in person or by questionnaire (13). The EMA Guideline on the follow-up of patients administered with gene therapy medicinal products provides similar recommendations on evaluating the risk profile of a gene therapy product to determine the need for LTFU.

Given the relatively recent introduction of CAR T cell therapy to clinical practice, data on delayed physiologic effects, survivorship, and patient-reported outcomes (PROs) in those treated with CAR T cell therapies are still limited. Nevertheless, recommendations have been emerging regarding the

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types of PROs which should be collected, and how often (14). These recommendations may be useful when designing LTFU studies to gather realworld data on the long-term impact of CAR T cell therapies.

Conclusion

We are still in the early days of the era of CAR T cell therapy, with much to learn about long-term outcomes of patients treated with these novel therapies. As development accelerates and access increases, we will gain valuable insight into outcomes and strategies for improving the safety and efficacy of these game-changing treatments.

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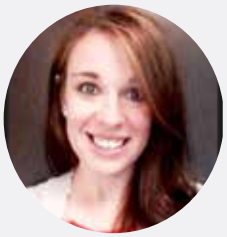

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