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COMMENTARY

# The FDA's Regulatory Framework for Chimeric Antigen Receptor-T Cell Therapies

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**Chimeric antigen receptor-T (CAR-T) cells are the product of several decades of work in different scientific disciplines that has culminated in the development and approval of therapies that are effective against certain relapsed or refractory hematologic malignancies. In addition, CAR-T cells are under investigation for the treatment of other hematologic malignancies and solid tumors, as well as autoimmune and infectious diseases.[1]**

CAR-T cells are a form of cell-based gene therapy that use a genetic construct that redirects T cells to recognize and kill a specific target, usually a cell surface molecule unique to a class of cells. The most advanced products in development, two of which have received regulatory approval, utilize T cells harvested from the patient who will ultimately receive the product. These autologous cells are then further processed, transfected using a lentiviral vector expressing a protein construct that in one embodiment consists of the cytoplasmic domain of a T-cell receptor joined via a costimulatory domain and a hinge region to an immunoglobulin head.[2] The cells are then expanded in culture and further formulated and characterized for quality control prior to their administration back to the patient. Other novel chimeric constructs, additional genetic alterations to the T cells, and other viral and nonviral methods for introducing the constructs are under investigation.[3] It should be noted that the manufacturing and logistic obstacles that had to be overcome to successfully develop consistently made quality products were formidable, and both the chimeric constructs and manufacturing processes continue to evolve.[4]

There is tremendous activity in the CAR-T field, with >100 active investigational new drug applications in the United States alone. There are now two approved CAR-T cell therapies on the market in the United States. Tisagenlecleucel (Kymriah) was licensed (approved) on August 30, 2017, for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia refractory or in second or later relapse, and this product had the addition of an indication for relapsed or refractory large B-lymphoma indication on May 1, 2018. Axicabtagene ciloleucel (Yescarta) was approved on October 18, 2017, for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy (**Figure 1**).

Although CAR-T cells are considered regenerative medicine products in the United States, globally they fall within the rubric of Advanced Therapy Medicinal Products. These products include gene therapies and human cells, tissues, and cellular and tissue-based products requiring licensure. The key feature that these products have in common is that their clinical efficacy flows from an understanding of critical quality attributes and the implementation of a well-controlled manufacturing process; product quality and efficacy are inextricably linked together.

Advanced Therapy Medicinal Products are regulated by the US Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER). In November 2017, to better clarify the regulatory landscape for regenerative medicine products, including CAR-T cells, CBER issued a suite of regenerative medicine guidance documents.[5] In addition, because CAR-T cells are cell-based gene therapies, three of the suites of six draft gene therapy guidance documents published in May 2018 for comment are relevant to their production, particularly the guidance on chemistry, manufacturing, and controls for gene therapy products (**Table 1**). It should be noted that guidance documents describe ways that sponsors developing products can comply with the FDA's regulations. However, alternative approaches of complying with the regulations may be acceptable, particularly if well justified.

Along with the guidance documents recently released, the implementation of the Regenerative Medicine Advanced Therapy (RMAT) designation program perhaps has been of greatest interest to product developers in the CAR-T cell space. The enabling legislation for RMAT designation was passed and signed into law in December 2016 as part of the 21st Century Cures Act. It provided regenerative medicine products, including cellular therapies, tissue engineering products, cell-based, and other gene therapy products with all of the benefits of the Breakthrough Therapy (BT) designation. The two differences between BT and RMAT designation are: (i) for RMAT the level of evidence required is that the product demonstrates the potential to address an unmet medical need (rather than an improvement over an existing standard of care, as in the case with BT designations), and (ii) for RMAT there are additional options available to sponsors who receive accelerated approval for how they fulfill postapproval commitments (e.g., evaluation of the accelerated approval end point at a later time may be used to convert to a traditional approval).

As of May 1, 2019, there have been 100 requests and 34 products that have been granted RMAT designation,

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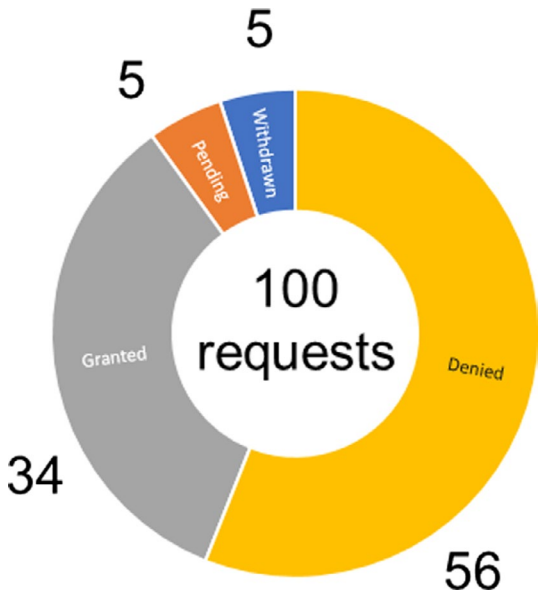


**Figure 1** As of May 1, 2019, the US Food and Drug Administration (FDA) had received 100 requests for Regenerative Medicine Advanced Therapy (RMAT) designation and had granted 34 of these requests. As of that date, five requests had been withdrawn, and five decisions were pending. Most designation requests have been for cellular therapies, including cell-based gene therapies. Of the 34 products granted RMAT designation, 20 have also received Orphan Drug designation and are for diseases affecting <200,000 individuals in the United States.

**Table 1 Summary of relevant recent regenerative medicine and gene therapy guidance documents**

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| Final guidance |
| Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception |
| Regulatory Considerations for Human Cell, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use |
| Evaluation of Devices Used with Regenerative Medicine Advanced Therapies |
| Expedited Programs for Regenerative Medicine Therapies for Serious Conditions |
| Draft guidance |
| Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs) |
| Testing of Retroviral Vector-Based Gene Therapy Products for Replication Competent Retrovirus (RCR) during Product Manufacture and Patient Follow-up |
| Long Term Follow-up After Administration of Human Gene Therapy Products |

reflecting the tremendous interest in the program. The most common reason for the agency to decline requests has been a determination that the application included inadequate preliminary evidence supporting designation. Less commonly, some sponsors have submitted clinical data obtained by another sponsor to support designation for a product that they intend to manufacture. The FDA does not consider this acceptable, because the clinical data provided must be obtained using the actual product that will be manufactured for use by the sponsor. The agency's position is supported by the well-documented challenge of reproducibly manufacturing the same cellular product at two different locations.

The same guidance describing the RMAT designation program also describes a novel clinical development pathway for collaborative product development between multiple institutions that may be applicable to CAR-T cell production.[6] In traditional drug development, one sponsor manufactures the investigational product, which is then studied in a multi-institutional clinical trial. The data collected are then submitted in support of the single sponsor's marketing application. In the collaborative pathway, multiple different sponsors manufacture the product according to an identical manufacturing protocol. They then enroll patients at their sites into a multi-institutional clinical trial. The data from that trial are then shared by the sponsors to support the submission of their own individual biologics license applications. The two key major recommendations for those interested in this pathway are to engage in a discussion with the FDA early on, and to address issues of data ownership and intellectual property as well. The FDA is very open to and encourages these early discussions regarding product development.

The INitial Targeted Engagement for Regulatory Advice on CBER producTs (INTERACT) program[7] was developed to provide sponsors at very early stages of development of a specific product with nonbinding regulatory advice on manufacturing, preclinical studies, and clinical development pathways. Obtaining such early advice can be particularly helpful in the case of products, such as CAR-T cells, as it helps identify the most streamlined paths forward toward the development of safe and effective products. In addition to taking advantage of early interactions with the FDA, one more piece of general advice to sponsors working in this area is that they may wish to be prepared for the possibility of early signals of significant efficacy by having scalable manufacturing processes that could support product licensure relatively early during the overall development process.

Although there have been tremendous advances in this field, there are still some major challenges to be overcome. In addition to the scientific challenges of improving safety and effectiveness and expanding applicability of CAR-T therapies to other indications, there are still major challenges to be addressed in clinical development and manufacturing. These challenges are relevant to both enabling more widespread availability of CAR-T cell therapies and to reducing their cost.

The lentiviral vectors currently used for introduction of the chimeric construct are difficult to generate in large quantities, as the production process in producer cell lines is relatively inefficient due to the inherent toxicity of the vectors to the cells in which they are made.[8] The result is a process that is capacity-limited and quite expensive. Efforts are under way in both the public and private sectors to develop cell lines that are much more efficient at producing lentiviral vectors, and it is also possible that the development of alternative methods for introduction of the chimeric constructs will result in increased production and reduced costs.

Consistency of manufacturing of CAR-T cell products is another issue that needs to be addressed. Because the starting material for production of the current generation of CAR-T cells products is obtained by leukopheresis of the patient that will ultimately receive the product, there is inherent variability in the input starting material due to various factors, including the patient's prior treatments. Identification of critical quality attributes leading to standardization of various processes can be challenging. Seemingly minor process changes, such as modest adjustment of the composition of the growth media during cell processing can lead to products associated with different clinical outcomes, and this can confound the analysis of parameters, such as the number of cells administered and clinical effectiveness.[9]

The two products currently marketed in the United States use centralized manufacturing facilities, which help to ensure product consistency. However, semiautomated devices have been developed that can be used centrally or deployed locally to manufacture CAR-T cells in a consistent manner.[10] It remains to be seen whether such devices will help facilitate the development of a decentralized production model that might be applicable to collaborative development programs.

In summary, CAR-T cells have already produced remarkable clinical results in certain hematologic malignancies, and they will likely find application in the treatment of other disorders. CBER will continue to work with sponsors by applying a flexible regulatory approach to the manufacturing, preclinical, and clinical development of these products in support of the availability of safe and effective products that benefit patients in medical need.

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