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 intrinsically 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,
the well-documented challenge of reproducibly manufactur-
ing the same cellular product at two different locations.

The same guidance describing the RMAT designation pro-
gram also describes a novel clinical development pathway
for collaborative product development between multiple
institutions that may be applicable to CAR-T cell produc-
tion.6 In traditional drug development, one sponsor manu-
factures 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 market-
ing application. In the collaborative pathway, multiple dif-
ferent 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 ap-
plications. 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) program7 was
developed to provide sponsors at very early stages of
development of a specific product with nonbinding reg-
ulatory advice on manufacturing, preclinical studies, and
clinical development pathways. Obtaining such early
advice can be particularly helpful in the case of prod-
ucts, 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 advan-
tage 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 li-
censure 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 chal-
enges to be addressed in clinical development and manu-
facturing. 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 tox-
icity 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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1. Caliendo, F., Dukhinova, M. & Siciliano, V. Engineered cell-based therapeutics: synthetic biology meets immunology. Front. Bioeng. Biotechnol. 7, 43 (2019).
2. June, C.H., O’Connor, R.S., Kawalekar, O.U., Ghassemi, S. & Milone, M.C. CAR T cell immunotherapy for human cancer. Science 359, 1361–1365 (2018).
3. Labanieh, L., Majzner, R.G. & Mackall, C.L. Programming CAR-T cells to kill cancer. Nat. Biomed. Eng. 2, 377–391 (2018).
4. Dai, X., Mei, Y., Cai, D. & Han, W. Standardizing CAR-T therapy: getting it scaled up. Biotechnol. Adv. 37, 239–245 (2019).
5. US Food and Drug Administration (FDA). <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/framework-regulation-regenerative-medicine-products>.
6. Marks, P. & Gottlieb, S. Balancing safety and innovation for cell-based regenerative medicine. N. Engl. J. Med. 378, 954–959 (2018).
7. US Food and Drug Administration (FDA). <https://www.fda.gov/vaccines-blood-biologics/industry-biologics/interact-meetings-initial-targeted-engagement-regulatory-advice-cber-products>.
8. Merten, O.W., Hebben, M. & Bovolenta, C. Production of lentiviral vectors. Mol. Ther. Methods Clin. Dev. 3, 16017 (2016).
9. Roddie, C, O’Reilly, M, Pinto Dias Alves, J, Vispute, K & Lowdell, M. Manufacturing chimeric antigen receptor T cells: issues and challenges. Cytotherapy 21, 327–340 (2019).
10. Lock, D. et al. Automated manufacturing of potent CD20-directed chimeric antigen receptor T cells for clinical use. Hum. Gene Ther. 28, 914–925 (2017).