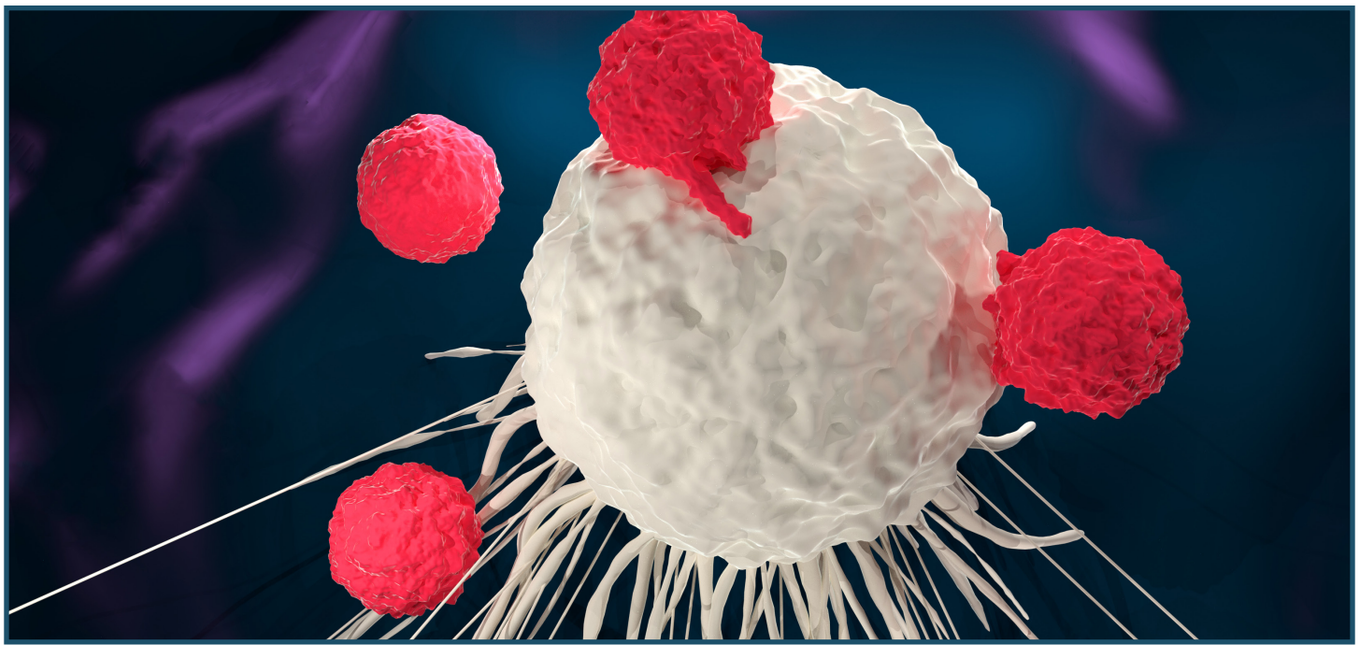

CAR T-Cell Therapy Challenges to Development & Approval

Chimeric antigen receptor T-cell (CAR T) therapy is a revolutionary immunotherapy that uses cells from the patient's immune system to fight certain kinds of cancer. The first two FDA approved CAR T therapies, Yescarta™ and Kymriah™, were both approved in 2017. Former FDA Commissioner, Scott Gottlieb, noted the significance of these approvals in his October 2017 press release stating that they represent milestones "in the development of a whole new scientific paradigm." More recently, two more CAR T therapies, Tecartus™ and Breyanzi®, were also approved, further indicating that the approval of these types of therapies are likely to continue.

After decades of research, CAR T treatments offer the potential for better and more personalized cancer treatments. However, like with many ground-breaking products, the developmental and regulatory pathway for these novel therapies is not always clearly defined. Regulatory agencies have had to adapt their own ways of thinking in the wake of these new approvals. As more CAR T therapies are developed, it is certain that regulatory processes will continue to evolve.

If you are involved in the development of CAR T therapies (or any type of novel therapy), it is critical to understand the current regulatory landscape, potential regulatory and clinical challenges that may arise during development, and how to adapt to any new regulatory developments proactively and efficiently.

CAR T Challenges & Strategies for FDA Approval

Novel concepts, such as CAR T therapies, often come with unique drug development challenges. When considering CAR T therapy, there are several strategies for overcoming these challenges to consider. Some potential challenges associated with CAR T development include:

1. Limited FDA guidance
2. Manufacturing and distribution logistics
3. Product safety and long-term follow-up

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LIMITED FDA GUIDANCE

FDA guidance documents represent the FDA's current thinking on a wide array of drug development topics. Unfortunately for novel therapies like CAR T-cells, available guidances from the FDA can be relatively sparse. This is partly because the FDA may still be determining its own best practices. Certainly, guidance documents do exist that cover cellular and gene therapies, but often these documents are broadly stated with no specific recommendations for CAR T products.

While the FDA is working to expand their library of guidances, the large number of actively recruiting CAR T-based clinical trials indicates an immediate and unmet need for additional FDA input. In the absence of formal guidance documents, leveraging existing information from the public domain can help put you on the right track. While this may not answer all of your questions and there may be nuances in your particular program that present unique challenges, gaining insight into what has worked in the past can help to prepare you for productive interactions with the FDA.

The Center for Biologics Evaluation and Research (CBER) maintains a list of approved cellular and gene therapy products that includes links to additional content. There you will find a wealth of information about each product, often including the summary basis of approval (SBA), individual subject-level reviews (e.g., clinical pharmacology, toxicology, manufacturing), information requests, risk evaluation and mitigation strategy (REMS) documents, the approved product label, and so forth. Keep in mind however, that this is a rapidly evolving field. Old issues about safety may become less of a concern, while new questions will continue to arise. The agency's position reflects the current state of knowledge about this class of treatments. Further complicating development is that the agency may be aware of data that are not in the public domain (and, for confidentially obligations, they cannot share).

While these resources can be very helpful for informing your development and regulatory strategy, it is also critical to gauge the FDA's thinking on your particular product and development program. One of the best ways to do this is to engage directly with the FDA in the context of a formal meeting. For CAR T and other cellular and gene therapies, you can reach out to the Office of Cellular and Gene Therapy Products in CBER to request a meeting appropriate for your stage of development (e.g., Pre-IND, Pre-BLA, End-of-Phase, Type C). During these meetings, the FDA can provide critical, on-the-record insights on a wide range of topics including the preclinical program, clinical trial design, safety considerations, regulatory strategy, and a host of other topics.

Finally, careful consideration of the nuances of your product that may present unique developmental or regulatory challenges is essential. For example, if your CAR T therapy is to be co-administered with another molecule or using a novel delivery device, additional regulatory requirements may apply (e.g., device and combination product regulations, additional safety assessments, etc.). It is important to begin interactions with the FDA early-on and to keep the lines of communication open. Doing so can help prevent costly delays and missteps that could hinder your program.

MANUFACTURING AND DISTRIBUTION

Unlike most drugs and biologics, current CAR T therapies use a patient's own cells to create an individualized treatment. Typically, a patient's cells are harvested at the clinical trial site, transported to a manufacturing site/laboratory where they are modified, shipped back to the clinical site where they may be stored temporarily, and then infused back into the patient – usually several weeks after being collected. Each step of this process adds additional layers of complexity to an already complex system. Potential variability in key product quality parameters, such as cell viability and cell potency and how these are impacted during storage and shipping are key considerations that may attract additional regulatory scrutiny.

Beyond gathering information about existing therapies and engaging with the FDA, it is important to generate appropriate plans for each aspect of the clinical and manufacturing process from harvesting the original cells through re-infusion back into the patient. It is also critical to anticipate potential problems along the way. Clinical site training is a key aspect of this and is often

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formalized as part of the REMS submitted with the BLA marketing application. Shipping protocols, storage protocols, and detailed manufacturing plans are another essential component, in addition to studies assessing the effectiveness of these plans for maintaining product quality. The testing strategy should include not only "ideal" conditions but also the impact of potential deviations such as unintended shipping delays and suboptimal storage conditions.

PRODUCT SAFETY AND LONG-TERM FOLLOW-UP

In a previous blog post, we described the potential toxic side effects of CAR T therapies, including cytokine response syndrome and on-target/off-tumor toxicity. Substantial risks of approved CAR T therapies also include multi-organ failure, late onset leukemia, neurotoxicity, and brain tumors. These toxicities are likely to be associated with any new CAR T therapy and as an additional complication, preclinical models are often incapable of identifying the full profile of side effects observed in humans. For these reasons, FDA reviewers will look for a thorough analysis of potential risk and risk mitigation, so that side effects can be rapidly and appropriately addressed.

In addition to acute side effects, it is also necessary to consider long-term safety outcomes. As cellular therapies, CAR T treatments have long-acting biological profiles. This makes them effective cancer treatments, but also introduces a potential for delayed adverse events, immunogenicity concerns, and negative effects on normal cell growth and development. As you prepare to transition to the clinic, consider these risks and the duration of long-term follow-up that will be required. Long-term follow-up studies to fulfill post-marketing requirements often involve collecting patients' safety information for 15 years. This type of long-term study is costly but commitment to understanding the full safety profile of the therapy is critical for regulatory approval.

Early-phase clinical trials should be carefully designed to ensure a comprehensive safety assessment, efficient product delivery, and optimal clinical and manufacturing procedures to maintain product quality and safety. Commonalities with existing therapies and the unique aspects of your particular product that may necessitate additional safety assessments should be carefully considered. These considerations, along with any experience gained during the clinical development of your product, will help inform the eventual REMS that will be submitted with the BLA.

Being prepared for long-term follow-up means that late-stage clinical trials will likely need at least one year of follow-up data prior to commercial approval and post-market follow-up periods of up to 15 years should be expected. There is some potential for this period to be shortened based on the mechanism of action and biological profile of the product, including persistence of cells in the patient, duration of expected response, and expected survival rates of the population. Early discussions with the FDA and careful study design of early-stage clinical trials may allow you to reduce long-term follow-up timelines.

Regulatory Tools Used for CAR T Therapy Approval

FDA designation programs that have been used in the approval of CAR T therapy products include: priority review, breakthrough therapy, orphan drug, accelerated approval, and regenerative medicine advanced therapy (RMAT). These tools can significantly reduce the time to approval and marketing of a CAR T therapy drug.

- **Priority review:** will prompt the FDA to take action on an application within 6 months instead of the standard 10-month time frame.
- **Breakthrough therapy:** is granted when preliminary clinical evidence is significantly better than other existing therapies for a drug intended to treat a serious condition. A drug with breakthrough therapy designation will benefit from fast-track designation features, intensive guidance as early as Phase I, and organizational commitment involving senior managers.
- **Orphan drug:** will benefit from tax credits and removal of the prescription drug user's fee.
- **Accelerated approval:** helps advance timelines by allowing a sponsor to use a surrogate endpoint if the disease population represents an area of unmet medical need.

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- **RMAT:** applies only to human cell or tissue products that are intended to treat, modify, reverse, or cure a serious disease. Like drugs that are eligible for accelerated approval, a drug must have preliminary evidence suggesting that it has the potential to address an unmet medical need to be designated as RMAT. Due to the strict requirements to qualify as RMAT, very few drugs have obtained this designation.

B-Cell Malignancies & Solid Tumors

Currently approved CAR T therapies are not proven to be as efficacious in solid tumors as they are in relapsed or refractory B-cell lymphoma. These therapies target CD19, which is extensively and uniformly expressed in acute lymphoblastic lymphoma cells, but not other types of cancer cells, like solid tumor cells. Targets other than CD19 either suffer from similar problems or are expressed on normal cells, resulting in toxicity.

As discussed above, the toxicities associated with CAR T therapies can be substantial. This further highlights the need for establishing targets that are tumor-specific while simultaneously sparing normal cells from attack. A strategy that can effectively target solid tumor cells while preserving normal cells would both increase efficacy and limit side effects. To this end, researchers are exploring the potential in adapting the CAR T platform to better suit different types of cancer.

Advancements in CAR T-Cell Therapies

Cancer is notoriously difficult to treat due to the many mechanisms by which cancer cells evade immunologic attack. In addition, recognition of normal cells by the CAR T-cells resulting in on-target/off-tumor side effects remain a cause for concern. Development of therapies that effectively target and destroy cancer cells while maintaining a manageable side effect profile is a mainstay of oncology research.

There is research exploring the possibility of taking advantage of tumor cells' tendency to overexpress target receptors. By modifying the affinity of the CAR T-cell protein domains for existing targets, CAR T-cells could distinguish between cancer cells and healthy cells. This is just one example of the many different strategies in development that use genetic modification to maximize CAR T-cell efficacy and limit side effects. There are many advancements in the field that can be leveraged to push CAR T therapy into new indications.

Another consideration for CAR T-cell therapy programs is advancing the manufacturing processes. These therapies are often pursued by sponsors working with universities or single institutions. As such, scaling and manufacturing are not always considered from the start. With such a breadth of complexity in the manufacturing of CAR T-cell therapy products, it is essential to ensure a comprehensive understanding of the product and the process as early as possible and focus on optimizing that process throughout development.

Conclusions

CAR T therapies represent an exciting era of personalized medicine and we will undoubtedly see new CAR T drugs continue to reach the market. Understanding the hurdles in developing these therapies, such as a lack of CAR T-specific FDA guidances, the complexities of manufacturing and distribution, and potential safety concerns coupled with the need for long-term follow-up, the regulatory tools available, and the ongoing research will increase your chances of success and help get your product well on its way to commercialization.

Contact us to learn how we can provide support for CAR T therapy development and approval needs.

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