Fortrea

Regulatory strategy considerations for advanced therapies

Author

Alicia Baker McDowell, DRSc, MS, EMBA, Head of Regulatory Strategy and Product Development Consulting, Fortrea

The regulatory landscape for advanced therapies is quickly evolving and the number of therapies in development continues to increase.[1] To keep pace with these changes and assist product development, the FDA has published over a dozen regulatory guidance documents since 2020, spanning gene therapies for specific disease areas, chemistry, manufacturing, and controls (CMC) information and guidance for CAR T-cell products, among many others.

Navigating the dynamic regulatory environment in cell and gene therapy development involves a complex and iterative process. To support product development sponsors, this white paper shares regulatory considerations for facilitating early discussions with regulators, assessing the available expedited programs, building flexibility into clinical design and ensuring diversity and inclusion of under-represented populations in pivotal clinical trials.

The advantage of early and frequent regulatory interactions

Regulators are open to discussion and can provide early advice about complex development programs. By frequently meeting in their early stages of development, drug development sponsors can get guidance and substantive feedback on several key aspects of their proposed advanced therapy program.

INTERACT

An INTERACT (an acronym for INitial Targeted Engagement for Regulatory Advice on CBER/CDER ProducT) is an FDA meeting that can take place when some nonclinical and CMC data are available—before conducting pivotal non-clinical studies. The goals of this meeting are to discuss preclinical testing, aspects of manufacturing, first-in-human trials, clinical development strategies and assay design.

- **Chemistry, Manufacturing and Controls (CMC) strategy:** regulators can examine any available data on the drug substance or active pharmaceutical ingredient (API) and determine if the available CMC data can be used to support the proposed nonclinical studies and the clinical trials while also meeting relevant Good Manufacturing Practices (GMP) regulatory requirements. At a detailed level, these regulatory interactions can be used to review detailed CMC components, such as the virus titer or concentration, content ratio, capsids, replication-competent adenovirus testing, process impurities, container/closure system and pace of development
- **Nonclinical data:** to evaluate potential concerns from the use of the product, an early regulatory interaction can examine various data from *in vitro* and *in vivo* proof-of-concept, pharmacology, and toxicology studies, such as ectopic or unregulated expression of transgene, immunogenicity, long-term persistence, off-target distribution, insertional mutagenesis, germline transmission and environmental shedding

Pre-IND meeting

The Pre-IND meeting should be utilized to discuss the IND-enabling data and mitigate any potential clinical hold issues. This meeting also provides the opportunity to discuss the program moving forward, for example:

- **Clinical program design:** regulators can evaluate any proposed flexibility in a program design, such as an adaptive design, an innovative design or any other alternatives to a traditional multicenter trial (MCT)
- **Long-term follow-up:** long-term follow-up (LTFU) planning can also benefit from pre-IND discussions with the FDA. These observational studies can identify potentially delayed adverse events, such as the risk of malignancy, impairment of gene function and autoimmune-like reactions. The following factors are considered in determining the extent of safety monitoring that will be required for a product:
    - The toxicity of the product, and how likely the toxicity will occur
    - How long the patient will be at risk of adverse events
    - How the toxicities should be measured

  Some studies have a 15 year LTFU, while others, such as adeno-associated virus (AAV) products, may have LTFU up to 5 years due to a lower risk of AAV vector integration and a generally lower risk of delayed adverse events.

  The FDA has published a guidance document on long-term follow-up[2] and recommends working with the Office of Therapeutic Products (OTP), which is a reorganization of the former Office of Tissues and Advanced Therapies (OTAT). Early engagement can help shape post-marketing plans, examine the gene therapy delivery and make decisions about the LTFU, statistical analysis plan (SAP), registries, protocols and schedule of milestones.

Recent LTFU activity: boxed warning for CAR-T therapies

The FDA investigated reports received regarding T-cell malignancies, including CAR-positive lymphoma, among patients who received BCMA- or CD19-directed CAR-T cell immunotherapies.[3] The FDA now requests boxed warnings on all commercial CAR-T therapies as there is a "serious risk" of patients developing new cancers after treatment.

Sponsors now have the option to meet the FDA's demand and submit a supplement to offer the changes verbatim or file a supplement with different wording. Alternatively, sponsors may submit a rebuttal statement detailing their disagreements. Regardless of the pathway they choose, sponsors must submit a response within 30 days or face potential enforcement action, including monetary penalties and forced change of label.

Understanding expedited programs for serious conditions and designations

As part of their regulatory strategy, sponsors can also consider an expedited program they may qualify for when developing a treatment for a serious condition with an unmet medical need. The table below summarizes the programs, each of which has a few overlapping benefits.

Table 1: types of expedited programs

Name and competent authority	When to use	Potential benefits
Fast Track (FDA)	Nonclinical or clinical data demonstrate potential to address unmet medical need.	Facilitate development and expedite a product's review, such as possibility for a rolling review.
Breakthrough Therapy Designation (BTD) (FDA)	Preliminary clinical evidence indicates possible substantial improvement on a clinically significant endpoint(s) over available therapies.	Intensive guidance on efficient drug development, organizational commitments, rolling review and other actions to expedite review.
Regenerative Medicine Advanced Therapy Designation (RMAT) (FDA)	Cell therapy, therapeutic tissue engineering product, human cell and tissue product or any combination product using such therapies or products that is intended to treat, modify, reverse or cure serious or life-threatening conditions and its preliminary clinical evidence indicates potential to address unmet medical needs for the condition.	All breakthrough therapy designation (BTD) features, including early interactions to discuss any potential surrogate or intermediate endpoints; it may also have the potential to support accelerated approval and satisfy post-approval requirements.
Priority Review (FDA)	If approved, the treatment would provide significant improvement in safety or effectiveness.	Shorter clock for review of the NDA (6 months compared with the 10 month standard review).

continued...

Table 1 continued.

Name and competent authority	When to use	Potential benefits
PRIority MEdicine (PRIME) and Accelerated Assessment (EMA)	Treatment should demonstrate a potential benefit to patients with unmet medical needs based on early clinical data and offer major therapeutic advantage over existing treatments or benefit patients without treatment options.	The EMA will provide scientific advice at key development milestones in addition to organizational commitments, including a dedicated contact point and appointment of a rapporteur. For Accelerated Assessment, the normal assessment period for the MAA of 210 days is reduced to 150 days, if the qualification criteria are met.
Adaptive pathways (EMA)	A lifespan approach to drug development, authorization, reimbursement and the use of product.	Allows for early and progressive patient access to a medicine built on regulatory processes. With iterative development (approval in stages, beginning with a restricted population and expanding to wider populations), real-life evidence is generated to supplement clinical trial data. The early involvement of patients and health technology assessment (HTA) can help reduce uncertainties and enable the development of non-conventional products.[4]
Orphan Drug Designation (FDA)	Addresses a rare disease or condition is any disease or condition which is defined as affecting less than 200,000 persons in the U.S., or affecting more than 200,000 persons in the U.S. and for which there is no reasonable expectation that the cost of development; and making available in the U.S. a drug for such a disease or condition will be recovered from sales of such a drug in the U.S.	Marketing exclusivity for seven years in the U.S.; financial incentives in the form of tax credits or grant aid, along with scientific assistance and reduced application fees.
Orphan Drug Designation (EMA)	Intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition that affects not more than 5 in 10,000 persons in the community when the application is made, or that without incentives is unlikely to generate sufficient return to justify the necessary investment; and, no satisfactory method for the diagnosis, prevention or treatment of the condition has been authorized in the EU, or if such a method does exist, the new medicinal product will be of significant benefit to those affected by the condition.	Marketing exclusivity for 10 years; access to the centralized procedure for EU marketing approval; financial incentives in the form of tax credits or grant aid, along with scientific assistance and reduced application fees.
Accelerated Approval Program (FDA)	Surrogate endpoints and/or post-approval confirmatory studies show clinical benefit.	Earlier approval; however, through The Food and Drug Omnibus Reform Act of 2022 (FDORA), the FDA was granted authority in 2022 to require confirmatory trials underway at the time of accelerated approval. The FDA has issued Complete Response Letters due to a lack of progress on confirmatory trials. Given that there is a lack of clarity around the term "confirmatory trials underway," it is critical to gain clarification on expectations from regulators.

Considering diversity to meet regulatory requirements

While the FDA has previously encouraged sponsors to include traditionally underrepresented demographic subgroups, the Food and Drug Omnibus Reform Act of 2022 (FDORA) was enacted in December 2022 and included provisions to promote diversity and inclusion in clinical trials. Since 2022, the FDA has been asking sponsors to discuss their plans to ensure diversity and inclusion of under-represented populations in pivotal clinical trials for all Phase III/pivotal studies for drugs, biologics and medical devices that will support a marketing application. This also applies to pediatric studies and rare disease studies.

Even though sponsors are in a grace period, it will be ending soon now that the FDA has updated the guidance document and is moving toward the finalization of the draft. Many sponsors have been actively preparing Diversity Plans and submitting them to the FDA. By gathering the agency's feedback now, these sponsors will be better prepared to have a diverse population reflective of the real-world population represented in their program.

When it is mandated, the Diversity Plan should be submitted no later than when the protocol is submitted to the FDA for Phase III or other pivotal study, and the FDA may consider one Diversity Plan for an indication covering multiple studies.

At a high level, the "Diversity Action Plan" describes the rationale for enrollment goals, including the methodology used to derive target enrollment goals, and the measures to meet the goals, including strategies for enrollment retention, monitoring enrollment and mitigation to overcome barriers. More detailed information on Diversity Action Plans is discussed on our website.

Achieve your goals in a dynamic regulatory environment

At Fortrea, we encourage drug development sponsors to think ahead—as early as possible—when developing an advanced therapy. This involves considering a product's possible regulatory designations, establishing engagement with regulators, creating long-term follow-up plans for a program and determining how to meet the goals of diversity planning. Throughout development, an early focus on chemistry, manufacturing and controls (CMC) also helps identify critical issues and gaps to avoid potential delays in product development.

References

1. ASGCT Gene, Cell, & RNA Therapy Landscape, Q1 2024 Quarterly Data Report. https://www.asgct.org/global/documents/asgct-citeline-q1-2024-report.aspx. Accessed May 22, 2024.
2. U.S. FDA. Long Term Follow-up After Administration of Human Gene Therapy Products. Jan. 2020. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/long-term-follow-after-administration-human-gene-therapy-products. Accessed May 24, 2024.
3. U.S. FDA. FDA Investigating Serious Risk of T-cell Malignancy Following BCMA-Directed or CD19-Directed Autologous Chimeric Antigen Receptor (CAR) T cell Immunotherapies. Nov. 2023. https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/fda-investigating-serious-risk-t-cell-malignancy-following-bcma-directed-or-cd19-directed-autologous. Accessed Sept. 25, 2024.
4. Eichler, HG. EMA, PRIME, Adaptive Pathways. Feb. 2017. https://download2.eurordis.org/symposium/2017/6hans-georgeichler_adaptivepathways.pdf. Accessed May 28, 2024.

LEARN MORE at fortrea.com

Fortrea

©2024 Fortrea Inc. All Rights Reserved.
WP_0065_Strategic Advanced Therapy_0924