From Concept to Clinic:

Navigating the Regulatory Path of CRISPR-based Therapeutics

WhitePaper

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From Concept to Clinic: Navigating the Regulatory Path of CRISPR-based Therapeutics

Recently, the field of cell and gene therapies has experienced significant progress, especially with CRISPR (short for *clustered regularly interspaced short palindromic repeat*) gene editing therapies. From December 2023 to February 2024, the world's first CRISPR/Cas9 gene editing treatment, CASGEVY™ (exagamglogene autotemcel, or exa-cel), for the treatment of Sickle Cell Disease and Transfusion-Dependent Beta Thalassemia was approved by the FDA, EMA, MHRA and Kingdom of Saudi Arabia. The approval for CASGEVY™ underscores the safety and efficacy standards that CRISPR/Cas9 gene-editing therapies have reached in the field of cell and gene therapies.

The journey of translating CRISPR therapies from the bench to clinical trials is not driven solely by technical advancements, but also by a concerted effort that requires both consideration of established regulatory guidance as well as ongoing dialogue with regulatory bodies. CRISPR therapeutic applications frequently target genetic or rare diseases and are characterized by extended drug development timelines. To expedite the availability of such critical therapies, applicants may engage with the FDA's Expedited Programs, which include Fast Track, Breakthrough Therapy, Accelerated Approval, and Priority Review, to streamline drug development and review processes. A recent talk from the director of the FDA's Center for Biologics Evaluation and Research (CBER) indicated a growing propensity to employ Accelerated Approval for gene therapies addressing rare diseases. This shift signals the FDA's commitment to accelerating the entry of gene therapy products into the marketplace, thereby addressing the unmet medical needs of individuals with rare conditions.

In this whitepaper, we will guide you through the intricate regulatory journey of cell and gene therapies (CGTs), helping you optimize your pathway to success.

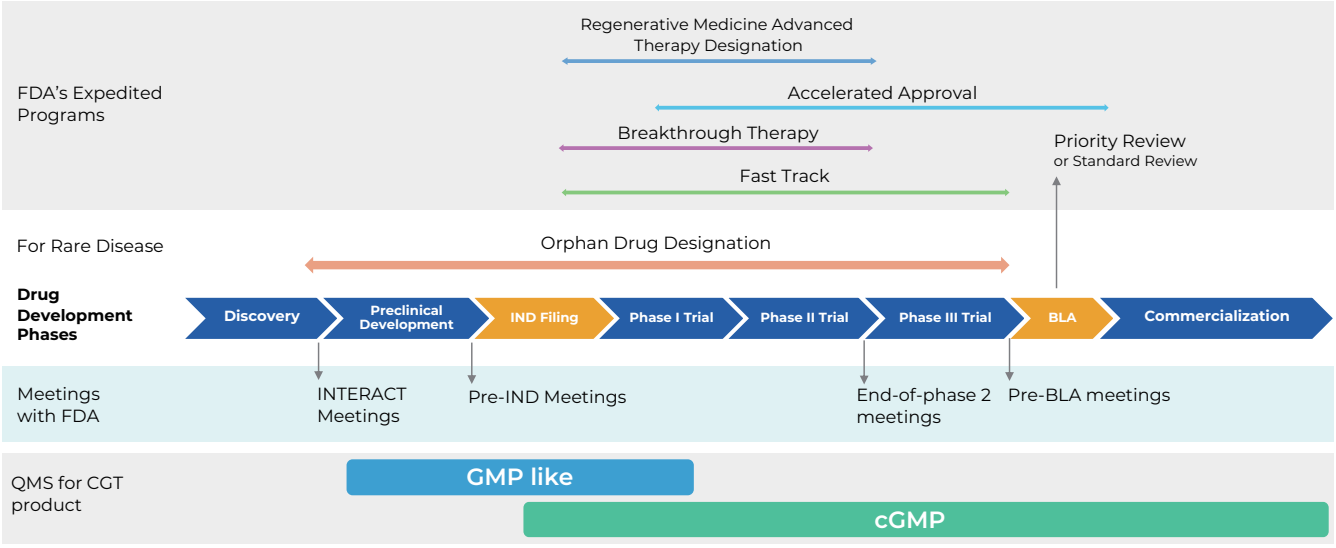

Figure 1: Regulatory Milestones in the CGT Drug Development Process

I. Discovery and Target Validation

The drug discovery process starts with basic scientific research. The major steps at this stage usually include target site screening and identification, high-throughput compound screening, hit validation, and lead candidate optimization. Target site screening and identification is the most critical of these steps, and the increasing usage of Genome editing (GE) has further expedited the lead candidate screening process.

It is possible to achieve GE through nuclease-dependent or nuclease-independent methods. CRISPR-Cas systems are one of the key gene editing technologies that rely on a nuclease to modify DNA, alongside others such as zinc finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs).

GE components are critical elements of CRISPR-based CGT products. When using CRISPR to modify cells *ex vivo*, sgRNA, Cas9 nuclease, and HDR donor templates (if applicable) are critical components used to produce the final therapeutic product. However, when administered *in vivo*, these components are actually part of the final product, as they are delivered directly to produce edits. Thus, it is critical for therapy developers to select appropriate GE components, design platforms, and optimization measures early in the discovery process to minimize the potential for off-target genome modification and GE components degradation.

Once a sponsor has an candidate product ready for clinical study evaluation and supported by preliminary preclinical proof-of-concept (POC) studies, but has yet to conduct definitive toxicology studies, an INitial Targeted Engagement for Regulatory Advice on CBER/CDER producTs (INTERACT) meeting with the FDA is highly advisable. This step can significantly contribute to a successful regulatory journey by initially setting the right course.

FDA encourages researchers or sponsors to initiate effective interactions with them to discuss the risks and benefits of target therapies, starting from the early stages of development to the Investigational New Drug (IND) submission, clinical trials and Biological License Application (BLA) stage.

II. Preclinical Development

Before evaluating an investigational product in a clinical study, it must first undergo preclinical testing to establish basic safety. This phase typically covers the selection of animal species, animal modelling of the disease, POC studies, and toxicology studies. Preclinical safety concerns about CGT products should be considered in terms of the type of genetically modified cells used, risks associated with the delivery method, and risks specific to the GE technology.

Common challenges and requirements regarding preclinical studies should be described in IND include:

- Establishing a stable manufacturing process to produce both preclinical and clinical batches.
- The animal species selection and the assessment of each animal species relevancy.
- The basis for the selection of animal models for predicting the efficacy and safety of CGT products.
- Addressing preclinical trial design issues, such as animal species insensitivity to the vector, clinical route of administration not used, or dose levels not covering the intended clinical ranges.
- Characterizing safety concerns or risks observed in preclinical trials adequately.
- Ensuring preclinical laboratory studies are in compliance with Good Laboratory Practice (GLP) requirements, except for *in vitro* and *in vivo* pharmacology/POC studies for CGT products, which may be specific and not GLP compliant.

In addition, the sponsors may apply for an orphan drug destination (ODD) to reduce costs and obtain FDA incentives. In general, data from clinical studies, animal models (*in vivo*), and *in vitro* studies are all possible bases for an ODD application. The sponsors need to determine the stage of ODD submission based on whether the data basis is sufficient.

> *For more information on the pre-clinical stage of CRISPR-based therapeutic development, please stay tuned for a detailed look at common pre-clinical challenges coming up soon.*

III. Investigational New Drug Application (IND)

The sponsor can apply for an IND after preclinical studies have been completed to determine the drug's bioactivity, preliminary efficacy, safety, and a stable manufacturing process under GMP requirements has been developed. The FDA recommends establishing communication via pre-IND meetings prior to IND application to determine clinical strategy, CGT product development strategy (e.g., thoughts of ODD) and whether current IND information is sufficient to demonstrate product safety on humans in the phase I clinical trials.

Following the FDA's comments from the pre-IND meeting and completion of requisite studies, the IND application of CGT products must be submitted to proceed to clinical trials. The sponsor should prepare and submit a complete documentation package, covering the Chemistry, Manufacturing, and Control (CMC), preclinical, and clinical aspects for the IND application. The package should be submitted in accordance with the number, section sequence, and heading of the Electronic Common Technical Document (eCTD) format, which is a harmonized common format for submissions to regulatory agency.

To promote the clinical translation of CGT products, the FDA has published several guidelines to provide greater support to applicants. These guidelines cover GE components, CAR T products, potency, manufacturing changes and comparability, clinical trial, CMC information in IND application, and more, reflecting the FDA's commitment to advancing CGT product development. For the GE components, the design, function, efficacy and potential off-target issues are the major points of focus in the FDA's review.

> *For more information on the CMC part, please stay tuned for a deep dive into CMC strategy for CGTs, in the upcoming series.*

For cell therapy and certain human gene therapy products, a Regenerative Medicine Advanced Therapy (RMAT) Designation may be appropriate. The request for a RMAT designation must be made either concurrently with a submission of an IND or as an amendment to an existing IND. Drugs that receive RMAT designation will be eligible to participate in the FDA's expedited programs and will have access to frequent communication with the FDA, technical assistance from the FDA, and the possibility of a rolling submission of BLA.

IV. Clinical Trials

Following IND approval, sponsors may initiate clinical trials. The FDA's Support for clinical Trials Advancing Rare Disease Therapeutics (START) Pilot Program exemplifies their support for advancing rare disease therapeutics, offering enhanced communication for a select number of sponsors to address novel drug and biological products issues.

Prior to clinical trials, registration and publication in public databases (ClinicalTrials.gov) and Institutional Review Boards (IRB) approval are mandatory. Clinical trials typically include Phase I, Phase II, Phase III and Phase IV trials. The progression from Phase I trials through Phase III trials involves gradually increasing the number of participants and study length to stepwise verify the safety, efficacy, and adverse reactions of the CGT products. Phase IV studies are carried out once the CGT product has been approved by FDA. During the FDA's exa-cel advisory committee meeting in October of 2023, the advisory committee emphasized the importance of using appropriate sample sizes in clinical studies in order to adequately capture variants that exist in the target population and mitigate the risk of off-targeting.

For CRISPR-based products, a thorough safety monitoring strategy with a well-defined toxicity grading system and a toxicity management plan is crucial for clinical trials. Special considerations should be given to adequately monitor any off-target editing and assess outcomes.

Another aspect that requires special attention is long-term follow-up. Due to the relative uncertainty of CRISPR-based products with respect to expected targeted edits, non-targeted edits,

and unintended edits at targeted sites, prior to clinical studies, subjects should be asked to provide voluntary, informed consent for long-term follow-up for up to 15 years. The sponsor of exa-cel, Vertex Pharmaceuticals, who will be the first to progress through this stage in CRISPR-based gene therapy development, explained their reliance on population-wide genetic data and plans for long-term follow-up to assess the actual impact of genome editing during the exa-cel advisory committee meeting.

Collecting and reporting data to the FDA

After IND filing and approval, IND application sponsors are expected to submit periodic amendments and reports (annual reports/Development Safety Update Report (DSUR), safety reports, protocol amendments and information amendments) to provide sufficient post-IND information for periodic review by the FDA.

V. FDA Review and Approval

The CGT drug developer can file an application to market the CGT products if it has adequate evidence from its early tests, preclinical and clinical studies that it is safe and effective for its intended use.

CGT products are regulated under the biologics regulatory framework to get the marketing approval via BLA to the FDA CBER. The BLA should include all information (CMC, preclinical and clinical data) obtained during the development process and should demonstrate the safety, purity, and potency of the biological products. Due to the complexity of biologics manufacturing, a pre-license facility inspection is typically required before BLA approval. The BLA Review Process and Major Steps for Completing the Review are shown in the figure below.

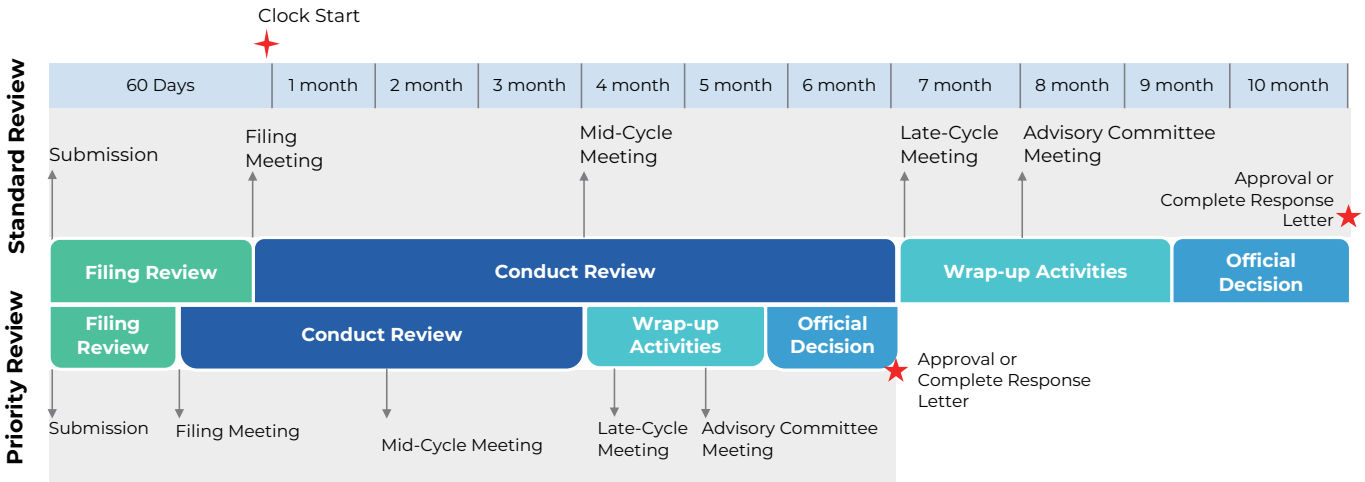

Figure 2. BLA Review Process and Major Steps for Completing the Review

FDA monitors all drug safety once products are marketed. Sponsors are required to provide certain information to the FDA regarding the post-market studies or clinical trials needed, e.g., postmarketing commitments (PMCs). Phase IV studies are carried out once the CGT product has been approved by FDA during the Postmarket Monitoring, providing additional information to demonstrate the safety and efficacy. The study participants consist of several thousand volunteers with the targeted disease/condition. Any adverse events occurring with the use of marketed drug should be reported, regardless of whether they are thought to be related to the drug. Reporting includes 15-day Alert reports and periodic reports. The FDA primarily monitors post-market products through the MedWatch program and FDA Adverse Event Reporting System (FAERS).

For more information on the clinical trials process for CRISPR-based therapeutics, please stay tuned for upcoming issues.

VI. Summary

Navigating the regulatory pathway from discovery to the clinic for CRISPR-based therapeutics is a complex and multifaceted process. It requires a well-planned strategy, attention to detail, and proactive engagement with regulatory agencies. By following established guidelines, engaging in early discussions with the FDA, and addressing safety concerns diligently, sponsors can pave the way for successful clinical trials.

Here are some key takeaways discussed in this whitepaper to help guide you through this journey:

- Design and optimize high-quality GE components, develop a detailed regulatory strategy early in your development process, and exercise meticulous attention to detail when establishing protocols to mitigate potential regulatory issues down the line.
- Engage proactively with regulatory agencies to foster open communication and address any concerns promptly to ensure smoother regulatory approval processes.
- Actively engage in information gathering at each project milestone to ensure a thorough understanding of the necessary requirements and development progress.
- Stay informed regarding the FDA's ongoing activities regarding CGT products and align your development strategies accordingly.
- Make strategic use of the FDA’s Expedited Programs for your CGT product to accelerate the regulatory process and gain quicker market access.

As we continue to delve into the nuances of this journey, it's clear that regulatory foresight is as crucial as scientific innovation in bringing these transformative therapies to patients who need them most.

Please be advised that the content contained within this document, including any recommendations, insights, opinions, or advice, is solely reflective of GenScript's perspective. The material provided herein is intended for general informational purposes only and should not be construed as official guidance from the FDA.

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