Gene Editing: The Regulatory Perspective

Subjects: Genetics & Heredity

Contributor: Sarfaraz K. Niazi

Gene or genome editing, often known as GE, is a technique utilized to modify, eliminate, or substitute a mutated gene at the DNA level. It serves as a valuable tool in the field of genetic manipulation. Gene therapy (GT) is a therapeutic approach that aims to correct mutations by delivering a functional gene copy into the body. In contrast, the mutated gene remains in the genome. It is considered a form of medical intervention. No approval has been granted for any product manufactured by GE, in contrast to the approval of 22 medications produced by GT. These GT products are priced at millions of US dollars each dose. The Food and Drug Administration (FDA) has recently implemented a guideline about gene editing, which aims to facilitate the expedited creation of genetically engineered (GE) goods. However, the FDA must provide further elucidation and necessary revisions to enhance the rationality of this guideline.

gene editing gene therapy FDA regulatory approval

Mutations cause human evolution and a myriad of diseases. Treatment for roughly a billion people with faulty, disease-causing genes was impossible before gene modification technologies. While the FDA has approved 22 gene therapy (GT) products [1], and the EMA [2] has approved 13 products (labeled as Advanced Therapy Medicinal Products) (ATMPs), neither agency has approved any GE product. However, many are under development [3]. Thus, the developers should improve their understanding of the scientific, technical, and regulatory perspectives based on the lessons learned from the GT products to reduce the cost and time of bringing them to patients. This is the primary focus of this paper.

The cost of GT and GE products to patients is exorbitant [4]. However, there are many creative possibilities to reduce this high cost and the long time it takes to secure regulatory approval. These include outsourcing the work, partnering with academic institutions, using special IND approvals, working closely with regulatory agencies, and questioning the listed testing requirements. In the future, this category will likely include GE products as well. In addition, a better understanding of individual variability and next-generation sequencing (NGS) technologies to discover new uncommon genetic illnesses have made individualized therapies more practical.

Regulators can take additional steps to support the uniformity of off-target (and on-target) effect measurement, such as putting the best practices for sample handling and analysis into place, as well as quality control checks. Because they are still being developed, methods for identifying on- and off-target effects are not specified in the EU rules for the quality, non-clinical requirements, and clinical requirements of genetically modified cells, for instance [5].

The impact of the in vivo cellular environment on gene editing efficiency is very important. This poses challenges in accurately forecasting the clinical outcomes of gene editing treatments in people, particularly when relying on non-clinical efficacy models. Given the potential scenario where gene editing treatments may not necessitate or lack pertinent non-clinical efficacy models, engaging in comprehensive inquiry and endeavors to establish such relevant ones is imperative. These efforts should be thoroughly deliberated and requested individually during regulatory interactions.

Japan's PMDA produced a Guideline on Assuring the Quality and Safety of Gene Therapy Products (not gene editing-specific). This causes scientific and political concerns. To keep potentially curative ATMPs orphan, they must have a significant advantage over authorized ATMPs. Most ex vivo GE products are GTMPs or cell treatments, meeting ATMP criteria. The FDA classifies all gene editing products (in vivo and ex vivo) as gene therapy in the US. For scientific reasons, clinical efficacy data may not be available to verify superiority, leaving clinical safety or non-clinical data to support a significant benefit claim.

References

1. FDA Approved Cell and Gene Therapy Products. Available online: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products (accessed on 6 March 2023).
2. EMA ATMP. Available online: https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview#advanced-therapies-in-the-product-lifecycle-section (accessed on 6 March 2023).
3. Alliance for Regenerative Medicine. Available online: https://www.mednous.com/gene-edited-therapies-produce-first-clinical-data (accessed on 6 March 2023).
4. Niazi, S.K. The Dawn of In Vivo Gene Editing Era: A Revolution in the Making. Biologics 2023, 3, 253–295.
5. European Commission. Directive 2001/18/ EC on the Deliberate Release into the Environment of GMOs; Directive 2009/41/EC on the Contained Use of Genetically Modified Micro-Organisms. Available online: https://food.ec.europa.eu/plants/genetically-modified-organisms/gmo-legislation_en (accessed on 6 March 2023).