Human Gene Therapy for Rare Diseases (FDA Draft Guidance for Industry)

The Food and Drug Administration (FDA) released a draft guidance, "Human Gene Therapy for Rare Diseases" (noticed via 83 FR 32303) for the development of human gene therapies (GTs) intended to treat rare diseases in adult and pediatric patients. This information is intended to assist industry sponsors of clinical trials in designing trial development programs for rare disease GT products.

Clinical trials follow a typical series, starting with preclinical validation studies in animals to early, small-scale, Phase 1 studies to late-stage, large scale, Phase 3 studies. This guidance covers industry considerations for GT product development through all phases of the clinical development program—from preclinical studies and investigational new drug application (IND) submission to late stage clinical trials (e.g. pivotal Phase 3 studies).

The guidance establishes considerations for product development, emphasizing the importance of a well-controlled manufacturing process and analytical assay to assess the critical quality attributes of GT products early in the development process. The specific considerations for GT products to consider prior to submitting an investigational new drug application include, among others, product-related variations (i.e. differences in product efficacy due to intrinsic individualistic differences) which may lead to variation or impurities in manufactured products, and potency assays which measure relevant biological activity including accuracy, precision, and sensitivity.

The draft guidance additionally outlines specific considerations for GT products through preclinical and clinical trials. The guidance outlines recommendations in the development of a preclinical program for an investigational GT product intended for treatment of rare diseases including preclinical proof-of-concept studies, biodistribution studies, toxicity studies, and additional non-clinical studies. The draft guidance provides the following recommendations for clinical trials: selection of study populations that match the genetic profile and disease severity of the therapeutic product, study design that allows for assessment of drug safety and efficacy profile while minimizing bias, careful dosage selection informed by pre-clinical studies, and safety considerations that include a monitoring plan to protect the safety of clinical trial subjects.

Context

A combination of better characterization of rare diseases, the discovery and optimization of new gene delivery vectors, and the development of site-specific genome editing technologies have revived gene therapy across the biomedical engineering and clinical trial landscape. These advances have encouraged industry players in gene therapy to stake new claims in rare disorder territory, where many diseases are mechanistically defined and controlled by a single gene.

Interest in gene therapies to treat rare disorders is not limited to the biotechnology industry—the unmet medical need and lack of existing treatments for these conditions has garnered government support. For example, the National Institutes of Health (NIH) has allotted over $200 million to the NIH Undiagnosed
Finally, the federal government has enacted policy aimed at promoting the development of drugs for rare diseases — including the Orphan Drug Act of 1983 [21] which incentivizes companies to develop novel therapeutics (including GTs) for rare conditions through a combination of tax breaks and extended marketing exclusivity. More recently, the Breakthrough Therapy Designation [22], enacted in 2012 by the FDA, expedites the development of drugs that are intended to treat conditions —including orphan diseases—where preliminary clinical evidence substantial improvement over existing therapies.

Policy History

This is the first version of this draft guidance.

The Science

Learn About the Science

CRISPR-Cas9 and Genome Editing [23]

SEE ALL EXPLAINERS [24]

Science Synopsis

Gene therapy [25] is defined as a technique that allows correction of altered (mutated) genes to treat or cure a genetic disease [26] (i.e. an inherited medical condition caused by a DNA abnormality). This technology allows for the addition, deletion, or replacement of genes in a patient’s cells to replace missing or malfunctioning genes. Some examples [25] of gene therapy products include nucleic acids, genetically modified microorganisms (e.g. viral vectors), engineered site-specific nucleases used for human genome editing (e.g. CRISPR / cas system, zinc finger nucleases), and ex-vivo genetically modified human cells.

A rare disease is defined as a disorder or condition that affects fewer than 200,000 persons in the United States (FDA Rare Diseases and Conditions [27]). Gene therapy approaches are particularly well-suited for rare disease patients in part because the NIH reports [28] that more than 80% of rare diseases have a known monogenic, or single gene, mechanism of action. Application of gene therapy to modify the genetic defect of the disease, unlike traditional treatment options, offers the potential to cure the underlying cause of the disease.

Current treatment approaches are symptomatic, meaning that they are aimed at reducing the signs and symptoms for the comfort and well-being of the patient, but do not affect the root cause of the disease. In addition, there is considerable unmet need in this space, with approximately 7,000 identified rare diseases [28], and yet only a few hundred with existing treatments. Even within approved drugs, the majority of current approaches work by mitigating symptoms, rather than providing a cure for the disease.

Due to scientific advances over the past decade, gene therapy has moved from a theoretical concept to a viable therapy to address genetic diseases. These recent developments have led to rapid growth of commercial interest in industry research and development of GTs. Yet, developing safe and effective products to treat rare diseases can be challenging. It is difficult to find and recruit patients, and even within specific diseases, there is genetic variability and patients have unpredictable clinical manifestations and rates of disease progression. In preclinical and clinical development, it is challenging to identify appropriate study endpoints to demonstrate study safety and efficacy.

Currently, three gene therapies have already been approved for commercialization in the United States and European Union: UniQure’s Glybera [29] for lipoprotein lipase deficiency [30] (a rare metabolic disorder) and the first approved gene therapy in the EU (2012), GlaxoSmithKline’s Strimvelis [31] for Adenosine deaminase deficiency severe combined immunodeficiency [32] (a rare immune disease) (2016) in the EU, and Spark’s LUXTURNA [33] for a rare inherited retinal disease [34] (2018) in the US and EU. The FDA has recently stated [35] that establishing industry guidance for the development of gene therapy products is increasingly important.

Scientific Assumptions

- **Gene therapy products are a therapeutic approach for the treatment of rare diseases** (Section II): Researchers have thoroughly investigated [36] the application of gene therapy products for the treatment of rare diseases, and almost all researchers are in agreement of the feasibility [37] of this approach.
- **Pre-existing antibody development to the gene therapy product may limit its therapeutic potential** (Section V): Although viral vectors are non-pathogenic viruses [38], they can give rise to an immune response in patients. As a result, a significant portion [39] of patients for GTs harbor pre-existing antibodies which can reduce the efficiency of these therapies, and contribute to immunogenicity [40], or an unwanted immune response. Researchers have investigated the impact of pre-existing antibodies on the therapeutic potential of gene therapies, and almost all agree [41] that drug neutralizing antibodies can limit the therapy’s success. However, there have been recent redesigns used in drug development to mitigate the effects of pre-existing antibodies in the therapeutic potential of gene therapies (e.g. viral vector engineering and serotyping [42]).
- **Gene therapy products have higher variability than drugs or well-characterized biologics** (Section III): Researchers have thoroughly investigated [43] the manufacturing of GT products, and almost all agree that GTs are complex products that have higher variability than traditional drugs. Notably, to address this variability, there have been recent advances in the standardization of manufacturing of GT products, including advances in bioreactors [44] for cell-based therapies.
- **Disease manifestations are likely to vary for rare diseases, making treatment development complex** (Section V): Researchers have thoroughly investigated [45] this topic, and almost all agree that rare diseases have numerous low-frequency genetic variants, making treatment development more complex.

Relevant Experts
Charles A. Gersbach, PhD, is an Associate Professor of Biomedical Engineering at Duke University. His research interests range from gene therapy, biomolecular and cellular engineering, regenerative medicine and synthetic biology.

Relevant publication:


**The Debate**

### Scientific Controversies / Uncertainties

There is scientific uncertainty regarding the long-term feasibility of applying GTs towards therapeutic applications, including rare diseases. In addition, previous clinical development of GTs has been hampered by the emergence of serious toxicities.

The host immune response to gene therapy vectors may contribute to unwanted immune response; circumventing the immune response to a vector is a major challenge with viral vectors in gene therapy. Viral vectors induce an immune response directed against them, like the reaction that is elicited when foreign viruses infect cells. This response can eliminate the vector and reduce the efficacy of GTs, further complications their efficacy in treating certain disorders.

Finally, *insertional oncogenesis* [48], or the non-specific integration of GT viral vectors in the genome, presents an additional safety concern. This random integration of viral vectors can lead to the activation of *oncogenes* [49] and ultimately to cancer development. In previous studies [50], patients treated by a GT for *X-linked severe combined immunodeficiency* [51], a rare immune disorder, developed leukemia due to this mechanism. Off-target effects may remain poorly understood in the near-term given that genomic integration of gene therapy, and therefore unintended consequences, may go *undetected* [52] for decades.

Importantly, despite recent technological advances in vector engineering that have led to improved drug efficacy and reduced immunogenicity, there are still pressing safety concerns stemming from technical limitations [53] of gene therapy viral vectors.

### Endorsements & Opposition

At present, there have not been any publicly reported endorsements of or opposition to this policy.

### Potential Impacts

This draft guidance serves [35] to advance the field of gene therapy while ensuring that new products are both safe for patients and meet the FDA’s standards on drug safety and efficacy. The novelty of gene therapy and difficulty in gaining full data on safety, efficacy, manufacturing, and long-term safety data complicates [54] GT drug oversight and creates regulatory challenges [55]. The present and longer-term potential of GTs to transform healthcare [56] and offer new treatments for countless inherited diseases. In fact, although originally intended as a treatment solely for inherited disorders, GT is now being applied to other conditions such as cancer. For example, the engineering [57] of cells for the immune system for targeted killing of cancer cells. In 2017, a steady stream of encouraging clinical results showed progress in gene therapies for hemophilia [58], sickle-cell disease [59], several serious inherited neurodegenerative disorders [60], an array of other genetic diseases, and multiple cancers [61] of the bone marrow and lymph nodes.

As stated [35] by FDA commissioner Dr. Scott Gottlieb, “Gene therapy represents one of the most promising opportunities for developing highly effective and even curative treatments for many vexing disorders.” This draft guidance indicates [62] the FDA’s awareness of a new era in the development of GTs towards clinical applications and the agency’s willingness [35] to adopt novel GT technologies addressing [63] unmet medical needs while also providing a comprehensive industry-focused regulatory framework.

### Status

This draft guidance was introduced as a proposed rule on July 12, 2018. The public comment period deadline was set to October 10, 2018, and later extended to December 10, 2018.

### Related Policies

- **83 FR 32302 - Human Gene Therapy for Retinal Disorders; Draft Guidance for Industry; Availability** [64]
  - This is a draft guidance for industry on human gene therapy for retinal disorders, including rare conditions.

- **83 FR 32306 - Human Gene Therapy for Hemophilia; Draft Guidance for Industry; Availability** [65]
  - This is a draft guidance for industry on human gene therapy for hemophilia, a rare blood clotting disorder.

### Recommended Citation


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