Molecular Therapy
Methods & Clinical Development
In the Spotlight

Optimizing regulatory frameworks for gene therapies in rare diseases: Challenges and solutions

Diane Berry,[1] Kate Donigan,[2] Lisa Kahlman,[3] James Long,[4] Christina Markus,[5] and Caitlin K. McCombs[6]

https://doi.org/10.1016/j.omtm.2024.101386

The advent of genetic medicines and advanced diagnostics has revolutionized the treatment landscape for rare diseases and, with over 10,000 identified conditions affecting millions globally, has the potential to improve many lives. Despite this progress, only 5% of rare diseases have FDA-approved therapies, highlighting a significant unmet need. This article examines the critical need for optimizing the regulatory environment to support the development and approval of gene therapies for rare and ultrarare diseases, which often face unique challenges due to their complexity in the midst of a rapidly evolving field. Key issues discussed include the mismatch between traditional regulatory paradigms and the nature of gene therapies, the need for innovative clinical trial designs, and the importance of flexible manufacturing processes. The article proposes targeted reforms to align regulatory frameworks with the needs of patients with rare diseases and the pace of science, emphasizing the value of a holistic evidence approach, platform technologies, and iterative manufacturing evaluations. By addressing these challenges, we can accelerate the development of life-changing therapies in order to realize the opportunity to provide treatments to patients with rare genetic disorders in their lifetime.

INTRODUCTION

With over 10,000 identified rare diseases affecting millions globally, innovative gene therapies hold significant promise.[1,2] However, the unmet need in rare disease is significant and urgent, as many of these diseases are severe, progressively debilitating, and often fatal, and only 5% of rare diseases have some FDA-approved therapy.[3] Fortunately, the rise in disease identification is occurring in parallel with rapid scientific advances in our ability to treat and possibly cure disorders down to the rarest patient populations. Precision genetic medicine can address the root causes of serious genetic diseases and offer the potential to alter disease trajectories and improve lives.

The journey from scientific breakthrough to patient bedside offers unique challenges, particularly in the context of regulatory oversight. This article examines the critical need to optimize the regulatory environment to foster the development and approval of gene therapies for rare and "ultrarare" diseases (a term not formally defined in the US but used to refer to conditions with extremely low prevalence).

At the heart of the issue lies a fundamental mismatch between traditional regulatory paradigms and the distinctive nature of rare disease gene therapies. Clinical trial design, endpoint selection, and manufacturing processes for these therapies often require the use of non-traditional approaches. The rarity of these conditions, combined with their heterogeneous and often progressive nature, necessitates modern, nimble strategies to demonstrate and evaluate safety and efficacy. Moreover, the sheer number of rare diseases and the associated complexities further compound these challenges.

While coverage and reimbursement are also critical access barriers,[4] this article proposes a series of targeted reforms aimed at aligning regulatory frameworks with the unique characteristics of gene therapies and the urgent needs of patients with rare diseases. The goal is to evolve our regulatory thinking to match the pace of scientific advancement. By advocating for a more holistic consideration of evidence, leveraging platform technologies, and promoting flexible, iterative approaches to manufacturing and control requirements, we can create a more conducive environment for rare disease gene therapy development and offer new hope to millions of patients worldwide who currently lack effective treatment options.

Although many of the challenges (e.g., few patients, heterogeneous disease presentations, and geographically dispersed populations) are well recognized to affect gene, cell, and other therapies for rare diseases alike, the focus herein is on gene therapies. This article illustrates unique barriers, highlights the need for broad-thinking solutions, and encourages awareness and ongoing advocacy to modernize multiple facets of regulation to more fully realize true patient benefit.

OPTIMIZING THE REGULATORY ENVIRONMENT

Rare disease prevalence spans a wide range; in the US, it is defined as a disease that impacts anywhere from a single patient up to 200,000 individuals out of the national population. Challenges in developing treatments for rare diseases—which are widely documented[5] and include disease heterogeneity, lack of prognostic factors, small numbers of patients available for clinical studies, often severe and progressive diseases with a lack of timely clinical endpoints for measurement, lack of prospective natural history data, etc.—are likely to be exacerbated in

[1]Chief Global Policy & Advocacy Officer, Sarepta Therapeutics, Inc., Cambridge, MA, USA; [2]Science and Regulatory Policy, Sarepta Therapeutics, Inc., Cambridge, MA, USA; [3]Public Policy and Public Affairs, Ultragenyx Pharmaceutical, Inc., Novato, CA, USA; [4]Clinical Pharmacy Services, DK Pierce, Zionsville, IN, USA; [5]FDA and Life Sciences Practice, King & Spalding, Washington, DC, USA; [6]American Society of Gene and Cell Therapy, Waukesha, WI, USA

Correspondence: Caitlin K. McCombs, American Society of Gene and Cell Therapy, Waukesha, WI, USA.
E-mail: cmccombs@asgct.org

the context of ultrarare diseases. This lengthens timelines and increases costs, ultimately threatening the short- and long-term commercial viability of these programs. To guard against that outcome and support the development of therapies for the increasing number of rare and ultrarare diseases, it is critical to address the following challenges.

Clinical trial design and endpoints

Rare disease patient populations can be a poor fit for the traditional, double-blind, randomized, controlled trial paradigm. Extremely small, heterogeneous patient populations complicate randomization and the analysis of small placebo-controlled studies. The use of placebos, particularly in the case of irreversibly progressive diseases, can be unethical and discourages patients from enrolling in clinical studies. Further, most endpoints in rare disease are novel, and there are little data to support prioritizing one endpoint over another for purposes of statistical analysis. The FDA continues to express preferences for traditional trial designs and, in some cases, has set criteria for the use of external controls that are too strict to be practicable. That preference appears even in formal guidance for rare diseases, where, arguably, external controls may be the most beneficial.[6,7]

AA

For certain rare diseases, particularly those that progress more slowly than can be assessed by clinical endpoints in a typical clinical trial time frame, the carefully considered use of accelerated approval (AA) may be the only feasible way to advance any treatment. However, there remains uncertainty regarding the acceptability of surrogate endpoints. Even when FDA permits the use of the AA pathway, there is often an expectation to establish a quantitative correlation between the surrogate endpoint and clinical benefit for the purpose of granting AA, which is at odds with the "reasonably likely to predict clinical benefit" standard and the post-approval requirement to subsequently confirm that the surrogate endpoint predicts clinical benefit. This likely means that some drugs that are safe and effective are not getting to patients promptly, which is inconsistent with the intent of the pathway.

Chemistry, manufacturing, and controls

Manufacturing gene therapies is different from traditional pharmaceutical processes. It is complex and highly dynamic and requires continued innovation throughout a product's life cycle. This is particularly true for rare diseases, where product-specific knowledge will continue to evolve as more patients are treated over time. Requiring sponsors to cement their manufacturing processes prior to clinical investigation, or potentially requiring the submission of a new investigational new drug application (IND) when significant manufacturing improvements are made (as stated in FDA guidance),[8] does not support continuous product improvement that ultimately benefits patients.

Rare disease expertise

While the FDA has rare disease experts on staff, given the sheer number of rare diseases, the FDA cannot be expected to have experts in every rare disease uniformly distributed across the agency. FDA rare disease experts are not always consulted in rare disease product reviews, and the FDA lacks a nimble mechanism to consult with external disease experts throughout the review process. The advisory committee process and its associated conflict of interest policies pose challenges, as there may only be a handful of available experts for a given rare disease.

Fortunately, the existing regulatory framework in the US provides tools and flexibilities to overcome the complexities of rare disease drug development, including regulations allowing the FDA to exercise the broadest flexibility concerning new therapies intended to treat life-threatening and severely debilitating illnesses.[9] However, variable implementation of this framework has created regulatory uncertainty.

To the FDA's credit, the agency has initiated pilot efforts to support the development of rare disease therapies. The rare disease endpoint advancement (RDEA) program[10] is focused on rare disease clinical endpoints, and the support for clinical trials advancing rare disease therapeutics (START) program[11] provides enhanced communication between the FDA and selected sponsors for rare disease therapeutics. The FDA also supports the development of individualized therapies through the Bespoke Gene Therapy Consortium,[12] a public-private partnership focused on eight specific diseases. Most recently, the FDA's Center for Biologics Evaluation and Research (CBER) and Center for Drug Evaluation and Research (CDER) announced a new rare disease innovation hub[13] to expedite treatments. These efforts combined represent a welcome acknowledgment by the FDA of the challenges in rare disease drug development and send a strong signal external and internal to the FDA of the urgency and importance of developing and approving medicines for patients with rare diseases. It will be important to see if these focused efforts can be scaled to deliver the tangible, broad, lasting change needed to improve patient outcomes as intended.

Congress and other stakeholders, including ultrarare patient communities, have also taken note of the challenges. In response, they have called for additional regulatory reform, such as the creation of a new regulatory pathway. Careful consideration of such proposals will be needed to evaluate whether they will in fact bring improvement or unintentionally create other hurdles that impede patient access.

What is clear is that as of 2023, CBER had over 2,500 active INDs for cell and gene therapies, necessitating broadly applicable and sustainable solutions to not delay safe and effective therapies from reaching patients. Fortunately, gene therapies have unique characteristics that can be leveraged to support meaningful, near-term actions.

Give full consideration to the totality of evidence in rare disease

Clinical development in rare/ultrarare diseases is challenged by small, often heterogeneous, patient populations. Additionally, the novelty of clinical endpoints can render the ranking of endpoints effectively random. It is critical to consider the totality of evidence by leveraging all possible data sources, including biomarkers, comparison to natural history, and real-world evidence,

in a consistent and predictable manner. A totality-of-evidence approach and novel statistical methods are particularly critical for small, heterogeneous patient populations, where the risks are greater of missing a primary endpoint and making a type 2 error—not approving a drug that is, in fact, effective. New regulatory pathways have been proposed for ultrarare therapy development that emphasize the importance of considering all available scientifically valid evidence, including mechanistic information, real-world data, and comparative studies, to determine if a therapy's potential benefits outweigh its risks.[14]

Fully leverage the mechanism of action of gene therapies to support approval

The FDA currently accepts surrogate endpoints and biomarkers for use in a particular drug/biologic development program on a case-by-case basis. This approach does not provide the much-needed regulatory certainty for the successful development of gene therapies for rare diseases. The mechanistic rationale underlying many gene therapies, which replace defective or missing proteins with functional ones, supports the use of protein expression as a robust surrogate endpoint reasonably likely to predict clinical benefit. For monogenic diseases where gene therapy addresses the root cause, protein expression is an upstream biomarker on the disease's causal pathway that may provide a more reliable and timely outcome measure than downstream clinical endpoints. In such cases, protein expression at a minimum threshold that is supported by nonclinical data should generally be considered sufficient as the basis for approval. This approach would align with the intent of the AA pathway by fully leveraging current science to speed up access to safe and effective therapies while continuing to gather long-term clinical data post-approval. In their forthcoming guidance,[15] the FDA should provide clarity on the characteristics of acceptable surrogate endpoints for monogenic rare disease gene therapies and ensure that the evidentiary standards for AA that reviewers apply align with the statutory reasonably likely criterion rather than imposing standards akin to traditional approval.

Maximize the use of platform approaches for gene therapy development

The fundamental principle of a platform approach to development, first legislated in the 21st Century Cures Act in 2016[16] and expanded in the Food and Drug Omnibus Reform Act of 2022,[17] involves leveraging a technology across multiple therapeutic products. For gene therapies, multiple products may share the same vector backbone that contains product-specific transgene inserts, making gene therapies ideal for a platform approach. This type of shared element enables leveraging data and processes across products, generating efficiencies that will support the development of products for ultrarare diseases that would not otherwise be commercially viable. The FDA has recently taken action in this space, releasing a draft guidance implementing the Platform Technologies Designation Program[18] and the Advanced Manufacturing Technologies Designation Program (AMTDP).[19] Platform approaches should be considered across the product life cycle, and potentially across multiple sponsors, to achieve maximum efficiency.

Enable iterative approaches to CMC requirements

In the context of gene therapy, process improvements are occurring at a higher frequency than other modalities due to rapidly evolving technology in this area. Sponsors should be encouraged to continually improve their manufacturing processes as more experience is gained to ensure the best possible product is delivered to patients. This can be achieved through a risk-based, phase-appropriate iterative evaluation of CMC requirements, considering such factors as rarity and unmet need, stage of development, and prior knowledge from related manufacturing processes. The FDA should work to further incorporate these considerations into their decision-making and integrate current risk management guidance to streamline expectations for sponsors. This includes recognizing that assays critical in late-stage development may not be possible or appropriate in early clinical development due to assay complexity, small sample sizes, and limited mechanistic understanding.

Engage in externally led scientific workshops focused on rare diseases

Rare disease drug development and review must be anchored in the latest scientific and clinical understanding of disease. This can be achieved through multi-stakeholder scientific engagements with industry, the FDA, and clinical and patient communities to support the sharing of disease expertise. Recent externally led scientific workshops focused on limb girdle muscular dystrophy (LGMD)[20] and neuronopathic mucopolysaccharidoses (MPSs)[21] provided a venue for scientific exchange between experts and regulators and may be viewed as a model for this type of engagement.

CONCLUSION

The development of gene therapies for rare and ultrarare diseases presents unique regulatory issues but also provides opportunities for innovative solutions. This article has highlighted key challenges in clinical trial design, endpoint selection, the AA pathway, and manufacturing processes. By implementing the proposed reforms, we can create a regulatory environment that appropriately applies scientific rigor, maximally leveraging the latest scientific advances to respond to the urgent needs of patients with rare diseases. This approach will foster innovation, accelerate development timelines, and ultimately increase the number of potentially life-changing treatments for millions of patients worldwide who currently lack effective options.

ACKNOWLEDGMENTS

Investigation and drafting was provided by employees of DK Pierce (Emma Selm-Keck and Miles Spenos). Conceptualization and review were provided by additional members of ASGCT's government relations committee. Review and administrative support were provided by ASGCT's senior manager of government affairs, Christina Mayer. This article has no funding sources to disclose.

AUTHOR CONTRIBUTIONS

Conceptualization, writing – original draft, writing – review & editing, D.B., K.D., L.K., and J.L.; writing support, writing – review & editing, C.M.; project administration, C.K.M.

DECLARATION OF INTERESTS

D.B. is an employee and shareholder of Sarepta Therapeutics. K.D. is an employee and shareholder of Sarepta Therapeutics. L.K. is an employee of Ultragenyx Pharmaceuticals. J.L. is an employee of DK Pierce. C.M. is an employee of King & Spalding. C.K.M. is an employee of the American Society of Gene and Cell Therapy.

REFERENCES

1. Haendel, M., Vasilevsky, N., Unni, D., Bologa, C., Harris, N., Rehm, H., Hamosh, A., Baynam, G., Groza, T., McMurry, J., et al. (2020). How many rare diseases are there? Nat. Rev. Drug Discov. *19*, 77–78. https://doi.org/10.1038/d41573-019-00180-y.
2. Global Genes (2024). RARE Disease Facts. https://globalgenes.org/rare-facts/.
3. Rutter, J. (2024). National Institutes of Health: Communicating About Rare Diseases. https://www.nih.gov/about-nih/what-we-do/science-health-public-trust/perspectives/communicating-about-rare-diseases
4. Berry, D., Donigan, K., Kahlman, L., Long, J., Markus, C., and McCombs, C. (2024). Ensuring Patient Access to Gene Therapies for Rare Diseases: Navigating Reimbursement and Coverage Challenges. Mol. Ther. Methods. Clin. Dev.
5. Chirmule, N., Feng, H., Cyril, E., Ghalsasi, V.V., and Choudhury, M.C. (2024). Orphan drug development: Challenges, regulation, and success stories. J. Bio. Sci. *49*, 30. https://pubmed.ncbi.nlm.nih.gov/38383975/.
6. FDA (2023). Rare Diseases: Considerations for the Development of Drugs and Biological Products [Guidance for Industry]. https://www.fda.gov/media/119757/download.
7. FDA (2023). Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products [Draft Guidance for Industry]. https://www.fda.gov/media/164960/download.
8. FDA (2023). Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products [Draft Guidance for Industry]. https://www.fda.gov/media/170198/download.
9. FDA (2023). Code of Federal Regulations. 21 CFR § 312.80. https://www.govinfo.gov/content/pkg/CFR-2023-title21-vol5/pdf/CFR-2023-title21-vol5-sec312-80.pdf.
10. FDA (2024). Rare Disease Endpoints Advancement (RDEA) Pilot Program. https://www.fda.gov/drugs/development-resources/rare-disease-endpoint-advancement-pilot-program.
11. FDA (2024). Support for clinical Trials Advancing Rare disease Therapeutics (START) Pilot Program. https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/support-clinical-trials-advancing-rare-disease-therapeutics-start-pilot-program.
12. National Center for Advancing Translational Sciences (2024). Accelerating Medicines Partnership – Bespoke Gene Therapy Consortium (AMP-BGTC). https://ncats.nih.gov/research/research-activities/BGTC.
13. Cavazzoni, P., and Marks, P. (2024). FDA Rare Disease Innovation Hub to Enhance and Advance Outcomes for Patients. https://www.fda.gov/news-events/fda-voices/fda-rare-disease-innovation-hub-enhance-and-advance-outcomes-patients.
14. Usdin, S. (2024). Debating new pathways for ultrarare: Woodcock, patient advocates, biotech leaders call for reforms. https://www.biocentury.com/article/652564/debating-a-new-pathway-for-ultrarare.
15. FDA Center for Biologics Evaluation and Research (2024). Guidance Agenda: Guidance Documents CBER is Planning to Publish During Calendar Year 2024. https://www.fda.gov/media/120341/download.
16. US Congress (2016). 21st Century Cures Act [Public Law No. 114-255]. https://www.govinfo.gov/app/details/PLAW-114publ255.
17. US Congress (2023). Consolidated Appropriations Act [Public Law No. 117-328]. https://www.govinfo.gov/app/details/PLAW-117publ328.
18. FDA (2024). Platform Technology Designation Program for Drug Development [Draft Guidance for Industry]. https://www.fda.gov/media/178938/download.
19. FDA (2024). Advanced Manufacturing Technologies Designation Program; Draft Guidance for Industry [Draft Guidance for Industry]. https://www.fda.gov/media/174651/download.
20. The Speak Foundation (2024). LGMD Scientific Workshop. https://thespeakfoundation.com/scientific-workshop.
21. Reagan-Udall Foundation (2024). Qualifying Biomarkers to Support Rare Disease Regulatory Pathways. https://reaganudall.org/news-and-events/events/qualifying-biomarkers-support-rare-disease-regulatory-pathways