

Global regulatory progress in delivering on the promise of gene therapies for unmet medical needs

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The rapid expansion of the gene therapy pipeline in recent years offers significant potential to treat diseases with great unmet medical need. However, the unique nature of these therapies poses challenges to regulating them within traditional frameworks, even when developing in a single country. Various factors exacerbate the issues in commercializing products across regions, including the lack of established regulatory frameworks for developing gene therapy products in many jurisdictions. While some countries have established separate regulatory frameworks for advanced therapies/regenerative medicine products, differences exist between them. Recommended solutions to overcome these hurdles include fostering convergence among countries with separate regulatory frameworks for these products and utilizing reliance and recognition for countries without such frameworks. Additionally, regulators who choose to establish new dedicated frameworks for regulating gene therapies should consider the inclusion of key elements such as expedited regulatory pathways that offer early engagement with regulators, innovative clinical trial design, and adequate post-market confirmatory studies. Increasing the alignment of regulatory pathways across countries will be crucial to facilitating the development of, and access to, gene therapies on a global scale.

INTRODUCTION

Gene therapy holds the extraordinary potential to transform global health care. As a result, the gene therapy pipeline has grown tremendously. There are currently more than 1,800 active and recruiting interventional gene and cell therapy trials globally.¹ Furthermore, by 2030 more than 60 US approvals of cell and gene therapy products are projected, with more than 500,000 patients anticipated to be treated with gene therapies.² This anticipated growth is expected to address significant gaps in healthcare globally, and, as such, advances in regulatory infrastructure are critical to continued innovation in the field to increase regulatory certainty and to address health needs.

Scientific and regulatory barriers to gene therapy development exist in many countries, limiting expansion into global markets. To reduce barriers to access, regulatory frameworks that are not unduly burden-

some need to be established that support predictability, efficiency, and flexibility. Such frameworks will lay the foundation for ensuring patient safety and facilitating expeditious development for these complex and innovative products.

In recent years, the American Society of Gene and Cell Therapy (ASGCT) has led efforts to increase dialog across key stakeholders regarding the evolving regulatory framework for gene therapies and the advances necessary to foster continued development. This article summarizes key global regulatory challenges to the development of gene therapies and provides recommendations for solutions to overcome them.

GLOBAL REGULATORY CHALLENGES POSED BY THE CURRENT MODELS

Uniqueness in the development of gene therapy products

The ASGCT defines gene therapy as the introduction, removal, or change in DNA or RNA in the cells of a patient to treat a specific disease.³ For the purpose of this article, however, the term gene therapy will refer to the subset of *in vivo* and *ex vivo* therapies that are intended as single administration therapies with durable results. The curative potential and the opportunities to have a dramatic, long-lasting positive impact on a patient's health affect several aspects of the clinical development plan of these products.

Many challenges in the development and commercialization of these complex products have been discussed in depth in the literature.⁴⁻¹⁰ Specifically, among the challenges developers face in establishing quality, safety, and efficacy data necessary to support a favorable benefit/risk profile are correct dose estimation, the development of manufacturing processes and associated quality standards, invasive routes of administration, small patient populations for rare disease applications, and a potential lack of established clinical endpoints. In addition, gene therapies have varied potential and some

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theoretical, long-term risks, such as immunogenicity and tumorigenicity, as well as a potential for loss of expression over time. Critical quality attributes (CQAs) are not well established for many gene therapy products, and demonstrating a link to clinical outcomes is often difficult. Furthermore, expedited clinical and regulatory pathways to submission and approval put pressure on chemistry, manufacturing, and controls (CMC) timelines.¹¹

Capacity constraints in manufacturing, the high cost of goods, long lead times, and significant upfront investment requirements have a substantial impact on development, especially for products utilizing viral vectors. Available production capacity for viral vectors has been limited by the increase in the number of therapies being developed and the expanding sizes of target populations.¹² The limited capacity of existing good manufacturing practice (GMP) facilities results in long wait times for clinical trial material and increased cost of goods.

A comparative study of the regulatory submissions for advanced therapy medicinal products (ATMPs) with those for other biologics found that ATMP developers need to comply with more post-approval commitments, which can be a challenge to market performance.⁶ Furthermore, several non-regulatory issues affect gene therapy access post-approval related to the health technology assessment in some regions, valuation, and payment policies that are beyond the scope of this article. These topics have been discussed elsewhere in the literature.^{6,7,13,14}

Regulatory differences between countries with separate regulatory frameworks for advanced therapies/regenerative medicine products

In addition to the overall challenges in developing gene therapies, development across countries presents further issues. Different approaches have been developed that largely reflect national or regional priorities and needs, even in socially, economically, and legally similar countries.¹⁵

To support the evaluation and regulation of gene therapy products, regulators globally either stretch the boundaries of their existing medicinal product regulations or design and implement new regulations. Most countries belong to the first group and do not have regulations specific to gene therapy. Instead, regulation for gene therapy products typically captures them as a subset of products under existing legislation. Regulators experienced with gene therapies, however, have adopted requirements and practices that are unique to the development of these products.^{5,16,17} For example, both the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) have more than a dozen guidelines or guidance documents specific to gene therapy products. While these unique guidelines and practices enable development of gene therapies within a single country or region, regulatory requirements vary across regions. From a global perspective, differences between countries or regions with more advanced regulatory frameworks for gene therapy products pose challenges to sponsors with multinational development programs. One reason for the differences between regulatory agencies is

the lack of common experience between agencies due to the novelty of these products to the market. At the time this article was written only five products were approved in multiple regions. The challenges created by this limited common experience are compounded by the innovative clinical programs that may be necessary for gene therapy products, including trial design, endpoints, long-term follow-up, and CMC. Therefore, product and development complexities result in sponsor uncertainty regarding regulatory requirements across countries. For example, it might be challenging for companies to receive concurrence from regulators in different jurisdictions on a proposed novel or surrogate endpoint that includes changes to the gene or protein expression. There are also regional differences in vector-specific study duration recommendations for long-term follow-up.

Different timelines, documentation requirements, study requirements, and regulatory pathways exist across regions as well. For example, expectations for environmental risk assessments and genetically modified organism applications vary with each member state in the European Union (EU), resulting in a maze of requirements that are difficult to navigate.

The expedited pathway options for gene and cell therapy development offered by the FDA, EMA, and the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan have some similarities but differ in many ways. All of these expedited regulatory pathways are designed to enable efficient development of promising therapies, but the precise qualifications, restrictions, and benefits vary. The Priority Medicines (PRIME) scheme in the EU is intended to optimize development and enable accelerated assessments. The FDA offers both breakthrough therapy designation (BTD) and the regenerative medicine advanced therapy (RMAT) designation, which differ slightly in qualification requirements and benefits conveyed; however, both provide the opportunity for increased collaboration with the agency to support development efforts. Japan's SAKIGAKE designation allows accelerated approval of breakthrough therapies, including gene therapies.¹⁸ Other regions (e.g., Brazil) are also beginning to address ways to provide much needed support and incentives for these innovative products.^{19,20} The progress to date to enhance access to mechanisms that can support expedited development is promising. However, much uncertainty still remains regarding some aspects of expedited pathways in the countries that utilize them. Increased clarity and some degree of convergence on certain components, such as the eligibility criteria for various types of expedited pathways, could facilitate global development.²¹

Lack of established regulatory frameworks for developing gene therapy in many countries

As mentioned previously, most regulators globally repurpose existing medicinal product policies and frameworks to meet the needs of gene therapy products.¹⁶ Many countries do not have the research and medical infrastructure necessary for the creation of regulatory frameworks that would support the timely and efficient introduction of gene therapies, leaving many patients without access to transformative treatment. The US, EU, and Japan have made significant

advances in developing regulatory frameworks for gene therapies. Other countries, such as Brazil and Canada, have also recently developed or proposed separate regulatory frameworks for the development of gene and cell therapies.^{19,20,22} Addressing the challenges to development in countries that are still in need of a regulatory path will require addressing infrastructural limitations to ultimately allow patient access to gene therapy in these countries. While this long-term goal is optimal, whether new frameworks are necessary, as opposed to leveraging established frameworks in other countries, is a point for discussion.

Additional challenges to global development

Challenges to gene therapy development in multiple countries also include sourcing and using quality raw materials to manufacture gene therapy products. Obtaining quality raw materials may be difficult due to factors including the need to use human and animal-derived materials, the biological complexity of the materials, variable lot-to-lot performance characteristics, and the use of research-use-only materials restricted from clinical use. Many materials used in manufacturing gene therapy products are from single sources, with corresponding challenges in logistics and import and export requirements when the raw materials used to manufacture gene therapy products are sourced outside of the country in which the final drug product might be used, as they often are. Import and export requirements for starting materials, clinical samples, and finished products can represent barriers to efficient gene therapy development.²³

RECOMMENDATIONS TO OVERCOME REGULATORY CHALLENGES

Foster regulatory convergence among countries with separate regulatory frameworks

Overcoming the challenges to global development of gene therapies will involve convergence of regulatory requirements and technical standards among countries with separate regulatory frameworks. For this discussion, it is important to highlight the distinction between “harmonization” and “convergence.” Harmonization is the development of shared technical guidelines to be utilized across participating authorities, while convergence involves the alignment over time of the regulatory requirements across individual countries or regions as a result of the gradual adoption of internationally recognized technical guidance documents, standards, and scientific principles.²⁴

Harmonization is typically the long-term goal for regulatory consistency across regions. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) is the predominant organization creating harmonized pharmaceutical guidelines. Currently, gene therapy is excluded from most of the existing ICH guidelines. However, development of a guideline for gene therapy products was endorsed by the ICH in June 2019, focused on pre-clinical biodistribution studies for gene therapies.²⁵ Development of ICH guidelines involves a slow and meticulous process, and thus ICH guidelines may not provide near-term help to the wave of gene therapies that are currently under development.

Convergence tends to be more rapid and less formal than the ICH process. One step toward encouraging greater regulatory convergence is the establishment of international standards in the field of gene therapy. While voluntary for sponsors to follow, standards provide guidance that could facilitate greater shared expectations by national regulatory authorities, especially if widely adopted by gene and cell therapy product developers. While standards development can also be a lengthy process, several entities are addressing this need in the gene and cell therapy space, which may assist in keeping pace with the rapid developments in the field. Several organizations, including the Standards Coordinating Body for Gene, Cell, and Regenerative Medicines and Cell-Based Drug Discovery (SCB), the National Institute of Standards Technology (NIST) within the US Department of Commerce, and the US Pharmacopeia (USP), are working to develop and advance standards to support gene therapy.

The call for action on regulatory convergence is growing stronger. Fostering global regulatory convergence for cell and gene therapies has been noted as a priority for FDA’s Center for Biological Evaluation and Research (CBER),²⁶ for the EMA,²⁷ and for the World Health Organization (WHO).²⁸ FDA CBER’s leadership has identified pre-clinical study requirements, environmental assessments, CMC information, and clinical outcomes as appropriate areas for increased global regulatory convergence.

Build on multi-stakeholder collaboration

Given the importance of streamlining requirements for multinational gene therapy development programs, ensuring similar regulatory paths and expectations would serve to incentivize and de-risk development. As such, regulators should continue to collaborate with several stakeholders such as industry, patients, physicians, academicians, and payers, to address common problems. The ASGCT is providing ongoing opportunities for establishing connections among multiple stakeholders globally. For example, the Society recently co-hosted a half-day virtual conference with the Brazilian Society of Cellular and Gene Therapy on advancing clinical development of gene therapies in Brazil, which drew academic researchers, industry attendees, clinicians, and regulators from Brazil.²⁹ Additionally, there is a need to establish gene and cell therapy-specific public-private partnerships to support the removal of barriers to the development of such therapies. The Innovative Medicines Initiative (IMI) in Europe, a public/private partnership with the goal of removing barriers to the development of innovative medicines, represents a model of such a multi-stakeholder collaboration.

Utilize work-sharing, reliance, and recognition

Experienced regions have many guidelines and could serve as a model for smaller agencies that are currently developing new frameworks. Efforts to facilitate product development globally can be significantly supported by leveraging certain regulatory and technical standards used in experienced regions.

Smaller agencies, however, also have an opportunity to leverage the work of larger agencies through reliance and work sharing. Work

sharing is a process by which National Regulatory Authorities (NRAs) of two or more jurisdictions share activities to accomplish a specific regulatory task, facilitating a more efficient review process. The WHO is facilitating good reliance practices through its draft working document on the topic published in August 2020.³⁰ According to the WHO, reliance is the act whereby the NRA in one jurisdiction may take into account and give significant weight to assessments performed by another NRA or trusted institution, or to any other authoritative information in reaching its own decision. In some cases, regulatory input from one jurisdiction could be used as a basis for action in another jurisdiction. A notable example is the Mutual Recognition Agreement (MRA) between the US and the EU, which allows health authority inspectors to rely upon information from inspections conducted within each other's borders. The MRA specifically excludes ATMPs from its scope. We highlight this as a missed opportunity in streamlining gene therapy development. A key recommendation is that advanced therapies be included under the framework of the MRA. The COVID-19 global pandemic, which has presented significant challenges for global health authority inspections, is a key example of why incorporating ATMPs in the MRA is critically important. Specifically, inclusion of ATMPs in the MRA may have provided a mechanism for health authorities to leverage inspections performed by NRAs given travel restrictions due to the COVID-19 pandemic.

Reliance and work-sharing approaches will facilitate timely access to safe, effective, and quality-assured medical products, potentially without the development of complex frameworks and the establishment of a large organization. These approaches may have particular value for gene therapies for which the new and complex nature of the products and the development programs will strain the existing infrastructure of smaller regulatory agencies. For example, approval of a gene therapy product by the FDA or EMA could form the basis for approval in other countries, leveraging the dossiers used to support initial approval. Countries could also partner with more advanced health authorities up front, with the goal of adopting the initial decision. To build on this concept, the WHO recently published a draft working document, which outlines these principles and provides an excellent discussion of principles and considerations.³¹ While many countries may seek to establish new regulatory frameworks to support gene therapy development, we would recommend a heightened focus on reliance to avoid delays in the introduction of safe and effective products to market. For regulators that do choose to create their own dedicated regulatory frameworks for gene therapies and other innovative products, inclusion of certain elements may facilitate timely development.

RECOMMENDATIONS FOR ELEMENTS TO INCLUDE IN DEDICATED FRAMEWORKS

Consider developing regulatory mechanisms for accelerated pathways and early engagement

In the past few years, regulators have been working on several initiatives to help developers provide patients with more expedient access to gene therapy products. Regulatory pathways in different countries have been adapted to address the need to facilitate and expedite the

overall development and review of products that address an unmet medical need in treating a serious or life-threatening condition. To enable early access to patients in need of these innovative medicines, regulators have implemented facilitated pathways. The approach has often been twofold with the use of either expedited or adaptive pathways.³²

Expedited pathways aim to shorten the development and/or review timelines for therapies that provide significant advantages over current treatments (or are the only treatment option) for serious diseases in order to get them to patients as expeditiously as possible. Expedited pathways include designation programs that offer mechanisms such as increased, earlier communication with regulators to facilitate streamlined development. Accelerated approval and adaptive licensing (such as conditional approval) make use of different evidentiary requirements, such as the use of surrogate endpoints and authorization based on nonconfirmatory evidence that needs to be confirmed after marketing.^{32,33} Priority review or accelerated assessment programs provide shortened review times for marketing authorization applications. These pathways are critical for ensuring that gene therapy products are available to patients as quickly as possible. We recommend appropriate application of these innovative pathways to ensure expedient development.

Such pathways continue to require evidence of safety and efficacy, in some cases facilitating examination of that evidence earlier in the development process. For example, the FDA's "rolling review" allows for submission of individual completed modules one at a time rather than all at once. "Real-time review," which has been utilized by the FDA's Real-Time Oncology Review pilot program, allows regulators to start the review of a module before the application is complete.³⁴ A consideration for regulators would be to allow for real-time review of CMC data for marketing authorization applications. Agencies might even consider a model whereby they could start reviewing sections of a module before the module is complete and allow for submission of pre-agreed CMC data during the review of the marketing application.

Allow for innovative clinical trial design

Gene therapies are often developed for rare diseases, and therefore large trials are not feasible. In addition, gene therapies often demonstrate early and compelling signals of clinical efficacy resulting in accelerated development programs. For example, the typical paradigm of clinical trial requirements is shifting for gene therapies. Consolidating the phase I, II, and III processes into phase I, phase II/III, and post-approval trials is becoming common. Given the rapid advances in this area, as well as the early efficacy data frequently obtained for these products, regulators are, and should be, more open to entertaining discussions about innovative clinical trial designs. For example, the FDA issued several guidance documents that address novel clinical trial designs.³⁵⁻³⁷

As many gene therapies currently under development target orphan diseases, the small patient populations may require consideration of alternative trial designs and statistical techniques that maximize

data from a small and potentially heterogeneous group of subjects, such as single-arm study design with historical control.³⁸ Because gene therapies may demonstrate safety and efficacy in early trial phases, accelerated approval using novel or surrogate endpoints may allow more expedient access to patients with serious or life-threatening conditions, with post-approval confirmation of clinical benefit based on endpoints that may take years to evaluate. Gene therapies frequently enable a more direct assessment of the treatment effect on the cause of disease, such as changes in protein levels, so they may be particularly amenable to assessment with surrogate endpoints.³⁹ Including flexibility in clinical trial design in new regulatory frameworks could contribute to the efficient development of gene therapies across the countries adopting such frameworks.

Use post-market confirmatory studies

Global health authorities should incorporate approaches to support expeditious approval of gene therapy products, leveraging post-market commitments to continue evaluation of uncertainties after market entry. As the FDA has previously noted, “We’re going to be looking at accelerated approval endpoints for earlier approval on questions of efficacy with more vigorous long-term follow-up.”⁴⁰ An important application of this concept would apply to the evaluation of questions regarding durability. To ensure that patients receive access to treatment in a timely fashion to address unmet needs, it is critical that long-term questions, such as durability, be assessed in the post-market setting. Doing so allows the opportunity to confirm durability of response and long-term safety, while providing treatment accessibility to patients with serious conditions.

The question of durability for gene therapy products can be addressed by collecting long-term data through disease registries. Because the safety and efficacy data available before the approval of a gene therapy product may be limited, regulators typically require patient follow-up and disease registries to build long-term efficacy and safety data supporting the product’s risk/benefit profile. Registry contributions to strengthen gene therapeutic evidence have been discussed in the literature.⁴¹

A wide variety of post-market study designs for ATMPs is described in a recent paper by Fritsche et al.⁴² The authors report that many ATMPs’ post-marketing trials adopt explanatory trial-design features that focus on answering hypotheses that are more suitable to pre-market trials. They therefore suggest that real-world data generated from registry-based pragmatic trials could better inform the use of gene therapies across diverse and global patient populations, as well as across additional stakeholders (regulators, clinicians, and payers).

Regulators can advise sponsors on effective use of registries. For example, the EMA recommends planning for registries early in a product’s development. The agency provides guidance on a series of measures. These include early risk detection, adverse event reporting, and product-specific monitoring, taking into account the need for tailored approaches.⁴³ As such, our recommendation is that product availability should not be delayed because of health authority interest

in addressing the long-term question of durability up front. We encourage regulators to leverage the long-term follow-up approach to address such questions in the post-approval setting.

CONCLUSIONS

Gene therapies offer new hope to patients who suffer from debilitating diseases. Regulatory frameworks will need to evolve to address the unique nature of gene therapies and keep pace with the science. In the last few years, much progress has been made to address global regulatory challenges in gene therapy. Further enhancements can overcome potential regulatory barriers to bring innovative, complex new treatments to patients in need around the world. As this novel and promising class of products continues to grow, regulatory frameworks will have a significant impact. Whether through dedicated frameworks, work sharing, or regulatory reliance, globally aligned regulatory pathways will be critical for the advancement of gene therapy development and commercialization globally.

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DECLARATION OF INTERESTS

D.D. is an employee of Biogen, Inc. A.N. is an employee of BioMarin Pharmaceuticals, Inc. K.W. is an employee of Pfizer, Inc. The remaining authors declare no competing interests. The content of this article represents the authors’ opinions and may not necessarily represent the views of their employers.

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