Title: Regional disparities in access to gene therapies in the European Union, United States, Japan, and China

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Abstract: Understanding the regional differences in approved gene therapies, clinical trial development, and regulatory frameworks is crucial for ensuring equitable access and addressing justice issues in advanced therapeutics. This review aimed to evaluate the differences between the US, EU, Japan, and China and offer policy recommendations to promote harmonization between these countries and regions. Gene therapy approvals show significant regional disparities, with the U.S. leading with 23 approved therapies, followed by the EU with 16. Few products are accessible worldwide reflecting challenges in obtaining cross-border approvals. Moreover, access is uneven within regions like the EU, with high-income countries having better accessibility. High costs and complex reimbursement processes exacerbate these issues, with some products being withdrawn from the market due to pricing disputes. Regulatory differences, such as differing data needs, further delay access in countries, like Japan, where gene therapy products are unavailable until years after a product is ready for approval. Clinical trial activity mirrors these disparities, with China's growing number of trials potentially reshaping the landscape. Harmonizing regulations across regions could streamline the approval process for therapies, making them more efficient and reducing disparities. Furthermore, key solutions include incentivizing cost reductions, adopting innovative payment models, and aligning evidence/reimbursement requirements.

Plain Language Summary:

What is this article about? This article looks at if and how patients can access new gene therapy products in the EU, US, Japan, and China. By looking at the availability of these therapeutics, upcoming clinical trials, and each region and country's process for approving these treatments, we hoped to better understand if patients in all of these areas are actually able to receive these life-saving treatments. Understanding if there are access problems and the extent of them is the first step to changing policies to make gene therapies more available for the patients who need them.

What were the results? There are many differing access issues between these four countries and regions that make gene therapies hard to reach for patients across the globe. First, more products are available faster in the EU and US with the US having the most products. Because each country or region has differing approval systems with differing evidence requirements for approvals, this often results in delays in product

approvals in areas, such as Japan, which often only approves products a few years after the EU and/or the US. However, China may be changing these dynamics since the country may have more clinical trials than both the US and EU.

What do the results of the study mean? These results show that there must be global policy changes to make these therapeutics available for patients. The best recommendation is to make approval processes for gene therapies more similar between countries and regions, so it is easier for manufacturers to make their therapy available to more patients.

Keywords: gene therapy; gene therapies; access; ELSI; ethical issues; clinical trials; regulatory systems; reimbursement

Article Highlights:

1. Introduction
    - Technological advances (e.g., CRISPR, lipid nanoparticles) and investment are increasing the potential safety and efficacy of gene therapies. However, access to gene therapies remains inequitable due to high costs, regulatory challenges, and complex manufacturing.
    - Ethical issues around access must be explored to guide infrastructure and policy solutions. Global differences in access are growing; availability in the U.S. and EU is better studied than in emerging regions like China and Japan.
    - Understanding regional access patterns is essential to promoting global equity and justice. Analyzing regulatory frameworks and market authorization processes helps identify barriers and propose harmonized solutions.
2. Unbalanced Gene Therapy Approvals
    - The number of gene therapies approved varies widely:
        - U.S.: 23; EU: 16; China: 17 (mostly domestic-only); Japan: 9
    - Most therapies are approved and available only in the country/region of development.
    - Very few therapies (e.g., Zolgensma) are available across all major regions.
    - Within the EU, product approval doesn't guarantee access across all member states due to cost and resource disparities.
    - Regional exclusivity limits global access and widens healthcare inequities.
    - Market availability is also threatened by high costs and pricing disputes (e.g., Glybera, Skysona, Zynteglo). EU has seen multiple gene therapies withdrawn due to failed reimbursement negotiations, not lack of efficacy.
3. Unequal Clinical Trials Development
    - Clinical trial activity correlates with potential future access:
        - U.S.: 964 active/recruiting trials; EU: 685; China: 659 (plus 459 of unknown status); Japan: 58
    - China is emerging as a major player, potentially rivaling the U.S. and EU.
    - Lack of clinical trials may delay future access to gene therapies in some regions.

- Presence of trials doesn't guarantee benefits for local populations, echoing concerns from traditional drug development.
- U.S.-based CROs conduct trials in low-income regions with little local benefit, a trend that may extend to gene therapy. Over-investment in rare disease therapies could divert healthcare resources from more widespread conditions.

4. Uneven Approval Timelines and Systems
   - Approval processes and regulatory classifications vary by country:
     - Japan favors conditional approvals with limited data.
     - U.S. uses designations like priority review and breakthrough therapy.
     - EU uses the PRIME program and defines gene therapies as ATMPs.
   - These differences lead to approval lags—therapies often reach EU or Japan a year or more after U.S. approval.
   - Delays stem from both regulatory timelines and company decisions about where to seek approval based on ROI.
   - Disjointed regulatory systems slow down global access to life-saving therapies.
5. Conclusion: United through Policy Harmonization
   - Lack of international policy harmonization hinders multi-region gene therapy approval.
   - Even the U.S. and EU struggle with alignment despite similar ethical concerns.
   - Harmonization could speed approval and access across regions while addressing clinical development gaps. However, cultural and ethical differences must be respected in convergence efforts.
   - Potential solutions include:
     - Incentivizing manufacturers to lower costs (e.g., manufacturing innovation).
     - Alternative payment models (e.g., rebates, value-based payments).
   - Large-scale policy change is needed to make gene therapies accessible and prevent further inequality in healthcare innovation.

1. Introduction

Gene therapies offer an innovative path for addressing rare and severe diseases, replacing time- and resource-intensive treatments with more efficient alternatives and enabling solutions for previously untreatable conditions. This new class of advanced therapeutics functions by altering a patient's genetic code by introducing new genes or inactivating disease-causing genes [1]. However, recent breakthroughs in biotechnology, such as CRISPR editing tools and lipid nanoparticle delivery systems, along with increased investment in research and manufacturing, are raising hopes that future gene therapies to reach the market will be safer and more effective for patients [2-3]. Yet, the benefits and therapeutic value of this new class of advanced therapeutics continue to be inequitably distributed across patient populations due to various factors, such as high cost per dose, lack of effective regulatory infrastructure, complex manufacturing needs, and more [4]. To broadly increase equity and patient access, it is vital to 1) better understand the many ethical intricacies of existing access disparities to 2) help policymakers and academics address these gaps through infrastructural and policy changes. It is important to note that understanding access and finding solutions to increase patient access to gene therapies is only one aspect of larger questions about these therapeutics' role in medicine. For instance, it does not address other ethical issues of gene therapies, such as the potential for overtreatment, the possibility of limited therapeutic benefit, and improper allocation of resources to gene therapy research [5].

As such, an important area of potential access concerns is the differences in accessibility and resource allocation of gene therapies between various global regions. While these therapeutics are more commonly available in high-income countries and regions, the nuances of access within these areas remain less well understood [6]. For instance, it is unclear how the US and the EU, two of the largest players in the gene therapy space, differ in terms of access to these treatments for patients. Though both regions have historically had the greatest number of approved therapeutics and been the first to approve many products in this class of therapeutics, other world regions have begun to catch up [7]. In recent years, countries such as Japan, and China, have seen an exponential boom in gene therapy clinical development with some of these countries beginning to rival the US and the EU's gene therapy advantage [8]. A more nuanced understanding of these different region-based trends in access is the first step to ensuring that patients across the globe have equitable access to these potentially life-saving treatments as well as more broadly answering the question of whether justice is being upheld in the current regulatory and policy ecosystem.

By critically evaluating various aspects of the clinical trials and market authorization processes in these countries, we gain further insights into whether current infrastructure and regulatory frameworks are sufficient in ensuring equitable access by providing a more concrete understanding of these equity and access challenges. Only by characterizing these global issues and differences is it possible to create solutions to increase access and move towards a world with greater international harmonization of advanced therapeutics.

Before continuing, it is important to acknowledge that access to gene therapies is influenced by a highly complex set of factors, including the high cost of development and manufacturing, strategic decisions by pharmaceutical companies, national regulatory frameworks, physician adoption, clinical indications, and the size of the target patient population. For instance, while differences in regulatory systems can contribute to delays in global approvals, decisions by pharmaceutical companies about whether to pursue market entry in a given country can be equally critical. However, the primary aim of this manuscript is to examine the role of regulatory systems specifically, as they represent an area more directly shaped by public policy intervention. Unlike the internal strategic decisions of private companies, regulatory pathways and incentive structures can be adjusted through governance and legislative reform. By focusing on this particular angle, the manuscript seeks to contribute meaningful insight toward shaping policy solutions that can improve access in a more systematic and equitable way.

2. Unbalanced Gene Therapy Approvals

[insert table 1 here]

The most basic way to characterize access to gene therapies is to analyze what therapeutics are available in each region. Table 1 draws information from the respective regulatory organizational webpages of the EU, US, and Japan regarding approved gene therapy products. According to the FDA, the US currently has 23 products available for patients, whereas, according to the EMA, the EU only has 16 products (Table 1). China has at least 17 products entirely made and are only available within the country [9]. Only one of China's products was produced outside the country, which is a variation of Zolgensma, one of the first and most globally available gene therapies. According to the PMDA, Japan follows with 9 approved gene therapy products, which are a mix of gene therapies generated by companies both inside and outside of Japan (Table 1).

When referring to Table 1, it is concerning that most regions, both in the West and East, have widely different product approvals, since most products appear to be produced and only approved within a region. For instance, Japan has created two gene therapies, Collatagene and Delytact, treating ischemia and glioma, respectively. However, these

products are only available on the Japanese market despite the potential benefits they could have for cardiac and cancer patients in other world regions. This is also true for China, which has numerous gene therapies tackling a wide variety of conditions but is only approved in the Chinese market. Similarly, most gene therapies developed in the US are not available in other regions—particularly in Japan, China, and even the EU. In fact, several US gene therapy products, such as Adstiladrin, Lyfgenia, and Elevidys aren't approved for patients in the EU, let alone in other regions of the world. The only gene therapy available across all 5 regions is Zolgensma. However, this is likely because it is one of the oldest gene therapies and has taken 6 years from when it was first approved in the US to be approved in other regions as well. Additionally, only 4 other gene therapies are available across at least 4 regions, except China. However, it is also important to note the geographic diversity of the EU. Just because a gene therapy product is approved throughout the EU, it does not mean that each member state must make it available within their country. Access to these treatments is frequently restricted to wealthier EU nations because of their high cost and complicated manufacturing procedures, excluding others and exacerbating the challenge of equitable healthcare access. As a result, most gene therapy products appear to be localized to the countries that created those therapies, thus severely restricting global access. This is concerning as it limits access to life-saving treatments by region, leaving patients in countries without strong manufacturing capacities for gene therapies or financial resources to pay for the therapies at a significant disadvantage.

However, the availability of products alone is not sufficient to ensure access due to manufacturers' growing movements toward removing gene therapy products from the market if it becomes too cumbersome for countries to navigate the reimbursement and pricing process [10]. This has been a long-standing issue since one of the first gene therapies available on the market, Glybera, was removed from all global markets in 2017 despite its clinical efficacy because of its high cost, which could not be justified with the lack of patient demand since it treats a very rare condition where only about 1 patient in a million suffers [1 - revisions]. This is especially a prevalent problem within the EU, which has already seen two gene therapy products, Skysona and Zynteglo, be removed from the market due to failed pricing negotiations rather than therapeutic efficacy. The EU has also seen similar product removals from the market with other advanced therapeutics, such as Provenge, a cell therapy treating prostate cancer for the same reason. If more companies refuse to negotiate prices with the EU or other regions, it could create significant access challenges, leaving patients unable to receive life-saving treatments due to regulatory and industry deadlocks. However, this lack of pricing agreement is only one aspect of a larger, systemic issue surrounding the pricing of gene therapies.

3. Unequal Clinical Trials Development

Because it appears that many gene therapies are often created within a region and approved in limited areas, the level of clinical trial development in a country or region offers a unique perspective on the future availability of therapeutics in that region. Multi-national clinical trial databases, such as clinicaltrials.gov and euclinicaltrials.eu, provide detailed information about active, registered clinical trials in each country. As of November 11th, 2024, the US is currently leading with 964 active or recruiting clinical studies for gene therapies and their various new iterations, including CAR-T therapies and CRISPR-based therapies. Next, the EU follows with 685 active or recruiting clinical trials (Table 2). However, China closely follows the US and EU with 659 active or recruiting clinical studies (Table 2). There are also 459 additional clinical studies of unknown status in China, making the exact number of active trials unclear but potentially even higher than in the US or EU (Table 2). Finally, Japan only has 58 active trials (Table 2).

[insert table 2 here]

Though this data cannot be used to conclusively make statements about a country's development, it still provides evidence of long-suspected changes in the gene therapy landscape. Particularly, clinical trial development doesn't just provide insight into the likelihood of products becoming available in a region but also shows whether a region even has sufficient infrastructure and resources to run clinical trials for gene therapies. For instance, the top players in this field may be changing as China appears to be rapidly growing as a large developer of gene therapies, especially compared to Japan which has less than 100 trials. Similarly, this could be an early indication that the EU, regionally, could be falling behind the US and potentially China since it has fewer trials that could translate into more concrete outcomes, such as approved therapeutics. As a result, in the status quo and long-term future of gene therapies, access may be limited if fewer clinical trials are occurring in these areas, delaying the introduction of new treatments and widening the gap between regions. Furthermore, the presence of clinical trials in a country or region does not guarantee that patients there will benefit, as global health research has historically faced disparities in benefit sharing [11]. This dynamic is particularly evident in the growing role of U.S.-based contract research organizations (CROs), which increasingly conduct trials in low-income countries to meet the rising demand for human subjects for many traditional therapeutics [12]. They often leveraging local regulatory flexibility while offering little assurance that participating populations will benefit from the resulting therapies [12]. Though this hasn't occurred specifically for gene therapies, it is a trend that could emerge as these therapies gain more attention. Though Africa is not a focus of this paper, it

nevertheless still means that these access disparities must be addressed from many angles to truly ensure fair access to gene therapies in Asia, EU, US, and Africa.

On the other hand, by allocating more resources toward gene therapies, it may still create an alternative accessibility issue. In most countries and regions, including the US and EU, resource availability for healthcare is not unlimited and thus must be adequately apportioned and prioritized. By focusing more resources on gene therapies that often only benefits a small patient population, it is a possibility that there would be fewer resources for diseases affecting larger groups of the population. As a result, policymakers and researchers alike must take care to prioritize effective utilization of resources for gene therapies as well as promote greater investment of gene therapies for broader disease areas. In fact, there are already many gene therapies in the clinical pipeline that are beginning to address diseases with larger patient populations, such as cardiovascular disease and certain forms of breast cancer and T1 diabetes [13-14].

4. Uneven Approval Timelines and Systems

Gene therapy access issues go beyond surface-level comparisons and are often embedded in more implicit structures, such as regulatory processes, which differ greatly across countries and regions. In fact, each country has its own distinct requirements for safety and efficacy, unique regulatory designations, and even definitions of the term gene therapy to approve a gene therapy product for market. In Japan, for instance, an analysis by Arato and Nomura in 2024 showed that regulatory authorities in the country allow for a greater number of single-arm trials for therapeutics generated nationally, even in cases where an randomized controlled trail (RCT) would have been feasible and where similar therapeutics created in the US or EU had required RCT over single-arm trials [15]. Notably, products such as HeartSheet and Stemirac were granted conditional approval despite limited clinical data and criticisms from parts of the scientific community regarding the strength of evidence [15]. These examples illustrate how Japan may be more lenient in the level of efficacy data required prior to granting market access, particularly when there is a perceived unmet medical need, highlighting a regulatory environment that prioritizes rapid access alongside ongoing post market surveillance [2 - revised]. Additionally, special designations for gene therapy approval in the US include priority review, accelerated approval, fast-track status, and breakthrough therapy designation. However, the EU has an entirely different set of programs, which include the Priority Medicines (PRIME) program, conditional approval, and accelerated assessment. In terms of definitions, the EU classifies gene therapies as a type of Advanced Therapy Medicinal Product (ATMP), while Japan categorizes them as Regenerative Medical Products (RMPs), which highlights how each country's distinct classification reflects broader differences and resulting differences in regulatory and

manufacturing requirements. For instance, a product considered a biologic requires different inspection processes and documentation expectations than a regenerative product.

These widespread differences in approval processes can be seen in the time it takes to get gene therapies approved in different regions. For instance, many gene therapies approved in the US can take up to another year before becoming available in the EU (Table 1). The delay is even longer when considering availability in Asian countries. For instance, gene therapies, like Luxturna and Kymriah, which have been available in the US and EU did not become available in Japan until recently. This lag is not solely due to regulatory timelines as pharmaceutical companies must also make strategic decisions about when and where to pursue approval based on financial resources, market potential, and anticipated return on investment. Though delays can originate from company decisions about when to seek approval, they are compounded by the varying length and complexity of regional regulatory processes that significantly influences decision-making regarding which region's approval processes to pursue. Nevertheless, this gap is increasingly of concern since it slows patient's ability to receive potentially life-saving treatments and populations to lose health during these delay periods.

5. United through Policy Harmonization

Despite each region's unique gene therapy ecosystem that contributes to differential access and access challenges, there is still great hope in being able to improve these issues for patients globally. The core source of these access issues stems from the lack of large-scale international harmonization of policies between countries because gene therapy ecosystems are highly localized to a region [16]. Even the US and EU have much need for convergence, despite efforts. As a result, it is difficult to get gene therapies approved in multiple regions when companies must navigate complex authorization processes, meet different evidence-generation needs, and negotiate various reimbursement models across regions. However, gene therapy ethical issues are often similar between regions since many issues stem from concerns of safety and efficacy. By converging the regulatory processes across regions, it could streamline the therapeutics approval process in multiple regions, allowing patients to receive many more life-saving treatments at a faster pace as well. It also addressed additional issues, such as with clinical development, since gene therapies could more easily be approved, especially in regions that may not have the strongest clinical development of gene therapies.

Though greater international convergence takes an important step towards increasing access for patients who need potentially life-saving treatments, especially in

markets outside of Europe, it is still not the entire solution. Particularly, when converging policies between regions that may have cultural and, thus, ethical differences, policymakers must work to ensure that these policies respect the different values between the regions. Gene therapy costs have been rising exponentially each year, with some treatments estimated to cost upwards of 3 million USD, which poses further barriers on patients' ability to access these treatments [17]. Not only that, but in many cases, the cost of gene therapies is determined by varying reimbursement systems and price control systems, especially within the EU, making the final cost of gene therapies highly variable and uncertain. The solution requires policymakers to either incentivize manufacturers to lower the cost of gene therapies, such as by streamlining manufacturing, or invest in innovative alternative payment models, including rebate systems and value-based payment. Additionally, addressing only access issues for gene therapies does not resolve other ethical concerns with gene therapies, such as whether there is long-term benefit to gene therapies or whether there are certain conditions that shouldn't be treated with gene therapies.

To advance truly equitable global access to cell and gene therapies, it is essential to recognize the economic underpinnings of the current pharmaceutical innovation system, especially when considering alternative payment models as is suggested above. While the primary focus has been on the inequities of global gene therapy access, these disparities are also rooted in the economic structure of pharmaceutical innovation, especially for advanced products like gene therapies. The current system encourages investment in risky and expensive drug development by allowing companies to sell new medicines, especially for rare conditions, at higher prices for a limited time [3 - revised]. This is meant to help cover not just the cost of the successful drugs, but also the many that fail during development. As such, therapies that are often labeled as "high-cost" are not necessarily expensive to manufacture. This is especially true in the United States, which contributes a large share of the world's spending on gene therapy clinical trials research and development (Table 2) [3 - revised].

As a result, large-scale reform must go beyond harmonizing regulatory pathways to effectively begin solving these access concerns. It must include harmonizing a global pricing model based on differential pricing, where higher-income countries and populations bear a greater share of global development costs, through the construction of a politically viable and globally coordinated system. Such a system would include tiered pricing based on income and ability to pay, international subsidy mechanisms for the poorest countries, and possibly the pooling of purchasing power across regions to negotiate fair access terms. Importantly, value assessment frameworks must also evolve to account for the unique attributes of cell and gene therapies, including their potential for long-term cure and their impact on health system sustainability [4 - revised].

Though each country has its own unique access concerns, ultimately, large-scale change is required to both ensure access for patients now as well as prevent these barriers from becoming even larger issues. Without further change, there will be little reason to continue investing in innovative gene therapies if they are simply inaccessible to the people who truly need them.

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