Regulatory Matters

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Editorial

Gene therapy is a groundbreaking and fast-growing area in pharmaceutical advancement, providing promising treatments that potentially cure genetic disorders by directly altering the genes within a patient's cells. With increasing knowledge in the nature of genetic disorders and the help of advances in genetic engineering and biotechnology, gene therapy has evolved rapidly. Its path to clinical application is complex, often involving significant technical challenges and ethical considerations. Due to this complexity, regulatory guidance and frameworks are crucial in governing the design, testing, and application of gene therapy in human trials, ensuring that these therapies are safe and effective before making them available in the clinical setting.

In this article, by emphasising the rigorous regulatory frameworks that govern this area, Arunon Sivananthan offers an overview of the emergence of gene therapies, detailing the guidance provided by the US FDA and EMA and some stringent measures required to ensure the safety and efficacy of gene therapy products. I hope readers will gain value.

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Navigating the regulatory landscape of gene therapy

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Introduction

Gene therapy is at the forefront of the pharmaceutical industry, offering the potential to treat and even cure various genetic disorders. By modifying genes within a person's cells, gene therapy targets the underlying causes of disease by either replacing faulty genes, deactivating malfunctioning ones, or introducing new genes to fight illness. This groundbreaking approach promises to transform treatment for conditions once considered incurable.

The first gene therapy approved in Europe was Glybera (alipogene tiparvovec), approved by the European Commission in 2012 to treat lipoprotein lipase deficiency, a rare disorder causing pancreatitis and other complications due to impaired fat breakdown.[1,2] Despite its pioneering nature, Glybera was not approved in the US, highlighting the varied regulatory requirements across regions.[3,4]

Following Glybera, other gene therapies have gained regulatory approval. Examples include Kymriah (tisagenlecleucel) and Yescarta (axicabtagene ciloleucel), chimeric antigen receptor (CAR)-T cell therapies that were approved in 2017 for certain blood cancers.[1,2,5] These therapies demonstrate the growing scope of gene-editing technologies in medicine.

Regulatory frameworks are essential for safeguarding the safety and efficacy of gene therapies. Regulatory authorities like the US FDA and EMA rigorously assess the risks and benefits of these therapies.[6,7] This includes assessments of nonclinical testing in laboratories and animals, phased clinical trials to evaluate safety and efficacy in humans, and post-marketing surveillance to track long-term outcomes. These steps help protect patients from risks like unintended genetic changes or long-term adverse effects, ensuring gene therapies meet stringent quality and safety standards.[8]

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Key aspects of this collaboration include:

- Parallel Scientific Advice programme from the US FDA and EMA, providing consistent guidance in new medicine development;[9]
- Coordinated approval timelines, reflecting joint efforts in review and approval of new medicine;[10]
- Joint inspections of manufacturing facilities to ensure compliance with both US and EU regulations;[10,11]
- Shared pharmacovigilance data for safety and efficacy monitoring across regions, for example for COVID-19 vaccines during the pandemic.[12]

As the landscape of gene-editing technologies continues to evolve, ongoing dialogue and cooperation between regulators, researchers, and industry stake- holders will be critical in overcoming challenges and unlocking the full potential of gene therapies for patients worldwide.

Overview of US FDA and EMA gene therapy guidance

US FDA gene therapy guidance

The US FDA's guidance on human gene therapy emphasises a structured approach to nonclinical testing, manufacturing, and clinical trial design.[13,14]

In terms of nonclinical recommendations, the US FDA stresses the importance of conducting robust studies to evaluate the safety and potential efficacy of gene therapies. These studies include both in vitro and in vivo experiments using appropriate models to assess biodistribution, persistence, and potential toxicity. Such research helps predict how the gene therapy product will behave in the human body and identify any safety concerns before clinical trials commence.

Regarding manufacturing recommendations, the US FDA underscores a thorough characterisation of the gene therapy product, including vector design, production, and purification processes. The US FDA provides specific requirements for the Chemistry, Manufacturing, and Control (CMC) sections in Investigational New Drug (IND) applications for gene therapies.[6] These requirements include detailed descriptions of the gene therapy product's composition, manufacturing process, quality control measures, and stability data. Manufacturers must demonstrate control over critical manufacturing steps to ensure the identity, quality, purity, and potency of the product throughout its shelf life. Also, manufacturers must demonstrate rigorous testing and documentation of raw materials and starting materials to prevent contamination and ensure consistency. Stringent control of materials is emphasised to safeguard the quality of the gene therapy product.

As for all clinical trials, a clinical trial design for gene therapies should include an appropriate patient population, well-evidenced treatment and dosing regime, appropriate safety and efficacy endpoints, as well as efficient on-trial and long-term safety monitoring.[14,15] Specifically, the unique challenges posed by rare diseases, such as small patient populations, require carefully designed clinical trials. The US FDA suggests using adaptive trial designs and incorporating natural history data to support efficacy assessments.[13] Adaptive trials allow for modifications based on interim data without compromising the trial's integrity, and clear criteria for patient selection and monitoring are crucial to accurately assess the therapy's safety and efficacy.

EMA gene therapy guidance

The EMA's quality guidelines outline detailed requirements for controlling the vector, transgene, and final product, focusing on ensuring the product is safe, effective, and reproducible, with consistent quality throughout its lifecycle.[7] The nonclinical guidelines, similar to those of the US FDA, require extensive studies to assess the safety and biodistribution of gene therapy products. These studies should be conducted in relevant animal models and include evaluations of genotoxicity, immunogenicity, and tumorigenicity to identify potential safety concerns before human trials. For clinical guidelines, the EMA recommends clinical trial designs that adequately demonstrate the efficacy and safety of gene therapy products. Innovative trial designs, patient registries, and real-world evidence are encouraged to support marketing authorisation applications, helping streamline the approval process while ensuring high standards of efficacy and safety.

Understanding where and how the gene therapy vector distributes throughout the body is crucial to ensure the therapy targets the intended tissues without affecting others.

To facilitate the development of innovative therapies, the EMA offers regulatory flexibility. This includes providing scientific advice, engaging in early dialogue with developers, and employing adaptive pathways to expedite the approval process while maintaining high standards of safety and efficacy.[7,16] The EMA advocates a risk-based approach for developing and evaluating advanced therapy medicinal products (ATMPs), including gene therapies.[17] This approach involves identifying and prioritising risks based on their potential impact on patient safety and product efficacy. By focusing on the most significant risks, developers can allocate resources more effectively to address them.

Interestingly, the EMA also released a guideline on environmental risk assessment (ERA) for ATMPs containing genetically modified organisms (GMOs). The ERA is a required component of the marketing authorisation application to evaluate the potential environmental impact of such medicinal products. This includes evaluating the likelihood of gene transfer to other organisms, the persistence of GMO in the environment, and any potential risks to human health and biodiversity.[18]

Expedited review and approval of promising therapies for unmet medical needs

Both the US FDA and EMA offer streamlined processes to fast-track the review and approval of gene therapies aimed at addressing unmet medical needs, allowing innovative treatments to reach patients sooner.[19,20]

The US FDA has several expedited programmes suited to gene therapies. The Regenerative Medicine Advanced Therapy designation, specifically designed for regenerative medicine therapies like gene therapies, provides intensive guidance, rolling reviews, and early US FDA engagement to discuss potential surrogate endpoints that could support accelerated approval. In addition, the US FDA's Breakthrough Therapy designation and Fast Track designation are applicable to gene therapies that demonstrate substantial improvement over existing treatments or address serious conditions with unmet medical needs.[19]

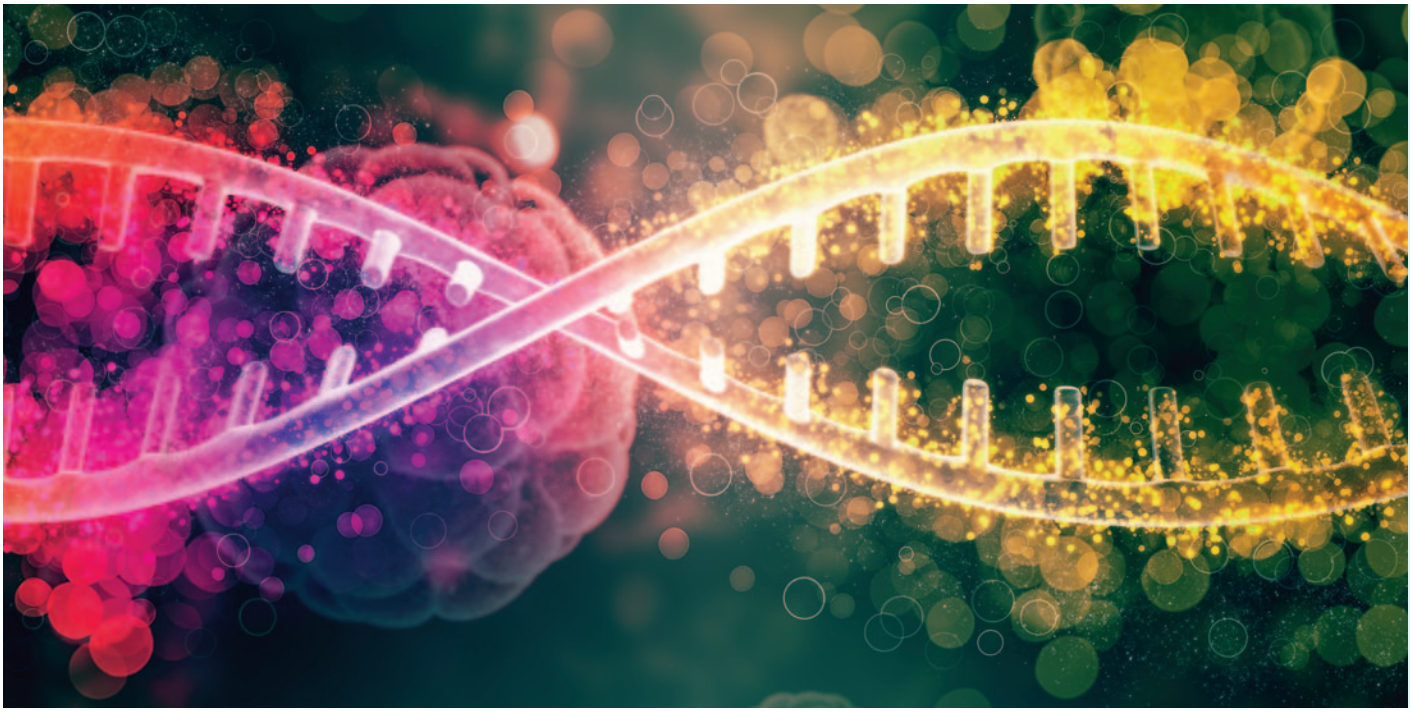
In tandem with these efforts, the EMA launched the PRIority MEdicines (PRIME) scheme, which supports the development of medicines for conditions with unmet medical needs, particularly where no alternative treatments are available or where the medicines offer significant benefits over existing therapies by offering early and enhanced scientific and regulatory support. Between 2016 and 2021, among the medicines approved under the PRIME scheme, seven were ATMPs, including CAR-T-cell therapies.[20]

Furthermore, the collaborative question-and-answer guidance document, issued by both the EMA and US FDA, underlines the joint consensus on crucial areas such as control strategy, process validation, stability, and Good Manufacturing Practice considerations in addressing the challenges of expedited medicine development under the PRIME and Breakthrough Therapies schemes.[21] This collaboration reflects the ongoing efforts of both regulatory authorities to maintain rigorous standards while facilitating the timely availability of life-saving therapies.

Measures for stricter gene therapy studies

Comprehensive nonclinical studies to address biodistribution and potential off-target effects

The primary challenge in nonclinical studies of gene therapy is ensuring that the therapy products are thoroughly assessed for their biodistribution and potential off-target effects. Understanding where and how the gene therapy vector distributes throughout the body is crucial to ensure the therapy targets the intended tissues without affecting others.[14,15,22]



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The US FDA recommends extensive biodistribution studies to map the distribution of gene therapy vectors across the body.[14,15] These studies are designed to identify both target and non-target tissues, assess potential off-target effects, and ensure that the therapy reaches the intended sites. Evaluations of potential off-target effects include the risk of insertional mutagenesis, particularly in gonadal tissues, to prevent germline integration. These assessments are crucial for predicting human responses and minimising unintended genetic modifications.

The EMA's guideline on the quality of gene therapy medicinal products outlines nonclinical biodistribution study requirements, emphasising the importance of understanding the distribution, persistence, and clearance of gene therapy products in both target and non-target tissues.[7,22] Like the US FDA, the EMA stresses the need to evaluate off-target effects and insertional mutagenesis risks, particularly in germline cells. Thorough testing ensures the safety of gene therapy vectors, addressing concerns about unintended genetic alterations.

Vector design and manufacturing controls to ensure product consistency and safety

Another significant challenge is ensuring product consistency and safety through robust vector design and manufacturing controls. Variability in vector design or production can lead to inconsistencies in therapy outcomes.[7,15]

The US FDA recommends designing vectors with high specificity and minimal off-target effects.[6,15] This involves using tissue-specific promoters and enhancers to ensure targeted gene expression. In addition, the US FDA outlines stringent manufacturing controls in the CMC section of IND applications. This includes detailed descriptions of the vector design, production process, purification methods, and quality control measures to ensure product consistency and safety.

Similarly, the EMA emphasises the importance of stringent quality control measures in the manufacturing process to ensure the purity, potency, and stability of gene therapy products.[7] The EMA also advises developers to use vectors with well-characterised safety profiles and employ advanced techniques to minimise the risk of off-target effects and insertional mutagenesis, thus ensuring that the gene therapy remains effective and safe throughout its lifecycle.

> Sponsors are required to prepare a long-term follow-up study protocol to monitor patients for delayed adverse effects.

Detailed requirements for clinical trial conduct

To ensure robust data collection and analysis, the US FDA requires comprehensive clinical trial protocols, particularly for gene therapy trials. These protocols must specify primary and secondary endpoints, detail patient selection criteria, and describe the trial design's ability to adequately address safety and efficacy questions.[14] The US FDA particularly underscores the importance of selecting clinically meaningful endpoints that focus on improving patients' reported outcomes.[14,23] For first-in-human trials of gene-editing products, the US FDA recommends enrolling patients who have no other feasible or warranted treatment options. These patients should also be at a less advanced or a moderate disease state due to the potential risks of the products in those with severe disease.

The protocols should also outline the methods for monitoring and reporting adverse events throughout the trial. A safety monitoring strategy should be defined. For example the trial should have an appropriate toxicity grading system and a toxicity management plan in place, especially for monitoring off-target editing and any side effects of on-target editing. Additionally, recognising the potential for delayed adverse effects induced by gene therapies, the US FDA recommends long-term follow-up (LTFU) studies of up to 15 years to monitor patients for delayed adverse effects.[14,15,23] Sponsors are required to prepare an LTFU study protocol that includes detailed elements such as visit schedules, sampling plans, monitoring tests, and maintenance of case histories. Moreover, sponsors must report serious adverse events and unexpected suspected adverse reactions, as well as submit periodic safety reports to the US FDA.[15,23]

The EMA also emphasises comprehensive

clinical trial protocols for gene therapy products, with a particular focus on patient follow-up and the monitoring of adverse effects with tailored approach considering the specific characteristics of the gene therapy products. For example, the EMA recommends LTFU for products involving viral vectors with a potential for chromosomal integration or latency at pre-treatment, 3-, 6-, and 12-months post-treatment for at least 5 years, followed by annual assessments until data do not indicate any risk to be followed. Recommendations are also provided for viral vectors without a potential for chromosomal integration or latency, plasmids, and non-viral vectors.[24]

Moreover, the EMA requires a detailed risk management plan to be submitted in a clinical trial application or a marketing authorisation application. This plan must encompass the pre-market and post-market surveillance strategies to ensure continuous monitoring of the product's long-term safety and efficacy. Any changes to the risk profile of the product, as observed during the clinical trial or post-marketing phase, should prompt a revision of the follow-up plan.[24,25]

Patients must fully understand the risks, benefits, and experimental nature of gene therapy trials, including available alternatives. Particularly, patients should be asked to provide informed consent to LTFU, which must describe the purpose of the follow-up, the expected duration, necessary assessments or procedures, and any adverse reactions that may be related to the gene therapy product under investigation.[14,15]

Conclusions

Navigating the regulatory landscape of gene therapy is a complex yet crucial endeavour for the safe and effective development of gene therapy products. The guidance provided by the US FDA and EMA are pivotal in ensuring that these innovative therapies meet the highest standards of safety and efficacy. By emphasising rigorous nonclinical studies, detailed clinical trial protocols, and long-term patient monitoring, these regulatory authorities address the scientific and ethical challenges associated with gene therapy. Their comprehensive oversight helps mitigate potential risks, such as off-target and delayed adverse effects, ensuring favourable benefit-risk profile of gene therapies in treating genetic diseases.

The US FDA and EMA are committed to fostering innovation in gene therapy while upholding stringent safety standards. Their collaborative efforts to harmonise regulatory requirements and streamline approval processes are crucial in facilitating development and ensuring patient access to cutting-edge treatments. As gene therapy rapidly evolves, regulatory frameworks must adapt accordingly to reflect new knowledge and technologies. This may involve integrating real-world evidence, leveraging advanced computational models for safety assessments, and fostering greater collaboration between regulators, researchers, and industry stakeholders. Future oversight may involve adopting more flexible and adaptive pathways to address the unique challenges presented by emerging gene-editing technologies. By remaining agile and forward-thinking, regulatory frameworks can continue to support the safe and timely development of innovative gene therapies.

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Disclosures and conflicts of interest

The author declares no conflicts of interest.

References

1. Horgan D, Metspalu A, Ouillade MC, et al. Propelling healthcare with advanced therapy medicinal products: a policy discussion. Biomed Hub. 2020;5;5(3): 1–23. doi:10.1159/000511678
2. Iglesias-Lopez C, Agustí A, Vallano A, et al. Current landscape of clinical development and approval of advanced therapies: Mol Ther Methods Clin Dev. 2021;23:606–18. doi:10.1016/j.omtm.2021.11.003
3. Boráň T, Menezes-Ferreira M, Reischl I, et al. Clinical development and commercialization of advanced therapy medicinal products in the European Union: how are the product pipeline and regulatory framework evolving? Hum Gene Ther Clin Dev. 2017;28(3):126–35. doi:10.1089/humc.2016.193
4. Gruber K. Europe gives gene therapy the green light. Lancet. 2012;380(9855):e10. doi:10.1016/S0140-6736(12)61992-8
5. Petraitytė G, Preikšaitienė E, Mikštienė V. Genome editing in medicine: tools and challenges. Acta Med Litu. 2021;28(2):205–19. doi:10.15388/Amed.2021.28.2.8
6. US FDA. Chemistry, manufacturing, and control (CMC) information for human gene therapy Investigational New Drug applications (INDs): Guidance for industry. January 2020 [cited 2024 Sep 18]. Available from: https://downloads.regulations.gov/FDA-2024-D-1244-0004/content.pdf.
7. EMA. Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products. 22 March 2018 [cited 2024 Sep 18]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-quality-non-clinical-clinical-aspects-gene-therapy-medicinal-products_en.pdf
8. Salazar-Fontana LI. A regulatory risk-based approach to ATMP/CGT development: integrating scientific challenges with current regulatory expectations. Front Med (Lausanne). 2022;9:855100. doi:10.3389/fmed.2022.855100
9. EMA. General principles EMA-FDA Parallel Scientific Advice (human medicinal products). July 2021 [cited 2024 Sep 18]. Available from: https://www.ema.europa.eu/system/files/documents/other/psa_general_principles_document-en.pdf.
10. EMA. Report on the Pilot EMA-FDA GCP Initiative. 18 July 2011 [cited 2024 Sep 18]. Available from: https://www.ema.europa.eu/en/documents/report/report-pilot-european-medicines-agency-food-and-drug-administration-good-clinical-practice-initiative_en.pdf.
11. EMA. EU and US reach a milestone in mutual recognition of inspections of medicines manufacturers. 12 July 2019 [cited 2024 Sep 18]. Available from: https://www.ema.europa.eu/en/news/eu-and-us-reach-milestone-mutual-recognition-inspections-medicines-manufacturers
12. EMA. Report on pharmacovigilance task: From EU Member States and the European Medicines Agency (EMA) 2019–2022. 2023 [cited 2024 Sep 18]. Available from: https://www.ema.europa.eu/en/documents/report/report-pharmacovigilance-tasks-eu-member-states-and-european-medicines-agency-ema-2019-2022_en.pdf.
13. US FDA. Human gene therapy for rare diseases: Guidance for industry. January

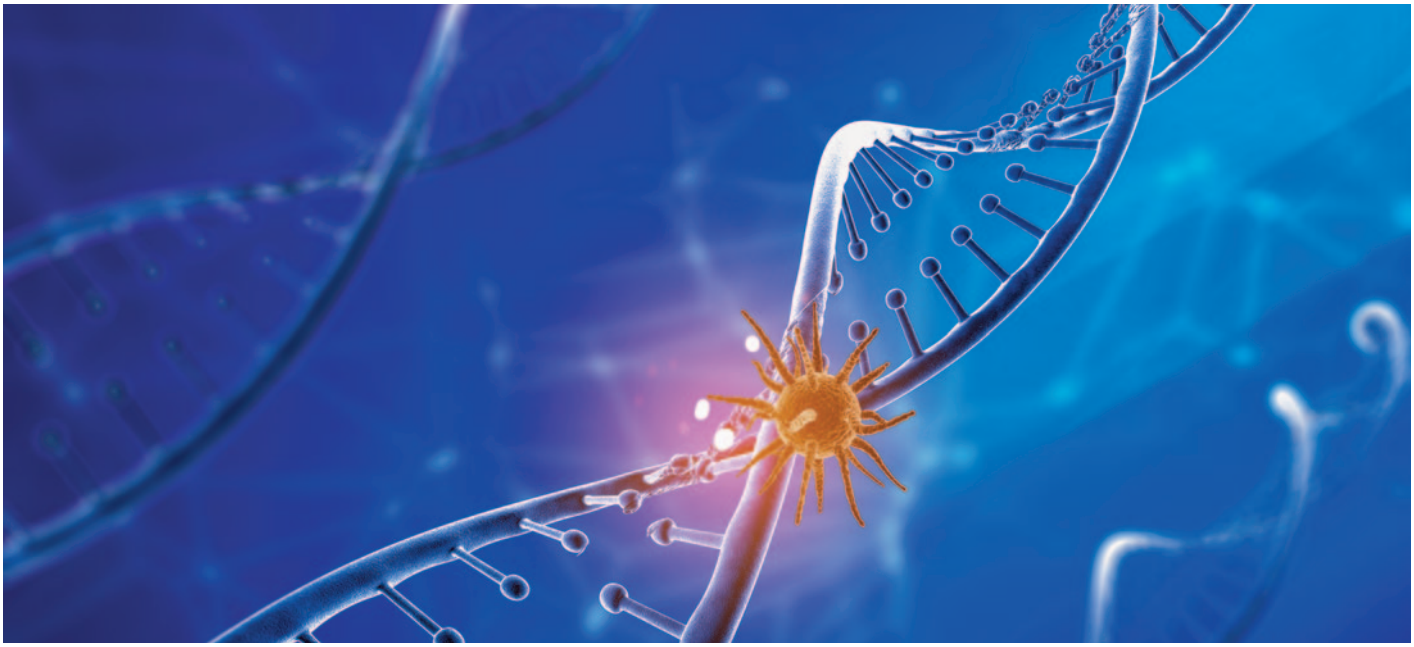

Photo: freepik

2020 [cited 2024 Sep 18]. Available from: https://www.fda.gov/media/113807/download.

14. US FDA. Human gene therapy products incorporating human genome editing: Guidance for industry. January 2024 [cited 2024 Sep 22]. Available from: https://www.fda.gov/media/156894/download
15. US FDA. Long term follow-up after administration of human gene therapy products: Guidance for industry. January 2020 [cited 2024 Sep 22]. Available from: https://www.fda.gov/media/113768/download
16. EMA. European Medicines Agency Guidance for applicants seeking access to PRIME scheme. 29 September 2023 [cited 2024 Sep 22]. Available from: https://www.ema.europa.eu/en/documents/other/european-medicines-agency-guidance-applicants-seeking-access-prime-scheme_en.pdf
17. EMA. Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to advanced therapy medicinal products. 11 February 2013 [cited 2024 Sep 22]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-risk-based-approach-according-annex-i-part-iv-directive-2001/83/ec-applied-advanced-therapy-medicinal-products_en.pdf.
18. EMA. Guideline on environmental risk assessments for medicinal products consisting of, or containing, genetically modified organisms. 11 December 2006 [cited 2024 Sep 22]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-environmental-risk-assessments-medicinal-products-consisting-or-containing-genetically-modified-organisms-gmos_en.pdf
19. US FDA. Expedited programs for regenerative medicine therapies for serious conditions. February 2019 [cited 2024 Sep 22]. Available from: https://www.fda.gov/media/120267/download
20. EMA. PRIME enables earlier availability of life-changing medicines. 03 March 2022 [cited 2024 Sep 22]. Available from: https://www.ema.europa.eu/en/news/prime-enables-earlier-availability-life-changing-medicines
21. EMA and FDA. EMA–FDA joint Q&As on quality and GMP aspects of PRIME/Breakthrough Therapy applications. 04 December 2023 [cited 2024 Sep 22]. Available from: https://www.fda.gov/media/174736/download?attachment
22. EMA. Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells. 12 November 2020 [cited 2024 Sep 22]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-quality-non-clinical-and-clinical-aspects-medicinal-products-containing-genetically-modified-cells-revision-1_en.pdf
23. US FDA. Providing clinical evidence of effectiveness for human drug and biological products. May 1998 [cited 2024 Sep 22]. Available from: https://www.fda.gov/files/drugs/published/Providing-Clinical-Evidence-of-Effectiveness-for-Human-Drug-and-Biological-Products.pdf.
24. EMA. Guideline on follow-up of patients administered with gene therapy medicinal products. 22 October 2009 [cited 2024 Sep 22]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-follow-patients-administered-gene-therapy-medicinal-products_en.pdf.
25. EMA. Guideline on safety and efficacy follow-up – risk management of advanced therapy medicinal products. 20 November 2008 [cited 2024 Sep 22]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-safety-efficacy-follow-risk-management-advanced-therapy-medicinal-products_en.pdf

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