Molecular Therapy
Methods & Clinical Development
Review

Impact of genetically modified organism requirements on gene therapy development in the EU, Japan, and the US

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Advanced therapies are emerging as an important class of medicinal products; among these, gene therapies are advancing at an exceptional rate. However, one of the major challenges for gene therapies relates to the additional regulatory requirements for genetically modified organisms. In this paper, we provide an overview of the regulatory requirements for genetically modified organisms in the European Union, Japan, and the United States. We share our experience in managing these requirements and their impact on the adeno-associated virus gene therapies that are under development at Pfizer. Specifically, we discuss the relative complexity of the approval process and the impact of risk assessment expectations on the clinical development of genetically modified organisms. We also compare the regulatory processes and timelines of various regions based on our experience with adeno-associated viral vectors. Finally, we propose that genetically modified organisms, for which pathogenicity and replication competency are well controlled, should be regulated solely under medicinal product regulations and be exempt from additional requirements for genetically modified organisms. Even if an exemption is not implemented, it should still be possible to significantly reduce the sponsor and agency burden by simplifying and harmonizing documentation and data requirements as well as timelines for applications for genetically modified organisms.

INTRODUCTION

Advanced therapies are becoming an important class of medicinal products and include a diverse range of therapies, including cellular therapies, gene therapies, and tissue-engineered therapies.[1–3] Dr. Peter Marks of the U.S. Food and Drug Administration (FDA) described the growth in 2019 as "the leading edge of a wave of these new therapies."[4] Currently, gene therapy products are being studied in over 3,000 ongoing clinical trials, over 100 of which are Phase 3 trials.[5]

Despite exciting growth, the development of gene therapies is challenging. One significant challenge relates to the additional regulatory requirements of genetically modified organisms (GMOs). Recombinant viral vectors, such as adeno-associated virus (AAV) vectors used for *in vivo* gene therapy, are categorized as GMOs by the European Union (EU).[6–8] In the EU, the legislation on GMOs was primarily intended to protect food consumers and the environment. However, it also applies to medicinal products containing or consisting of GMOs, which must comply with either EU Directive 2001/18/EC[9] or EU Directive 2009/41/EC,[10] resulting in a complex regulatory environment. The situation is further complicated by the differences in the transposition of these EU directives into national law in the EU member states, resulting in significant variability among EU countries, which is challenging for a sponsor to navigate when executing a pan-EU clinical trial.[6–8]

In Japan, recombinant viral vectors, including AAV vectors, are categorized as living modified organisms, as defined in the Cartagena Protocol on Biosafety (hereafter, referred to as GMOs for consistency).[11] Based on this Protocol, the Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the use of GMOs (aka the Cartagena Act) was established in Japan in 2003.[12] Because the Cartagena Act covers a wide range of areas, from crops to manufacturing of alcoholic beverages, it is under the jurisdiction of six different ministries, including the Ministry of Health, Labour and Welfare (MHLW), the organization responsible for regulating medicinal products. Among other demands, the MHLW requires an applicant to assess the impact on biological diversity, which includes the completion of an environmental risk assessment (ERA).[13] It has been recognized that the review process can be challenging and time consuming not only by the pharmaceutical industry but also by the Japanese government.[14,15]

In the United States (US), gene therapies involving AAV vectors are subject only to general ERA requirements that are applicable to all drug products.[16] A GMO risk assessment is generally not required before a clinical trial in the US, because the FDA believes that, in

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most cases, a clinical study using a GMO will not significantly affect the environment because clinical trials are closely monitored and are limited to a designated study group.[17]

In the EU and Japan, where the requirements for GMO risk assessment must be met before initiating clinical trials, the regulatory process can create significant delays for starting a clinical trial.[14,18,19] Therefore, for product developers planning to conduct multi-regional clinical trials (MRCTs), it is critically important to consider the time required for both the preparation of the required documents and for the review of both clinical trial applications (CTA) and GMO submissions in each target country when planning development strategies.

This paper aims to describe the landscape for assessing environmental risks for medicinal products containing or consisting of GMOs in the EU, Japan, and the US. We compared the regulatory processes and timelines of various regions based on our experience with AAV vector products. Finally, we propose tangible solutions and the next steps that will help address the challenging regulatory environment related to GMOs and enable the future development of these potentially transformational therapies.

ERA REQUIREMENTS IN THE EU, JAPAN, AND THE US

EU requirements

In the EU, recombinant viruses are categorized as GMOs and must comply with either Directive 2001/18/EC on deliberate release into the environment[9] or Directive 2009/41/EC on the contained use of GMOs.[10] Directive 2001/18/EC builds on the Cartagena Protocol on Biosafety,[20] an international agreement on biosafety enacted under the Convention on Biological Diversity.[21] However, Directives 2001/18/EC and 2009/41/EC were transposed into the national laws in the 27 EU member states in different manners and are subject to diverse interpretations, resulting in a complex regulatory environment.[6–8] Furthermore, because these requirements were primarily designed for agricultural purposes, the information requested is often not easily applied to the development of medicinal products.

In general, the core GMO dossier, in accordance with Directive 2001/18/EC (prior to October 2019), is comprised of the Annex II "Principles for the Environmental Risk Assessment" (referred to as ERA), the Annex IIIA "Information required in notifications concerning releases of GMOs other than higher plants" (referred to as Annex IIIA),[10] and the summary notification information format (SNIF).[22] Annex IIIA requires detailed technical information such as characterization of the vector including modifications, method of GMO release, impact of the release on the environment including flora, fauna, and soil, as well as details on monitoring, control, and emergency response plans if the GMO is released. The ERA serves as a basis for identifying the need for a detailed risk assessment of the GMO release into the environment, justification for the assigned risk level, and implementation of risk mitigation strategies. Although not mandatory, clinical shedding data or a monitoring plan are expected to be provided in Annex IIIA. Finally, the SNIF summarizes key points covered in Annex IIIA and the ERA for public disclosure.[23]

In an attempt to address the interplay between the GMO and the medicine legislation and to reduce discrepancies across the EU with regard to the application of GMO legislation, the European Commission (EC) has collaborated with competent national authorities to produce a Good Practice Document, a question-and-answer document, and a repository of national regulatory requirements in October 2019.[24] In addition, recognizing that the information required in Annex IIIA and ERA is not relevant or specific to medicinal products, the EC introduced three new forms on their website.[24] Of the three forms, the "Common Application Form for investigational medicinal products that contain or consist of AAV vectors" is applicable for *in vivo* gene therapies containing AAVs. This new form, revised in December 2020, requires information relevant to medicinal products, including the "Biodistribution and Shedding" section, and incorporates the ERA as a section, effectively combining the old ERA and Annex IIIA into one form. However, not all member states have adopted this new form. Furthermore, each member state still requires additional supportive documentation,[25] some of which is needed in the local language, adding further complexity to the submission.[19]

In addition to documentation differences, national agencies have variable review timelines, differing languages, and differing views on the classification of products (deliberate or contained use).[7,8,19,25] A further complexity in some member states is that the competent authority reviewing the GMO and CTA may be the same (e.g., Germany, Italy, and Sweden), while in other member states, it is different (e.g., France, Spain, and Belgium).[25] A report by the Alliance for Regenerative Medicine published in October 2019 highlighted that these burdensome requirements have made Europe less competitive in attracting new advanced-therapy medicinal product (ATMP) clinical trials.[26] Although the framework for clinical trials in the EU changed with the implementation of the Clinical Trial Regulation in early 2022,[27] unfortunately, it offers no prospect of resolution, because national GMO applications are still mandatory. Therefore, additional solutions are still needed. The EC and industry have recognized that the clinical development of GMOs is slowed by the current regulatory framework governing GMOs.[19,28,29] The recent decision to temporarily exempt coronavirus disease 2019 (COVID-19) treatments from GMO requirements[28,29] was made to "accelerate the authorization and availability of successful vaccines against COVID-19."[29] The topic of permanent exemption is part of the ongoing discussion on the EC's pharmaceutical strategy.[30]

Japan requirements

In Japan, recombinant viruses are categorized as GMOs based on the Cartagena Protocol on Biosafety and are controlled according to the Cartagena Act.[12] The Cartagena Act is under the jurisdiction of six ministries. For human medicinal products such as vaccines and gene therapies containing GMOs, both the MHLW and the Ministry of Environment (MOE) are responsible for GMO oversight. In contrast, only the MHLW has approval authority for medicinal products, including gene therapies containing GMOs, under the Pharmaceutical and Medical Device Act.[31]

Regulation under the Cartagena Act is divided into two categories: one for Type 1 Use Regulations (similar to the EU deliberate release, Directive 2001/18/EC[9]) and the other for Type 2 Use Regulations (similar to the EU contained use, Directive 2009/41/EC[10]).[32] Use of GMOs for purposes of patient treatment in a clinical setting corresponds to Type 1 Use, and GMOs used for manufacturing purposes corresponds to Type 2 Use. For each type of usage, companies must submit the core documents per the regulatory notifications issued jointly by the six ministries mentioned above.[33,34] The core documents that are formally required are the Type 1 Use Regulation Form, the Biological Diversity Impact Assessment Form, and its appendices. These documents, except the appendices, are published in both Japanese and English on the website maintained by the MOE.[35,36] The submission should include additional details on gene therapy as specified in the MHLW notification.[13] The Type 1 Use Regulation Form describes how to handle the GMO based on the result of the applicant's assessment (see Table S1), and it must be approved before initiation of the first clinical trial in Japan.[37] Unlike in the EU, in Japan, once the application is reviewed and approved by both the MHLW and the MOE, a subsequent review is not required for each clinical trial protocol.

The purpose of a biological diversity impact assessment for Type 1 Use is to evaluate the potential adverse effects on biological diversity caused by the release of GMOs into the environment and to assess the need for appropriate management of relevant risks. The Pharmaceuticals and Medical Devices Agency (PMDA) is responsible for the preliminary review of the assessment dossier prepared by the applicant, and there are several features of PMDA review. First, PMDA requires a wide range of information on clinical and non-clinical, and chemistry, manufacturing, and controls (CMC) per their guidance.[38,39] Although these documents provide guidance on what information is required, it often takes a considerable amount of effort in back-and-forth discussions to determine the PMDA expectations. Additionally, as CMC and non-clinical consultations with the PMDA are mandatory before initiating a clinical trial for gene therapy,[40] multiple dossiers are required, and some of the information required is duplicative. Second, after the PMDA completes the preliminary review, the applicant must submit a formal application to both the MHLW and the MOE, which adds six months to the process.[37]

In addition to the long timelines, in our experience with these submissions, Japan has intensive data and information requirements for its submissions. For example, detailed CMC information is specifically required in Japan, which is generally not required during the GMO evaluation in the EU.[38,39] This includes detailed information about the GMO manufacturing process, specifications for the control of replication-competent viruses, and the results of a homology search to demonstrate that the donor nucleic acid of the GMO has no possible harmful sequences. Another requirement is related to viral-vector-shedding data in humans. The MHLW notification states that human shedding data are important in evaluating the possibility of horizontal transmission of nucleic acids.[13] Therefore, the PMDA asks the applicant to provide human shedding data at the time of the Cartagena review[38,39] and to specify the need for special patient management.[41,42] If shedding data cannot be provided to the PMDA at the time of the Cartagena review, more stringent shedding control and patient management, such as hospitalization, tend to be required, especially with novel viral vectors other than AAV, where the PMDA lacks extensive experience and is therefore adopting a conservative approach. Furthermore, unless the shedding profile in humans is known and agreed upon with the PMDA at the time of the Cartagena review, the applicant must commit to collecting shedding samples from Japanese patients in the initial trial conducted in Japan.[41,42] Given that this discussion with the PMDA takes place more than a year before clinical trial initiation, a detailed protocol (with information such as the exact type of shedding samples and patient management procedures) is usually not finalized, creating a significant challenge for applicants.

US requirements

In the US, the Code of Federal Regulations Title 21 Part 25 (21 CFR Part 25) requires an ERA for the approval of any medical products, including gene therapies.[16] Unlike the requirements in the EU and Japan, an ERA is not required at the start of clinical trials for investigational new drugs, except under special conditions. The main reason for this is that the FDA considers it unlikely that novel products will have a significant impact on the environment because products are used in a very limited number of individuals and carefully monitored in the clinical trial setting; therefore, investigational products typically qualify for a categorical exclusion from the ERA requirement during clinical development.[16,17] The 21 CFR Part 25 and FDA guidance provide additional information on when a categorical exclusion is applicable and also what information is needed for an environmental assessment in a submission of a biologics license application.[16,17] The FDA does require viral-vector-shedding data to be collected during clinical trials but emphasizes horizontal transmission, not environmental risk.[43]

Differences in ERA regulations and shedding assessments between the EU, Japan, and the US

The regulations for the ERA and viral shedding studies for recombinant viral vectors in the EU, Japan, and the US were evaluated and compared using various guidelines found on the official websites of the FDA, European Medicines Agency (EMA), EC, MHLW, and International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). Our findings are summarized in Table 1 (see Table S2 for further details). Unfortunately, there are no harmonized guidelines for ERAs and viral shedding. On the basis of Table 1, we developed a schematic chart describing the differences in the requirements for the ERA and vector-shedding studies and the timing of data submissions to authorities in the EU, Japan, and the US (Figures 1 and 2). In Japan, submission of an ERA is not required at the time of a new drug application for marketing authorization, whereas in both the EU and the US, an ERA must be included in the marketing authorization application/biologics license application.[17,45–47]

Table 1. Summary of the major regulations and guidelines for the environmental risk assessment or vector-shedding studies required by the FDA, EU, MHLW regulatory authorities, and the ICH

Region	ICH region	EU		JP		US	
Issuer	ICH	EMA	The European Parliament and the Council of the European Union	MHLW (and five other ministries)	MHLW	FDA	
Relevant document	ICH considerations: General principles to address virus and vector shedding[44]	Guideline on scientific requirements for the ERA of gene therapy medicinal products[45]	EU directive on the deliberate release[9] and EU directive on the contained use of GMOs[10]	Cartagena Act (Type 1 use and Type 2 use for medicinal products containing GMOs)[12]	Points to consider in ERA for approval of the Type 1 use for medicinal products containing GMOs[13]	Design and analysis of shedding studies for gene therapy and oncolytic products[43]	Determining the need for and content of ERA for gene therapies, etc.[17]
Year of issue	2009	2008	2001/2009	2003	2007	2015	2015
Positioning of each document	ICH considerations	EMA guideline based on EU Directive 2001/18/EC	EU directive	Japan local act	MHLW notification based on the Cartagena Act	FDA Guidance for Industry	FDA Guidance for Industry
Description of ERA for GMOs	NO	YES	YES	YES	YES	NO	YES
Description of requirements for vector shedding	YES	NO	NO	NO	YES	YES	NO
Description of timing of vector shedding studies	NO	YES	NO	NO	NO	YES	NO
Description of timing of submission of shedding data or ERA data	NO	YES	YES	NO	YES (for ERA)/NO (for shedding data)	YES	YES

ICH, International Council for Harmonization of the Technical Requirements for Pharmaceuticals for Human Use; EU, European Union; JP, Japan; US, United States; EMA, European Medicines Agency; MHLW, Ministry of Health, Labour and Welfare; FDA, US Food and Drug Administration; ERA, environmental risk assessment; GMO, genetically modified organism.

VOLUME OF DOSSIER, VOLUME OF QUERIES, AND REVIEW TIMELINE FOR GMO REVIEW FOR EACH COUNTRY

To visualize the challenges for GMO reviews in the EU and Japan, we compared the data required for GMO reviews, the number of queries received, and the overall timeline for approval in different countries for three of Pfizer's AAV-based gene therapy investigational compounds entering Phase 3 clinical trials.

Data were collected between January 2019 and December 2021 using an internal Pfizer archive and platform; thus, any application undergoing review at the time of data cut-off was noted as pending. Microsoft Excel was used for the data analysis.

Variable number of documents submitted and total page count for each country

The averages for the number of documents submitted and the total number of pages in the GMO dossier in the seven EU member states and Japan are summarized in Table 2. In European countries, the number of documents to be submitted varies from two to a maximum of 15. Here, we discuss the three countries with the highest number of requested documents and highest page count: Belgium, France, and Spain. All three countries require additional supporting documents as part of the GMO dossier. For example, a GMO submission in Belgium, France, and Spain requires the study protocol. In addition, Spain and France also need the protocol synopsis in the local language. In Spain, the investigational product manual is critical to the submission, whereas Belgian authorities require the investigator's brochure (IB) and the informed consent form (ICF), if available at the time of submission. These supporting documents can easily add more than 200 pages to the GMO dossier. These additional requirements are the root cause of the large GMO dossier sizes in the top three EU countries. In Japan, only three core GMO dossiers were required for regulatory review, and the average total page count was the third lowest among all the other countries.

Difference in volume of queries between Japan and the EU

The average number of queries received for the GMO applications in each country is shown in Figure 3. Japanese authorities generated a significantly higher number of queries than their EU counterparts. In Japan, as stated in the section "Japan requirements," a large

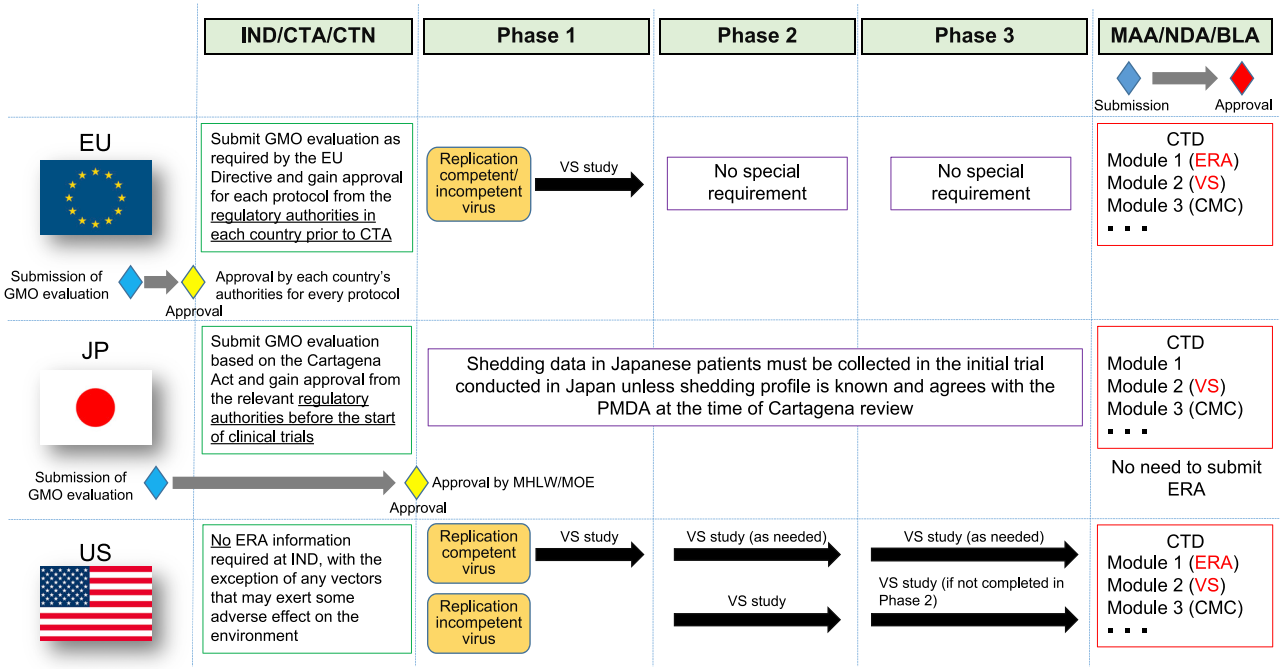

Figure 1. Differences in the timing of environmental risk assessments and vector-shedding studies as regulated by the EU, Japan, and the US

IND, investigational new drug; CTA, clinical trial application; CTN, clinical trial notification; MAA, marketing authorization application; NDA, new drug application; BLA, biologics license application; EU, European Union; GMO, genetically modified organism; VS, vector shedding; ERA, environment risk assessment; CMC, chemistry, manufacturing, and controls; JP, Japan; MHLW, Ministry of Health, Labour and Welfare; MOE, Ministry of the Environment; US, United States.

number of PMDA questions centered around CMC and human viral shedding (including the method of quantitative PCR measurement for human samples). In comparison, the number of queries from the GMO-reviewing authorities in the EU was generally low, ranging from 0 to 13. The queries received in EU countries can be grouped into three main categories: administrative queries (~30% of queries), queries on GMO handling (e.g., biohazardous waste disposal, ~40% of queries), and scientific/technical queries (~30% of queries). Importantly, it should be noted that none of the GMO-reviewing authorities in the EU commented on any of the supporting documents such as the study protocol, IB, or ICF in any of our submissions. Queries have instead focused on key GMO dossier contents, such as the Common Application Form, SNIF, or national GMO-specific application forms in each country.

Difference in review timelines between Japan and the EU

The average review timelines for GMO reviews for each country are presented in Figure 4. In our experience, the time and resources needed to go through the GMO approval process in Japan were considerably higher than those in the EU countries we examined. In the EU countries with large GMO dossiers, such as Belgium, France, and Spain, the average review period was more than 100 days. In the other four EU countries, with smaller GMO dossiers, the review period was fewer than 100 days, with the exception of Germany, which had a period of more than 200 days. Generally, the GMO review timelines for Pfizer investigational compounds in the EU were comparable to those of other industry sponsors, including smaller pharmaceutical companies,[48] suggesting that the trends observed in our survey results may be applicable to other applicants regardless of company size.

CONCLUSIONS AND PERSPECTIVES

The GMO regulations were largely developed out of environmental concerns regarding GMOs for agricultural use. Although well intended, the application of GMO regulations to medicinal products has created extreme variability in the processes needed to address national requirements and undue complexity by not being designed with medicinal products in mind. The World Health Organization's "Good Regulatory Practice Guidance" outlines key principles for regulation, which includes a requirement for proportionality: "Regulation should be created only when necessary and should be adequate for the aim and not excessive" and "The content and form of regulation should be appropriate to both the issue being addressed and the risk it poses."[49] On both these counts, the EU and Japanese GMO requirements are sub-optimal. For example, many companies have chosen to avoid development in the EU[19,50] and/or Japan because of the additional regulatory burden imposed by the GMO requirements. Furthermore, thousands of patients have been treated for decades, and there have been significant advances in our understanding of the science underlying gene therapies. Therefore, GMO requirements impose a significant and arguably unnecessary regulatory burden on the global development of gene therapies. As such, many of the most

Before initiation of the clinical trial

Region	EU		JP	US
International treaty	N/A	Cartagena Protocol on Biosafety		N/A
Local act	EU Directives 2009/41/E (contained use)	EU Directives 2001/18/EC (deliberate release)	Cartagena Act (Type 1/ Type 2 use regulations)	The Code of Federal Regulations Title 21 Part 25 (21 CFR Part 25)
Objective	Overall evaluation of GMO, including ERA		Assessment of the impact of GMO on biological diversity	ERA
Subject to regulation	GMO		GMO	Human drugs and biologics, including GTMP
Review authority	Review authorities in each member state		PMDA (for pre-review) MHLW/MOE (for review and approval)	FDA
Scope	ERA and impact on untreated individuals (human shedding data are NOT required[a])		ERA and impact on untreated individuals (human shedding data are required[b])	ERA (only in special cases, such as highly novel vectors)

a: If shedding data for humans are available, they should be provided. If no shedding data for humans are available, theoretical description of potential for shedding from nonclinical shedding data should be provided.
b: Evaluation is required per the MHLW notification

Clinical trials

At the time of application for marketing authorization (MAA, NDA, and BLA)

Region	EU	JP	US
International treaty	N/A	N/A	N/A
Local act/ Guideline	Guideline on Environmental Risk Assessments for medicinal products containing, or consisting of GMOs	Pharmaceutical and Medical Device Act	The Code of Federal Regulations Title 21 Part 25 (21 CFR Part 25)
Objective	Review for approval of ATMP	Review for approval of Regenerative Medicine (including gene therapy)	Review for approval of GTMP
Subject to regulation	ATMP	Regenerative Medicine	Human drugs and biologics, including GTMP
Review authority	EMA and EC	PMDA (for review) MHLW (for approval)	FDA
Scope	ERA and impact on untreated individuals (human shedding data are required)	Impact on untreated individuals (human shedding data are required)	ERA and impact on untreated individuals (human shedding data are required)

Figure 2. Assessment of environmental risk assessment and shedding of GMO in the EU, Japan, and the US and their timing
EC, European Commission; GTMP, Gene Therapy Medicinal Products; PMDA, Pharmaceuticals and Medical Devices Agency; FDA, US Food and Drug Administration; MAA, marketing authorization application; ATMP, advanced therapy medicinal product; EMA, European Medicines Agency.

promising therapies in the market are not uniformly available across the EU, Japan, and the US. To date, only one *in vivo* gene therapy has been approved in all three regions.

We believe that the long-term goal in both the EU and Japan should be to consolidate national oversight under medicinal-product regulations and exempt medicinal products from additional GMO requirements. The pathogenicity and replication competency of GMOs are very well controlled, and the results of thousands of clinical trials over the past 25 years clearly show that the environmental risks associated with gene therapy are negligible.[51] Recently, a white paper was endorsed in the EU by three major trade associations, calling for an exemption of GMO requirements for medicinal products such as gene therapies.[19,50] This white paper lays out the rationale for why independent GMO requirements for medicinal products are overly burdensome and that appropriate GMO oversight can be achieved through existing regulatory frameworks for medicinal products. The white paper describes that a proof of principle for this proposal was demonstrated recently when the EC granted an exemption from GMO requirements for COVID-19 vaccines,[28,29] which seemed to have a major positive impact on the time required for vaccine development.[19]

Table 2. The average number of documents submitted and the total number of pages in the GMO dossier for Pfizer AAV investigational compounds

Country	Number of investigational compounds participated	Number of documents submitted (±SD)	Average of total pages for GMO application (±SD)
Belgium	2	14.0 (±1.4)	343.0 (±62.2)
France	3	13.0 (±3.5)	266.5 (±68.8)
Germany	3	4.3 (±0.6)	96.3 (±31.6)
Greece	2	3.0 (±0)	122.5 (±0.7)
Italy	2	2.0 (±0)	65.0 (±2.8)
Japan	3	3.0 (±0)	72.0 (±9.7)
Spain	3	12.7 (±1.5)	313.0 (±14.8)
Sweden	2	4.0 (±0)	123.5 (±0.7)

Each value represents the average number of documents and total number of pages for GMO dossiers submitted for Pfizer investigational compounds undergoing GMO approval. Data are presented as mean ± SD.
AAV, adeno-associated virus.

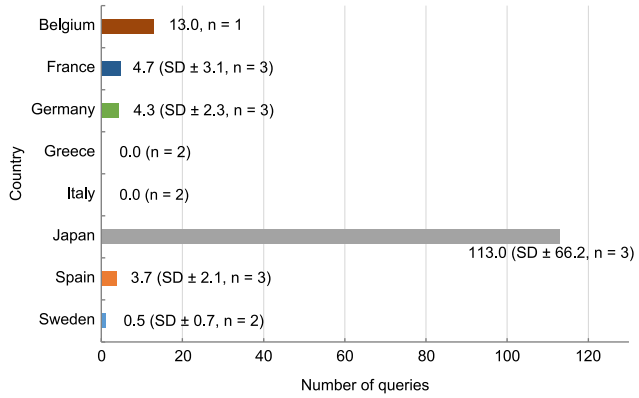

Figure 3. Average GMO queries received per country for Pfizer AAV investigational compounds
Each value was calculated by taking the average number of queries sent by competent authorities. Data (n ≥ 2) are presented as mean ± SD. The countries in which GMO applications are being developed have been noted. AAV, adeno-associated virus.

Although legislative change is neither quick nor easy, the expected benefits to patients in pursuing this change will be significant. Meanwhile, we are encouraged by the interim measures taken by regulators to improve product development within the current legal constructs. We are aware that the EC and the EMA are continuing to improve the GMO process. For example, as noted earlier, the EC developed Common Application Forms for gene therapy GMO applications that were implemented in some, but not all, member states.[24]

We also acknowledge the improvement in Japan. In response to comments that the review of the Cartagena process was complicated and time consuming, the PMDA established consultation schemes for the Cartagena Act in 2019.[52,53] Additionally, in 2019, mock-ups of the Type 1 Use Regulation Form for AAV,[41] herpes simplex viruses, and adenoviruses,[42] and in 2021, a mock-up of the Biological Diversity Impact Assessment Form for AAV were created,[39] which significantly increased the understanding of the information required for the application. Furthermore, in 2021, the MHLW changed the timing of approval for the Type 1 Application from before submission of the first clinical trial protocol application to before the initiation of the first clinical trial in Japan.[37] However, the GMO process still needs nearly a year to obtain approval, which adds considerable time and complexity to the start of gene therapy clinical trials in Japan.

Therefore, despite positive changes, there remains a significant amount that can be done to improve existing processes. In our experience, there are three key challenges imposed by the GMO requirements, and each is a potential area for improvement:

- Documentation: The number, type, and length of documentation required vary widely and are largely duplicative with the information included in medicinal-product dossiers.
- Data: There is great disparity in the kinds of data needed and the point at which data are needed during the development of a GMO product.
- Timelines: The time required to gain regulatory approval for GMO utilization can be significant and prohibitive for a country's inclusion in a MRCT.

One specific example of a potential area where improvement in the process and international convergence of requirements would be welcome is vector shedding. Discrepancies between the timing of documentation and data requirements for vector shedding, as described in Figure 1, create significant global development challenges. Aligned recommendations regarding the purpose, scope, timing, and execution of shedding studies would greatly facilitate global development. For example, we propose that the impact of horizontal transmission through shedding on untreated individuals should be separated from the ERA and be evaluated together with the medicinal product itself from the viewpoint of product safety.

Given the growing trend of simultaneous global drug development, excessive GMO requirements may prevent the inclusion of these countries in global studies, resulting in prolonged development timelines and delays in the availability of advanced therapies for diseases with unmet medical needs. Conversely, failure to consider these GMO requirements may also delay therapeutic development and increase the time taken to reach patients. Thus, it is important to maximize country participation in MRCTs without delay, and it is equally important to create a feasible development plan that includes an evaluation of the regulatory differences between target regions.

Beyond the EU, Japan, and the US, other country regulators may seek to introduce new GMO legislation or guidelines and can sometimes replicate the approach taken in developed markets as the model to follow. In this paper, we have shown that there are shortcomings in

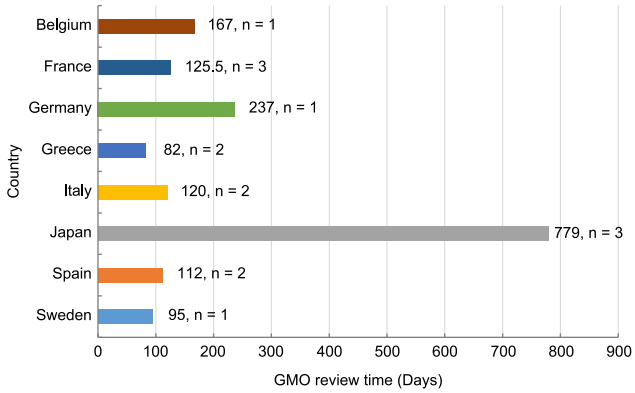

Figure 4. Average GMO review timeline per country for Pfizer AAV investigational compounds

Each value was calculated by taking the mean duration (days) from submission to approval across Pfizer investigational compounds that underwent GMO approval. The countries in which GMO applications are being developed have been noted.

the approaches taken in the EU and Japan related to the regulation of GMOs, which delays the execution of clinical trials and ultimately impedes patient access. Therefore, we would urge regulators in other regions aiming to introduce initial guidance or regulations on GMO assessment to follow the US FDA approach (of granting a categorical exclusion to investigational products from the need for an ERA at the time of initiation of clinical trials) and have medical product reviewers address GMO aspects within the regulatory review of the application.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.omtm.2022.05.012.

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AUTHOR CONTRIBUTIONS

Conceptualization: G.T., S.H., N.S., J.M., T.F., and K.W.; Data curation, S.H. and T.F.; Formal analysis, S.H. and T.F.; Visualization, G.T. S.H., and T.F.; Writing – original draft, G.T.; Writing – Review and Editing, G.T., S.H., N.S., J.M., T.F., and K.W.

DECLARATION OF INTERESTS

G.T., S.H., N.S., J.M., and T.F. are Pfizer employees. K.W. was employed at Pfizer during the writing of this manuscript, but is currently employed at LEXEO Therapeutics. The content of this article represents the authors' opinions and may not necessarily represent their employers' views.

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