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REVIEW ARTICLES

Regulatory Aspects of Vaccines

Sevda ŞENEL[*°], M. Kürşat DERİCİ[**], Burcu DEVRİM[***]

Regulatory Aspects of Vaccines

SUMMARY

In order to get a marketing authorisation, a vaccine product must fullfill the national/international requriements for efficiency, safety and quality. Due to its complex structure, the manufacture, control and regulation of a vaccine requires special expertise and procedures when compared to that of a small molecule drug. In this paper, the registration procedures of vaccines in different countries including Turkey, European Union, USA and the countries covered by the World Health Organization (WHO) will be reviewed and the regulatory requirements and related guidelines are summarised.

Key Words: *Vaccines, Regulatory, Marketing authorisation, Turkish Medicines and Medical Devices Agency (TMMDA), European Medicines Agency (EMA), Food and Drug Administration (FDA), World Health Organization*

Aşılarda Yasal Düzenlemeler

ÖZ

Bir aşı ürününün ruhsat alarak piyasaya çıkabilmesi için ulusal ve/veya uluslararası resmi kılavuzlara uygun etkinlik, güvenlilik ve kaliteye sahip olması gerekmektedir. Küçük moleküle sahip bir etkin madde ile karşılaştırıldığında, karmaşık yapısı nedeniyle aşı için üretim, kontrol ve yasal düzenlemeler özel uzmanlık ve prosedürler gerektirmektedir. Bu derlemede, aşıların Türkiye'de, Avrupa Birliğinde, ABD'de ve Dünya Sağlık Örgütü (DSÖ)'nin kapsamındaki ülkelerde ruhsatlandırılma süreçleri verilecek, ve bu süreçte takip edilmesi gereken yasal düzenlemeler ve ilgili kılavuzlar özetlenecektir.

Anahtar kelimeler: *Aşılar, Yasal düzenlemeler, Ruhsatlandırma, Türkiye İlaç ve Tıbbi Cihaz Kurumu (TİTC K), Avrupa İlaç Ajansı (EMA), Gıda ve İlaç Dairesi (FDA), Dünya Sağlık Örgütü (DSÖ)*

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[*] ORCID: 0000-0002-1467-3471, Hacettepe University, Faculty of Pharmacy, Department of Pharmaceutical Technology, 06100-Ankara, Turkey,
[**] ORCID: 0000-0002-8260-7492, Kırıkkale University, Faculty of Medicine, Department of Medical Pharmacology, 71450, Yahşihan-Kırıkkale, Turkey,
[***] ORCID: 0000-0002-9238-259X, Ankara University, Faculty of Pharmacy, Department of Pharmaceutical Technology, 06100 Tandoğan-Ankara, Turkey,

[°]Corresponding Author: Sevda ŞENEL
Phone: +90 312 310 12 41, E-mail: ssenel@hacettepe.edu.tr

INTRODUCTION

Immunization provides significant and highly cost-effective improvements to human health, particularly to that of children. Hundreds of millions of doses of vaccine are used every year; and their quality, safety and efficacy determine the success of national vaccine programs to control vaccine-preventable diseases. Regulatory issues are involved in every aspect of vaccine development, manufacturing, and marketing approval. The assessment, licensure, control, and surveillance of vaccine products are major challenges for regulatory authorities. To obtain a license (or marketing authorization), manufacturers must produce a vaccine by an approved procedure, in approved facilities, and by an approved staff. International standardization has been established to ensure the quality of vaccines as well as the equivalence between different producers. Requirements for vaccine licensure vary in different countries and regions. In the United States, procedures are generated by the Center for Biologics Evaluation and Research (CBER) at the U.S. Food and Drug Administration (FDA). In European Union (EU), the marketing authorization can be obtained either by Central Authorization through European Medicines Agency (EMA) or National Authorization through National Regulatory Authorities (NRAs). If a company wishes to request marketing authorization in several EU Member States for a medicine that is outside the scope of the centralized procedure, it may use the national authorization routes, including the mutual-recognition procedure or decentralized procedure. The World Health Organization (WHO) prequalification (PQ) is also possible to provide vaccines for use in low-in come countries. In this chapter, the regulatory aspects in different regions of the world will be reviewed in regard to safety, quality and efficacy of the human vaccines, and comparative overview of the guidelines will be presented.

LICENSING OF VACCINES IN THE EUROPEAN UNION

Before a vaccine can be marketed in the EU, a marketing authorization (MA) is needed. The vaccines are authorized and monitored by the EMA, which is responsible for the scientific evaluation, supervision and safety monitoring of medicines in the EU. EMA grants the MA after an evaluation of the risk-benefit ratio of the vaccine product based on a dossier, which presents quality, safety and efficacy properties of the product.

The European Commission and EMA work with the WHO on a range of issues, including vaccines intended for markets outside the EU (medicines reviewed under EMA's so-called 'Article 58 procedure', which will be described in more detail in coming sections).

EMA brings together scientific experts from across Europe by working closely with the national regulatory authorities in EU Member States, in a partnership known as the European Medicines Regulatory System, which is based on a network of around 50 regulatory authorities from the 31 EEA countries (28 EU Member States plus Iceland, Liechtenstein and Norway), the European Commission (EC) and EMA (The European Regulatory System for Medicines, 2016). The Committee for Medicinal Products for Human Use (CHMP) is the EMA's committee responsible for human medicines as well as vaccines. The CHMP determine whether the medicine meets the necessary quality, safety and efficacy requirements and that it has a positive risk-benefit balance. The CHMP establishes a number of working parties, which are composed of members selected from the list of European experts maintained by the Agency, and have expertise in a particular scientific field. The Vaccines Working Party (VWP) was established to provide recommendations to the CHMP on all matters relating directly or indirectly to vaccines. For veterinary vaccines, The Committee for Medicinal Products for Veterinary Use (CVMP) is responsible. VWP works in cooperation with the European Directorate for the Quality of Medicines (EDQM). The Scientific Advisory Group on Vaccines (SAG-V), composed of independent European experts selected according to their specific expertise is convened at the request of the CHMP to provide independent recommendations on scientific or technical matters relating to vaccines under evaluation by the CHMP, or on any other scientific issue relevant to the work of the CHMP that relates to this area (Committee for Medicinal Products for Human Use, 2004).

Vaccines are needed to be considered differently than the chemical pharmaceuticals because they are derived from living organisms with a molecular composition too complex to be defined by physical or chemical means. Furthermore, due to the inherent variability of living organisms, there is always a possibility of contamination of materials with agents coming from starting materials or the environment; therefore vaccines require special quality control and quality assurance mechanisms. The primary legal responsibility for the safety, quality, and efficacy of the vaccines belongs to the manufacturer. Besides, particularly in the countries where vaccines are manufactured, the national regulatory authorities also play a critical role in assuring product quality. The EMA

publishes scientific guidelines on human medicines that are harmonised by the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). For marketing authorization application (MAA), all information and documents proving the quality, efficacy and safety of the product is assembled in a common format called Common Technical Document (CTD), which became the mandatory format for new drug applications in the EU and Japan in July 2003, and the strongly recommended format of choice for NDAs submitted to the FDA, US (ICH-Multidisciplinary Guidelines, 2019). The CTD is organized into five modules (Figure 1). Module 1 is region specific and Modules 2, 3, 4 and 5 are intended to be common for all regions. Module 1, contains documents specific to each region; Module 2, begins with a one-page general introduction to the pharmaceutical, including its pharmacologic class, mode of action, and proposed clinical use, which is followed by quality overall summary, nonclinical overview, clinical overview, nonclinical written and tabulated summaries, clinical summary; Module 3, contains information on quality; Module 4, contains non-clinical study reports, and Module 5, contains clinical study reports.

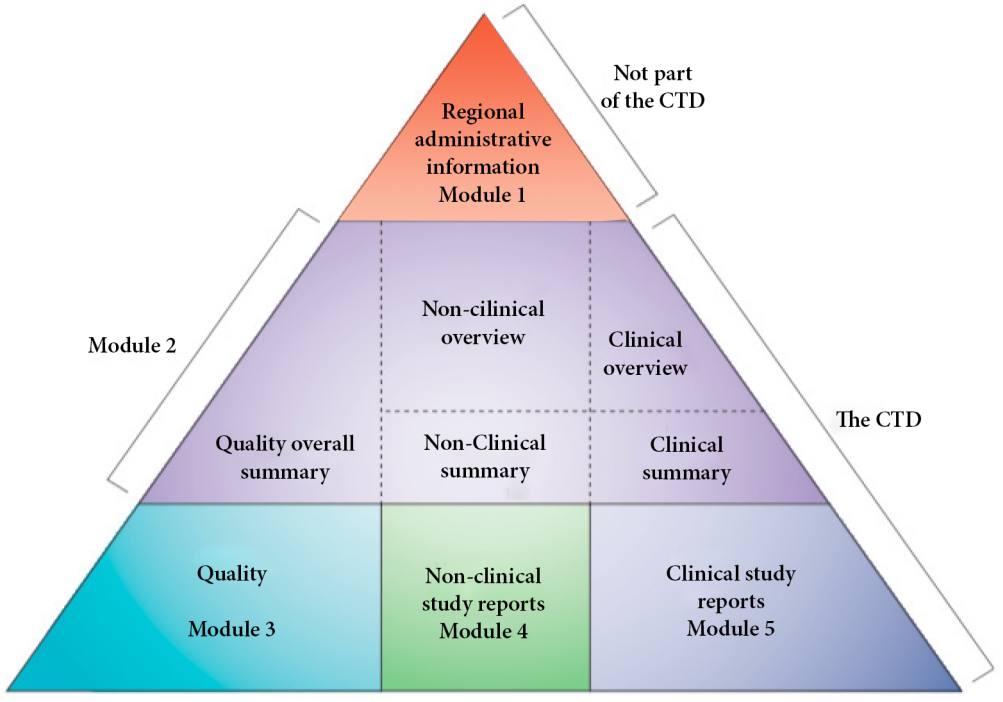

Figure 1. Common Technical Document (CTD) triangle (ICH.org)

The Vaccine antigen master file (VAMF) is a standalone part of the MAA for a vaccine (Guideline on the Scientific Data Requirements for a Vaccine Antigen Master File, 2005). One given VAMF contains all relevant information of biological, pharmaceutical and chemical nature for one given vaccine antigen, which is common to several vaccines from the same MA applicant or marketing authorization holder (MAH). The VAMF certification consists of a centralized assessment of the VAMF application dossier submitted by the MAA/MAH, which results in a certificate of compliance to Community legislation, issued by the EMEA. This certificate is valid throughout the European Community. The use of the VAMF certification system is optional.

Vaccine manufacturing is required to ensure that vaccines are produced and controlled in accordance with quality standards, intended use and that registration information or product specification is required, and does not place patients at risk due to inadequate safety, quality or efficacy. To achieve this quality objective reliably, the Pharmaceutical Quality System (ICH Q10), which is based on International Organization for Standardization (ISO), incorporating Good Manufacturing Practice (GMP) regulations, and complements ICH "Q8 Pharmaceutical Development" and ICH "Q9 Quality Risk Management", must be comprehensively designed and correctly implemented (ICH Harmonized Tripartite Guideline, Quality Risk Management (Q9), 2006; ICH Harmonized Tripar-

tite Guideline, Pharmaceutical Quality System (Q10), 2007; ICH Harmonized Tripartite Guideline, Pharmaceutical Development (Q8), 2009; EudraLex, 2013).

The safety, immunogenicity and efficacy data of new candidate vaccines and changes in the prescribing information of licensed vaccines are performed and documented according to EMA's Guideline on Clinical Evaluation of Vaccines (Guideline on Clinical Evaluation of Vaccines, 2006), which includes considerations for trials intended. After authorization of a vaccine product, it is essential that the safety of all medicines is monitored throughout their use in healthcare practice. Pharmacovigilance has been defined by the WHO as the "science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem". EMA coordinates pharmacovigilance in the EU and operates services and processes in line with EU legislation. Good Pharmacovigilance Practices (GVP) are a set of measures drawn up to facilitate the performance of pharmacovigilance in the EU in which the chapters on product- or population-specific considerations are available for vaccines (Good Pharmacovigilance Practices, 2017).

In the EU, there are two main routes for authorising the vaccines: Centralized authorization route, and national authorization route (European Commission-Mutual Recognition, 2019).

Under the *Centralised Authorization Procedure* (CP), pharmaceutical companies submit a single marketing-authorization application to EMA (Regulation (EC) No 726/2004 of the European Parliament and of the Council, 2004). CHMP or CVMP carry out a scientific assessment of the application and give a recommendation on whether the medicine should be marketed or not. CP is compulsory for products derived from biotechnology. Evaluating a MAA under the CP is 210 days, clock stops when additional questions need to be addressed. On request, the CHMP can reduce the timeframe to 150 days if the applicant provides sufficient justification for an accelerated assessment (European Commission- Authorisation Procedures, 2001). Applicants for accelerated assessment are supposed to justify their claim that the medicinal product is expected to be of major public health interest, particularly from the point of view of therapeutic innovation. Following the review process by the CHMP, the EMA forwards its opinion to the European Commission (EC) to start the decision-making phase. The Commission's Secretariat-General then notifies the decision to the MAH. Once granted by the EC, the centralized marketing authorization is valid in all EU Member States as well as in the European Economic Area (EEA) countries Iceland, Liechtenstein and Norway.

For National Authorisation Procedure**,** each Member State in the EU has its own national authorization procedures. The registration is completed within the period specified in the regulation of the member country (210 days). Similar to centralized procedure, the clock stops if additional questions need to be addressed**.** The MA granted by this procedure is only valid in that Member State. If a company wishes to request MA in several EU Member States for a vaccine that is outside the scope of the centralized procedure, it may use one of the following routes (Authorisation of Medicines, 2019):

- Mutual recognition procedure (MRP): a marketing authorization granted in one Member State can be recognized in other EU countries;
- Decentralized procedure (DP): a medicine that has not yet been authorized in the EU can be simultaneously authorized in several EU Member States.

Mutual Recognition Procedure (MRP) may be preferred for licensing in one or more Member States. To be able to apply this procedure, the product must be licensed at least in one member country at the time of application. The member country in which the product is licensed is considered as the Reference Member State (RMS). The application is made to both the RMS and the competent authority of the country to be licensed. The reference country prepares a report on the product after 90 days of evaluation, and sends the report to the authority of the member country(s) to be registered. At the end of the procedure, the product is licensed in the applicant countries. The mutual recognition procedure is based on the 2001/83 EC directive (Authorisation of Medicines, 2019).

Decentralized Procedure (DP) may be preferred if a product is not necessarily covered by the central procedure and is not licensed in member states. Unlike the national procedure, applications are made at the same time in all Member States where it is desired to go on the market. Different than mutual recognition procedure, the product should not have been previously licensed in any member state. Applications are made to the competent authorities of the countries separately (European Commission-The Decentralised Procedure, 2004). If accepted in one country, the process continues as a mutual recognition procedure in other countries.

Licensing according to Article 58 of Regulation (EC) No 726/2004

The CHMP can carry out scientific assessments and give opinions, in cooperation with WHO, on medicines and vaccines for use exclusively outside the EU. Medicines eligible for this procedure, which is derived from Article 58 of the regulation founding the Agency, are used to prevent or treat diseases that impact global public health. This includes vaccines used in the WHO Expanded Programme on Immunization, or for protection against a public health priority disease. The procedure of Article 58 has been implemented in 2004, aiming at providing easy access to medicines of low and middle income countries and improving public health (Regulation (EC) No 726/2004 of the European Parliament and of the Council, 2004). Companies need to request eligibility for evaluation under Article 58 for a medicinal product before submitting an application. The eligibility request is made using the pre-submission request form. The eligibility of a product for evaluation under Article 58 is assessed by the EMA in consultation with the WHO. The EMA's CHMP confirms eligibility taking into account the WHO's position. The outcome of the eligibility evaluation is sent to the applicant and, if eligibility is refused, the reasons are stated. The evaluation procedure by the CHMP for Article 58 applications follows the same steps and timeframes as for the centralised marketing authorisation procedure. As the evaluation is conducted in partnership with the WHO, the WHO experts provides input to the procedure. As a result of the CHMP and WHO evaluation, the scientific opinion and its annexes are sent to the relevant stakeholders and a public assessment report on a scientific opinion in co-operation with WHO (European Public Assessment Report-EPAR) is prepared within 2 months following the adoption of the scientific opinion under Article 58. This public assessment report is published on the EMA website (Regulation (EC) No 726/2004 of the European Parliament and of the Council, 2004).

Authorization of Specifically Developed Vaccines

Normal seasonal flu vaccines are not intended to be used during a flu pandemic. For this purpose, pandemic-influenza vaccines need to be specifically developed. In the EU, EC and EMA have put two main procedures for the authorisation of pandemic-influenza in place to speed up the assessment and authorisation of vaccines for use during a flu pandemic: the mock-up and the emergency procedures (Vaccines for Pandemic Influenza, 2019). With *mock-up procedure*, a vaccine, which contains a strain of flu virus that few people have been exposed to but that could potentially cause a pandemic, can be developed and authorized in advance of a pandemic. When an actual virus strain causing a pandemic is identified, the manufacturer can include this strain in the mock-up vaccine and apply for the vaccine to be authorised as a 'final' pandemic vaccine. *Emergency procedure* allows a fast-track approval of a new vaccine developed after a pandemic has been declared. Authorisation of these pandemic vaccines is faster than for a normal vaccine, the submitted information is assessed in an accelerated timeframe, around 70 working days instead of the usual 210 (Vaccine Product Approval Process, 2018).

LICENSING OF VACCINES IN TURKEY

In Turkey, licences for vaccine products are provided by the Turkish Medicines and Medical Devices Agency (TMMDA). Licensing of vaccines is carried out in accordance with previsions of the "Regulation on Licensing of Medicinal Products for Human Use" (Regulation on Licensing of Medicinal Products for Human Use, 2005), which is prepared within the framework of Directive EU 2001/83/EC of the European Parliament. The common CTD format is used in applications. In cases where no national guidelines are available, the EMA guidelines should be followed.

LICENSING OF VACCINES IN THE UNITED STATES

FDA's Center for Biologics Evaluation and Research (CBER) is responsible for regulating vaccines in the United States (Vaccine and Related Biological Product Guidances, 2019). CBER is the regulatory body in charge of ensuring the safety, quality and effectiveness of vaccines in the United States. The CBER provides regulatory guidance to sponsors throughout vaccine development through a managed review process that encompasses the life cycle of development. The review of vaccine applications occurs among the CBER's Office of Vaccines Research and Review, Office of Compliance and Biologics Quality, and Office of Biostatistics and Epidemiology. The CBER continues to supervise the production of vaccines after approval of the vaccine and the manufacturing processes, in order to ensure continuing safety and efficacy. After licensure, monitoring of the product and of production activities, including periodic facility inspections, must continue as long as the manufacturer holds a license for the product.

FDA, also being one of the founding regulatory members of the ICH, follows the guidelines which are published by the ICH, for pharmaceutical product development relating to quality, safety, efficiency, and multidisciplinary topics. The ICH provides recommendations on methods to harmonize the interpretation and application of global regulatory requirements.

Regulations for the licensing of vaccines and other biological products in the Public Health Service Act are included in sections 600-680 of Title 21 of the Code of Federal Regulations (CFR) (USDA, 2019). Title 21 comprises regulations applicable to vaccines including labeling, adequate and well-controlled clinical trials, institutional review boards, protection of human subjects, nonclinical laboratory studies and current good manufacturing practices (CGMPs) (A System for the Prequalification of Vaccines for UN Supply, 2019).

Prior to licensure, vaccines are regulated by the Investigational New Drug (IND) Regulations. The vaccine developer (sponsor) must apply for permission to conduct a clinical study, also providing a summary of all laboratory and animal pre-clinical testing. The licensing stage follows the IND stage where clinical studies are completed. The biologics license application (BLA) containing the data derived from nonclinical and clinical studies is a request for permission to introduce, or deliver for introduction, a biological product into interstate commerce. For application, full description of manufacturing methods, compliance with CGMP requirements, data establishing stability of the product through the dating period, samples representative of the product for introduction into interstate commerce, and data describing the equipment and facility of each location involved in the manufacture is also required. The BLA must include the manufacturer's process for large-scale manufacturing of vaccine material. The regulations that pertain to the licensure and submission of a BLA are given sections 600-680 of Title 21 of CFR. Licensure of vaccines is based on demonstration of safety, purity, and potency as defined in Title 21 CFR 600 and the ability to manufacture product in a consistent manner.

In the States, veterinary vaccines are regulated by the Center for Veterinary Biologics (CVB) in the Animal and Plant Health Inspection Service (APHIS), a branch of the United States Department of Agriculture (USDA) (WHO-Prequalification, 2019). For approval process, all products are required to ensure compliance with the four characteristics, purity, potency, safety and efficacy which are outlined in the Virus-Serum-Toxin Act of 1913.

Postmarketing surveillance is a necessary component of vaccine-safety monitoring. Important objectives of postmarketing surveillance are to monitor increases in known reactions, to identify rare adverse reactions not detected during prelicensure studies, and to identify signals of possible adverse reactions that may warrant further study. Manufacturers are required to provide ongoing reports of the safety of licensed vaccines. The CBER carefully considers a vaccine manufacturer's proposal for postlicensure surveillance through pharmacovigilance plans submitted with the BLA.

PREQUALIFICATION PROCEDURE REGULATED BY WHO

WHO provides a service to UNICEF (United Nations International Children's Emergency Fund) and other United Nation (UN) agencies that purchase vaccines, to determine the acceptability of vaccines from different sources for supply to these agencies. This service is called prequalification. The prequalification (PQ) procedure, which was reviewed and endorsed by the WHO Expert Committee on Biological Standardization in October 2010, is published in WHO TRS 978, Annex 6 (The WHO Prequalification of Vaccines Procedure, 2010). The aim of PQ procedure is to ensure the safety, effectiveness and suitability of the vaccines provided through the UN for use in national immunization services in different countries for the target populations.

For acceptance of application, the candidate vaccine must be on the current list (Vaccines Prequalification Priority List 2018-2020, 2019) of priority products for UN prequalification, and must meet the mandatory characteristics for programmatic suitability, which is defined in the document "Assessing the programmatic suitability of vaccine candidates for WHO prequalification" (Assessing the Programmatic Suitability of Vaccine Candidates for WHO Prequalification, 2016). The PQ process includes, review of general production process and quality control procedures, testing of consistency of lots, and auditing manufacturing facilities with observers from the responsible National Regulatory Authority.

According to the procedure revised by the WHO, producers are required to submit a product summary file (PSF), following the Guide for Preparing a Product Summary File for Pre-qualification of Vaccine (Assessing the Programmatic Suitability of Vaccine Candidates for WHO Prequalification, 2016). Information, guidelines and recommendations harmonized by experts for use by producers and regulatory authorities are published in the WHO Technical Report Series (TRS). WHO-TRS are developed by the scientists and policy makers in the field of biological standardization to form a consensus on the production, quality control and regulatory control of biological medicines, including vaccines. The TRS have been prepared as detailed guidelines which are

available separately for each vaccine. Further guidelines for cell substrates, technical or regulatory functions, non-clinical evaluation or clinical evaluation are also available. The WHO provides International Biological Reference Materials which serve as reference sources of defined biological activity expressed in an internationally agreed unit. The WHO gives the latest information to the interested parties by setting consultation and expert working groups on technical issues that are important to the field, will address the biological prevention of potential pandemic threats, clinical and nonclinical testing of vaccines, risks of contagious spongiform encephalopathy, DNA vaccinations and various other issues (Assessing the Programmatic Suitability of Vaccine Candidates for WHO Prequalification, 2016).

OTHER COUNTRIES

Although most of the developed countries have national regulatory agencies, there might be slight changes in each country's requirements. For example, in the UK, licences for vaccines and medicines are issued by the Medicines and Healthcare products Regulatory Agency (MHRA). MHRA works closely with other bodies in a single medicines network across Europe and takes forward UK health priorities. The Committee on the Safety of Medicines (CSM) advises the MHRA on matters relating to the safety, quality and efficacy of vaccines and medicines. On 29 March 2017, the UK notified the EC of its intention to withdraw from the EU, a process known as 'Brexit'. Both the EMA and the UK is making preparations to ensure that they can continue to deliver on their mission and protect public and animal health after the UK leaves the EU on 30 March 2019. In Japan, national regulatory authority for reviewing the drugs and medical devices, overseeing post-market safety, and providing relief for adverse health effects is the Pharmaceuticals and Medical Devices Agency (PMDA), which is part of the Ministry of Health, Labor, and Welfare (MHLW), and established in 2004 by incorporating the Pharmaceuticals and Medical Devices Evaluation Center of the National Institute of Health Sciences (PMDEC), the Organization for Pharmaceutical Safety and Research (OPSR/KIKO), and part of the Japan Association for the Advancement of Medical Equipment (JAAME). The PMDA and they both handle a wide range of activities, from approval reviews to post-market surveillance. Current Japan PMDA regulations are laid out in the Pharmaceuticals and Medical Devices Act (PMD Act), also known as the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (PMDA, 2019).

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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