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Overview of Vaccine Regulations in European Union and Japan

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Abstract

In this article we identified the important considerations, in particular , on the preclinical assessments that would allow vaccines to proceed to clinical trials, and the differences on the regulatory pathway for the marketing authorization in each region like National procedure, Decentralized procedures, Centralized procedure, Mutual Recognition Procedure (MRP) monitored by European Medicines Agency (EMA) in Europe , Pharmaceuticals and Medical Devices Agency (PMDA) in relation with Ministry of Health, Labour and Welfare (MHLW) (determines if a proposed study meets the regulatory filing requirements in Japan), The various different types of vaccine regulations was studied with its approval , and development procedure are discussed.

Keywords: Vaccine Regulation, European Medicines Agency (EMA), Marketing authorization, Pharmaceuticals and Medical Devices Agency (PMDA), Ministry of Health, Labour and Welfare (MHLW)

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1. Introduction

Vaccines are convoluted biological therapeutic items that are being created using ever-more- new-fangled technologies. They can include live infectious agents as well as a variety of other components. Immunization with some vaccines is mandated in many European countries due to the significant individual and population benefits, and any safety hazard could harm people.

Regulatory authorities are protecting public health by allowing the use of safe and effective vaccines. There are Two European legislative texts: Regulation (EU) No. 726/2004 and Directive 2001/83/EC.

These activities are carried out by a variety of authorities, including member states and their national competent authorities, public health institutes and national technical institutes, including academia, and the European Commission in Brussels and the European Medicines Agency (EMA) in London. Another European agency, established in 2004 by Regulation (EC) No. 851/2004, is the European Commission.

Since 1995, the European Medicines Agency (EMA) has harmonize the scientific evaluation and supervision of medicines for use in the European Union, including vaccines

In collaboration with national health protection bodies throughout Europe, the European Centre for Disease Prevention and Control (ECDC) recognises, evaluates, current and emerging infectious disease threats to human health. (1)

The first legislation regulating smallpox vaccination was enacted in 1910, and the history of vaccination in Japan began with the smallpox immunisation in 1849. The government chose to promote immunisation against various infectious diseases that were causing major health problems at the time after World War II ended, and the Immunization Law was enacted in 1948. That law still serves as the legal foundation for Japan's immunisation programme. However, two significant adjustments have lately been applied. The first reform was the enactment of new laws in 1999, which strengthened and revitalised the infectious disease control programme, notably in terms of surveillance. (2)

2. Marketing authorization procedures in the Europe

2.1 National procedure

When a medical product or vaccine maker submits a marketing permission application in a single member state where the medicinal product or vaccine will be marketed, it follows national processes. The member states are solely responsible for product authorization, and it is only feasible if the medicinal product in

question does not come within the mandatory scope of the centralised procedure.

One of two approaches can be used to get a marketing authorisation for a pharmaceutical product that is valid in more than one European Union member state. There are two types of procedures: decentralised and centralised.(3)

2.2 Decentralized procedures:

There are two procedures that are decentralised. In one, a marketing authorisation application is simultaneously filed to many member states. In the other, a member state provides the first marketing permission, which is subsequently mutually acknowledged by the manufacturer of the pharmaceutical product or vaccine in other concerned member states; this is the mutual recognition procedure. The Coordination Group for Mutual Recognition and Decentralised Procedures-Human (CMDh), which meets regularly at the EMA, helps to streamline such procedures. The marketing permission application filed through one of two methods (Decentralised Or Mutual Recognition) must be similar to the marketing authorization application issued in the first member state, referred to as the Reference Member State (RMS). (3)

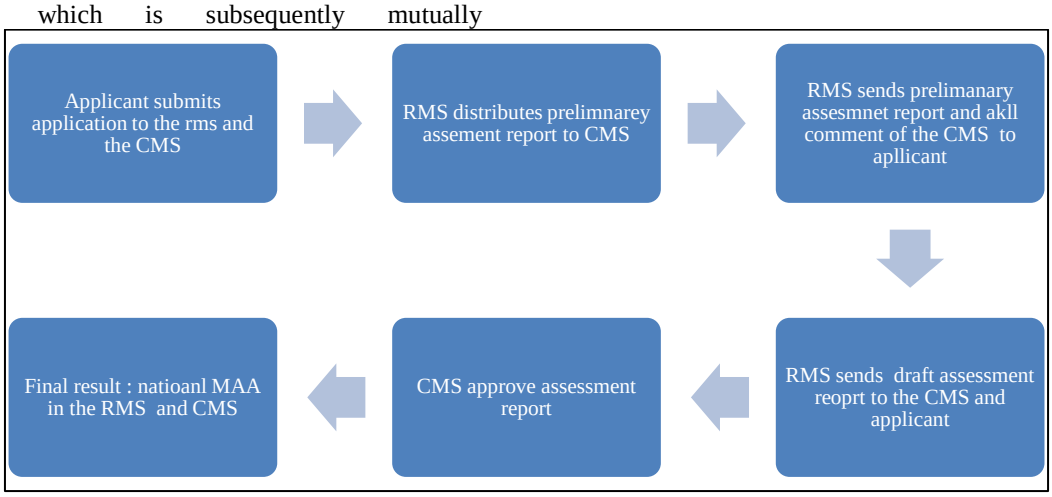

Figure 1. Decentralized procedures

2.3 Centralized procedure

EU regulations specify which pharmaceutical items must go through a centralised procedure in order to obtain a marketing licence valid throughout the European Union. Vaccines containing a new active component that do not fall under one of the mandatory therapeutic indications listed in Annex I of Regulation (EU) No. 726/20042 can use either the centralised or decentralised approach, but the centralised procedure is required for all pharmaceutical goods (including vaccines) Controlled production of genes coding for biologically active proteins in prokaryotes and eukaryotes, including transformed mammalian cells, or hybridoma and monoclonal antibody approaches were established using recombinant DNA technology. If the vaccination in question is classified as an advanced therapy medicinal product or an orphan medicinal product under Regulation (EC) No 141/2000, this registration procedure must be followed. The European Medicines Agency (EMA) and its Committee for Human Medicinal Goods (CHMP) are in charge of assessing the quality, safety, and efficacy of medicinal products submitted under this method. The CHMP is made up of one member from each EU member state plus an alternate, one member from Iceland and Norway (European Economic Area nations) plus alternates, and five co-opted members chosen for their competence and experience in reviewing pharmaceutical products. A large network of professionals from all throughout Europe assists the CHMP. The CHMP can form working groups, such as the Vaccines Working Party and the Biologics Working Party, to create recommendations and advise the CHMP on specific elements of product review. It should not take more than 210 days to evaluate a marketing authorization application, develop and discuss reports, and adopt an opinion. Although the dossier given by the marketing authorization holder serves as the foundation for evaluating the vaccine's benefits and dangers, additional sources of information, such as those from the European Centre for Disease Prevention and Control (ECDC) or the World Health Organization, are also used (WHO),The outcome of the evaluation is a positive (favourable) or negative (unfavourable) CHMP opinion recommending the medicinal products marketing licence. The CHMP may also consult a scientific advisory group or an ad hoc expert group comprised of leading experts in the relevant field who are selected based on the content of the questions referred by the CHMP Scientific advisory groups assist the CHMP on specific questions, particularly when scientific opinions differ. The CHMP can suggest full marketing authorization, conditional marketing authorization, or marketing authorization with exceptional circumstances based on positive assessments. The CHMP grants a full marketing authorisation to a medicinal product that has passed a positive benefit and risk assessment and does not require any specific requirements (studies or tests) to be completed and submitted after marketing. The CHMP may recommend conditional marketing permission for specific types of pharmaceutical products and in particular conditions, such as to address unmet medical

requirements of patients and to protect public health. It may be required to provide marketing authorizations based on less complete data than is typical and subject to certain obligations. Medicinal products aimed at treating, preventing, or diagnosing seriously debilitating or life-threatening diseases; medicinal products to be used in emergency situations in response to public health threats recognised by WHO or the European Union; or medicinal products designated as orphans should be included. These conditional marketing authorizations are valid for one year and can be renewed if the stated obligations are met. (3)

2.4 Mutual Recognition Procedure (MRP)

Since 1995, the MRP has been in existence in the EU. When a pharmaceutical product has already been granted authorisation by at least one country in the European Community, this procedure is used to gain marketing authorizations in one or more Member States. In this situation, the applicant proposes that one or more CMSs mutually acknowledge the RMS's authority. If the RMS marketing permission is based on an obsolete dossier format, the dossiers must be reformatted before the MRP may begin. The holder of a marketing authorization must submit an application to the RMS and each of the CMS's authorised bodies (s).The RMS provides the Assessment Report, or changes any existing one, within 90 days of receiving a valid application, and sends it along with other papers to the CMS(s) and the applicant. Following receipt of the Assessment Report and validation of the application by each of the CMS, the RMS starts the clock (s). The CMS(s) acknowledge the RMS's decision within 90 days. The CMS(s) competent authorities make a decision and award marketing permission thirty days after the procedure is completed. As a result, if the MRP ends with a favourable agreement, each CMS will receive a nationwide marketing authorization (s) (3)

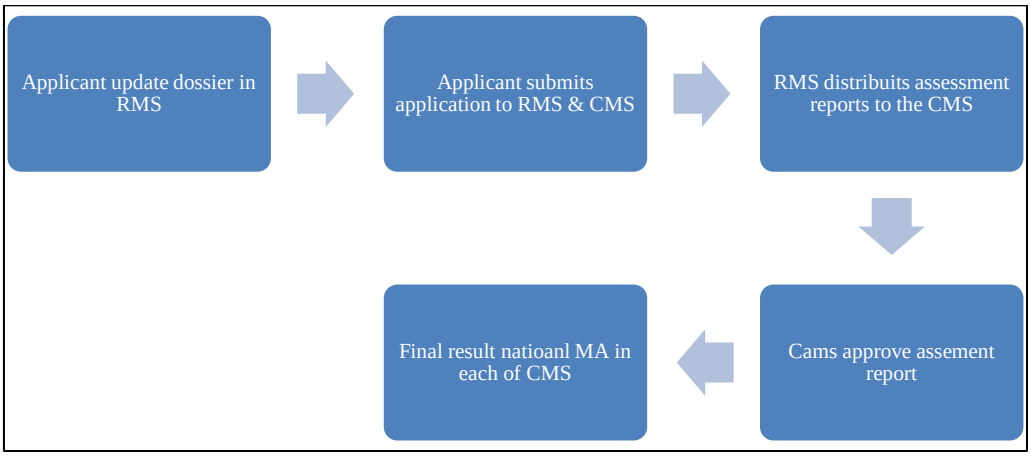

Figure 2. Mutual Recognition Procedure (MRP)

3. Marketing authorization procedures in Japan

In Japan, every applicant planning to conduct clinical trials must submit a clinical trial notification (CTN) to the PMDA before beginning the trial. The following documents are provided by the applicant:

- A declaration stating why the planned clinical experiment's funding is scientifically justifiable
- A protocol for the proposed clinical trial, an explanation document and consent form for informed consent
- An investigator's brochure

If the CTN is being submitted for the first time, PMDA will perform a scientific review and contact the applicant within 30 days. During this time, the PMDA and the application must resolve any questions, and the applicant cannot commence clinical trials

The applicant should have a "pharmaceutical affairs consultation on R&D strategy," which is not required but strongly encouraged, before submitting the CTN. This dialogue will assist PMDA and the applicant in identifying any key issues/inquiries that will take longer than 30 days to resolve. Following the completion of clinical trials, the applicant can submit a new drug application (NDA) to the PMDA, where all data is examined by a multidisciplinary PMDA reviewer (i.e., physicians, pharmacists, chemists, and biostatisticians), and the first council with the applicant is selected. (4)

In an interview-based board of review, the candidate presents to PMDA reviewers and external experts if necessary. MHLW finally gives permission after a second meeting with a PMDA reviewer and a non-PMDA expert, which resulted in a recommendation or opposition to a vaccine's approval.

4. Overview of EU regulatory landscape

Drug laws or pharmaceutical legislation began to evolve in the 1950s as an immediate and essential response to the thalidomide (Contergan) disaster, which left thousands of babies with deformed limbs and other lasting consequences. Medicinal product laws and principles in the EU evolved over the next few decades from a purely national obligation to a plethora of Directives and Regulations agreed upon by Member States and implemented across the EU. Parallel to this, regulatory and scientific criteria were developed to ensure the greatest possible level of safety and efficacy for all pharmaceutical products sold in the European Union. This unprecedented level of standardisation was spurred by the founding of the European Medicines Agency in 1995, which offered a suitable framework for

taking medicinal product licencing and regulation into hitherto unreachable dimensions.

In response to mounting needs imposed by scientific advancement and new technology, various niches in EU pharmaceutical legislation have been opened and populated with a specific legal framework.

Dedicated drug legislation is now divided into product class specific regulations, such as the Orphan Drug Regulation (Regulation No 141/2000) and the Advanced Therapy Medicinal Product (ATMP) Regulation (Regulation No 1394/2007), which provide tailored legal, regulatory, and scientific guidance to help with the development, licensure, and marketing of products that fall into those categories.

Additional legal provisions have been implemented in addition to product class rules, such as the Pediatric Regulation (Regulation No 1901/2006), which facilitates the development of medicinal products for children, or the post-marketing control of all medicinal products licensed in the EU, regardless of the pathway used for licensure or the licensing status. These latter aspects are covered by the Pharmacovigilance Act (Directive 2010/84/EU, Regulation (EU) No 1235/2010).

The former Clinical Trial Directive was converted into a Clinical Trial Regulation (Regulation (EU) No 536/2014), as were three Directives governing certain implants, medical devices, and in vitro diagnostics (Regulation (EU) No 2017/745, Regulation (EU) No 2017/745, Regulation (EU) No 2017/745, Regulation (EU) No 2017/745, Regulation (EU) No 2017/745, Regulation (EU) No 2017/745, Regulation (EU), (217/746).

Converting EU Directives to EU Regulations arose from a series of evolutionary lessons learned, including the fact that harmonisation of drug legislation implemented through an Council Regulation EC Regulation is generally more efficient and successful than harmonisation implemented through an EC Directive, which always runs the risk of implementing regulatory divergence rather than regulatory convergence among Community Member States.

Looking forward from the past to the future of regulating drug development, licensure, and control of medicinal products, medical devices, and diagnostics, a unique success storey emerges, with the possibility that new products and techniques providing access to previously unavailable therapeutic options will be integrated even more quickly into the existing set of pharmaceutical legislation**.** (5)

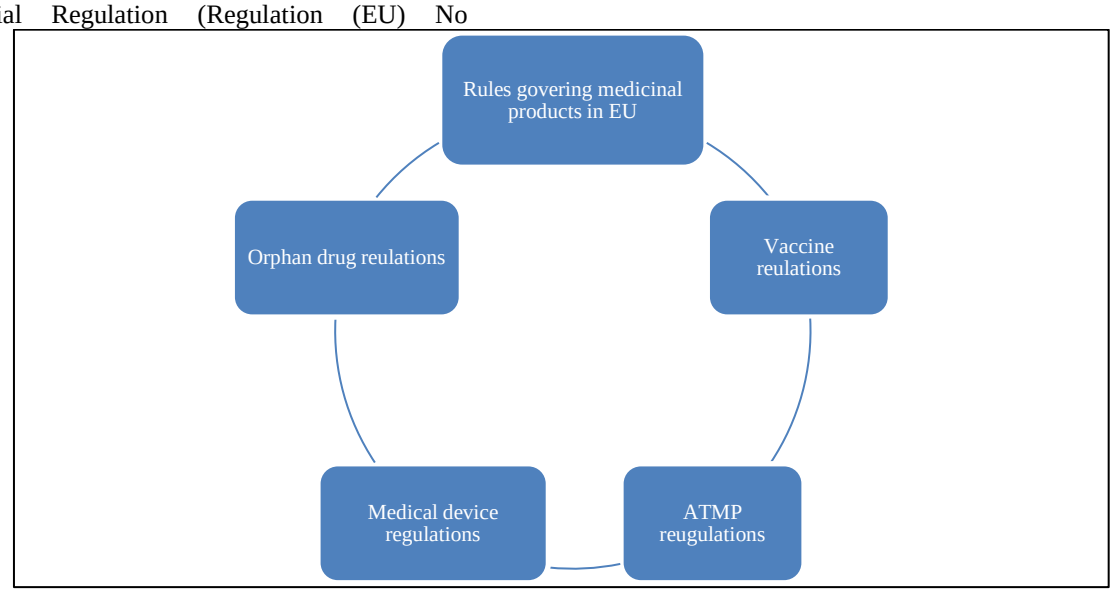

Figure 3. EU regulatory landscape

5. Overview of the Japan Regulatory Landscape

In 2010, the Japanese government issued the general non-binding guidelines "Guideline for non-clinical studies of preventive vaccines for infectious diseases" and "Guideline for clinical research of preventive vaccines for infectious diseases. Plasmid DNA vaccines and viral-vectored vaccines are specifically excluded from the scope of this guideline, thus specific recommendations for these gene-based vaccinations must be followed because this recommendation expressly excludes plasmid DNA vaccines and viral-vectored vaccinations from its scope, there are no particular guidelines in Japan for these gene-based vaccines. Furthermore, ICH S6 (R1), "Preclinical safety evaluation of biotechnology-derived pharmaceuticals, excludes viral vaccines, DNA vaccines, and gene therapy products.

As previously stated, Japan has a gene therapy notification. Despite the fact that it is unclear whether preventative gene-based vaccinations are appropriate, one applicant working on a plasmid DNA vaccine passed MHLW's preliminary evaluation for gene therapy products, setting a precedent for the applicant who plans to begin clinical trials for gene-based vaccines. (6)

6. Approval of vaccines in the European Union

Before a vaccine to be licensed in the EU, it must first go through extensive testing by the manufacturer and then be evaluated scientifically by regulatory

authorities. The European Medicines Agency (EMA) and other regulators in EU/EEA nations are among them.

The quality of the vaccination is checked during testing:

- It's purity
- It's contents, including inactive ingredients or "excipients"
- The method by which it is created

The vaccine's effects are then tested by the vaccine developer. This entails both laboratory and animal experiments.This is followed by a human clinical testing programme. The vaccine is tested in three steps of clinical trials, with each phase involving a larger number of patients. This programme must adhere to the regulators' stringent criteria, processes, and protocols. (7)

7. Development of Vaccines in Europe

Vaccine development is divided into two stages: preclinical and clinical. The safety of vaccines is determined in the preclinical period. This step comprises antigen selection as well as in vitro and in vivo safety studies. The results of the preclinical experiment can be used to plan the start of clinical trials. Clinical trials are conducted after preclinical investigations have been completed. Trials are conducted in four stages throughout clinical development.

- Phase 1 studies are small-scale tests conducted on healthy humans to determine the vaccine's safety and immunogenicity. Following the completion of the phase 1 study
- Phase 2 studies are conducted to determine the vaccine's efficacy. These trials are more extensive.
- Phase 3 studies are conducted on a wide scale to assess the efficacy of a treatment on patients. The company will be able to submit a Marketing Authorization Application to the EMA for vaccine licencing after demonstrating long-term safety and efficacy.After a vaccine has been licenced,
- Phase 4 trials are conducted. This phase is also known as pharmacovigilance, and it entails the detection of adverse reactions following immunisation.

A sponsor must submit a clinical trial application to the appropriate authority before the experiment may begin. The application for a clinical trial must be evaluated within 60 days. In Europe, a marketing authorization application must be evaluated within 210 days. The application fees for application evaluation are 2, 86,900 EUR13. (7)

8. Monitoring vaccine safety and reporting side effects

The approval of a vaccine for use, national authorities in the EU/EEA and the European Medicines Agency (EMA) track side effects in patients who have received the vaccine.

This ensures that any potential dangers are detected and addressed as soon as possible.

New information on the safety of all vaccines sold in Europe is monitored by the European Medicines Agency (EMA). It investigates a variety of topics.

- Patient, parent, and healthcare professional reports;
- Clinical studies;
- The medical literature
- Information shared by other regulators

The European Medicines Agency (EMA) investigates reported side effects to determine whether they are related to the vaccine. This rules out the chance that it was a coincidence or caused by something unrelated to the immunisation. This could be due to a medical condition or fear about getting the immunisation.

The European Medicines Agency (EMA) evaluates side effects reported by patients to see if they are linked to the vaccine. This eliminates the possibility that it was a fluke or caused by something unrelated to the vaccination. This could be due to a medical condition or apprehension about receiving the vaccine. (8)

Following are the example of vaccine which are sold in Europe (9)

Table 1. Example of vaccine which are sold in Europe

Vaccines	Diseases	Manufacturer
Vaxchora	cholera	Emergent Travel Health, Inc
Mosquirix	Malaria	BioNTech SE
M-M-RVaxPro	measles	Merck, Sharp & Dohme Corp.
BCG Vaccine AJV	TB	Pq Status
Prevenar 13	Pneumonia	Merck Sharp & Dohme Corp
Vaxelis	Bacterial Infection Tetanus	Merck and Sanofi Pasteur
Infanrix hexa	Whooping Cough (Pertussis)	GlaxoSmithKline.

Following are the example of vaccine which are sold in Japan (10)

Table 2. Example of vaccine which are sold in Japan

Vaccines	Diseases	Manufacturer
Pentacel and Vaxelis	Haemophilus Influenzae Type B (Hib) Infection.	Takeda

PPSV23	Pneumonia,	Merck Sharp & Dohme Corp.
DTP	Diphtheria,	Daiichi Sankyo
DTaP	Whooping Cough (Pertussis)	Glaxosmithkline Biologicals (Gsk) And Sanofi Pasteur
Tetanus	Bacterial Infection Tetanus	Daiichi Sankyo
IPV	Poliomyelitis (Polio)	Sanofi Pasteur
Cervarix	Precancers	Gardasil
MMR	Measles, Mumps,	Maurice Hilleman AtMerck & Co.
Hepatitis A	Hepatitis A Virus (Hav)	Sanofi Pasteur
Hepatitis B	Hepatitis B Virus	Daiichi Sankyo
Mosaic' HIV	AIDS	Merck Developer
TB	Tuberculosis	BCG Laboratory

9. Europe

Emerging vaccines Data

Clinical Trials

Clinical trials are human investigations that demonstrate the safety and efficacy of a vaccination.

These trials for COVID-19 vaccines must look at immunological responses, effectiveness, and safety. Clinical trials with COVID-19 vaccines are authorised and regulated by national authorities and ethics committees in each country. This protects the volunteers' safety and rights while they participate in the studies. It also assures that the data gathered throughout the research is reliable.

In the EU, clinical trials using permitted or investigational drugs must adhere to good clinical practise (GCP). This includes international ethical and scientific quality requirements for human study design, recording, and reporting. Compliance with these principles ensures that study participants' rights, safety, and well-being are respected, and that clinical-study data is reliable.

During the scientific review of a vaccine, if there are questions about the conduct of a clinical trial or the integrity of the clinical study data, the CHMP will consider examining the research site and will request an inspection. EMA collaborates closely with foreign partners, providing inspection information and organising inspections as necessary. (11)

Non Clinical

Vaccines, like all medicines, go through non-clinical or laboratory testing before being tested on humans.

These researches are carried out in a laboratory setting. They demonstrate whether the vaccine may pose safety issues, such as effects on reproduction or development in extreme circumstances.

Furthermore, firms frequently do the following non-clinical studies:

- Immunogenicity studies examine the sorts of immunological responses elicited by a vaccine. For example: They can study the production of antibodies or long-term immunological responses by immune system' memory cells,
- Animal-challenge studies:

These examine whether animals given a COVID-19 vaccine are protected from disease when exposed to SARS-CoV-2, the virus that causes COVID-19 disease.

- Bio distribution studies: some vaccine types require these to demonstrate how the vaccine reaches the body's tissues and organs. (12)

Pharmaceutical Quality Study

Pharmaceutical quality studies give data on the vaccine's effectiveness. This includes the following:

The vaccine's active ingredients, purity, and other compounds (such as stabilisers); the vaccine's manufacturing and quality control; the vaccine's stability and shelf life; and the best manner to store the vaccine.

A firm developing a COVID-19 vaccine must also submit extensive information to justify the usage of each vaccine ingredient as well as the manufacturing technique it employs.

Only facilities that have been approved and validated can produce the vaccine. It must show that the vaccine will be produced in those facilities in a consistent manner.

It must also follow agreed-upon rigorous criteria for each batch of vaccination released following approval. Because commercial batches of vaccines are sometimes produced at a significantly bigger scale than clinical study batches, companies must demonstrate that commercial batches are of the required quality. (13)

EU Harmonization of vaccine

The European Medicines Agency (EMA) is responsible for harmonising and coordinating GCP-related activities across the EU. It is involved in the following activities:

- GCP inspections for the centralised procedure are being coordinated,
- The GCP Inspectors Working Group is drafting guidelines on GCP themes.
- Advising on the interpretation of EU GCP requirements and related technical challenges;
- Creating EU-wide GCP inspection rules and accompanying procedures for the centralised procedure

Adapting COVID -19 vaccines to SARS – COV 2 Variant

Developers that want to adapt COVID-19 vaccines to address SARS-CoV-2 mutations can get help.

The nonclinical, clinical, quality, and manufacturing data needed to support the approval of such changes in the EU are detailed in a reflection paper from the EMA's CHMP.

New 'variant' vaccines, according to CHMP, will essentially rely on the same technologies and platforms as their 'parent' vaccines, but with a different antigen chosen to induce the immune response. The parent would be a COVID-19 vaccination that has already been licenced in the EU.

Risk Management Plan

Detailed requirements and guidance on the principles of risk management (GVP Module V) with a link to the format of the risk management plan (RMP template) as well as pharmacovigilance requriment for vaccines are included in the excellent pharmacovigilance practises (GVP P.I) Furthermore, fundamental RMP standards for COVID-19 vaccines have been defined to make the creation of RMPs by firms and their review by assessors easier and more consistent. While noting uncertainties in the pandemic scenario and offering strategies to prepare for pharmacovigilanc, the 'coreRMP19' addresses the preparation of MAHs' post-authorisation safety follow-up of COVID-19 vaccines. (14)

10. Japan

Emerging vaccines Data

Quality data

The quality data provided for regulatory approval should contain documentation on the variant vaccine's production process and specifications, documents on stability, and documents describing that the vaccine's manufacturing method is the same or very comparable to that of the parent vaccine. enumerate the differences between them Applicants should consider adding the following in their applications:

- Differences between a variant vaccine and a parent vaccine are explained.
- Data from studies that show that key quality parameters (such as purity and content) of the variant vaccination are the same as those of the parent vaccine, and that the variant vaccine is subjected to the same quality control as the parent vaccine.
- Data to demonstrate the uniformity of the manufacturing process
- Data on the stability of the variant vaccination at the time of application, with plans to collect more data.
- After the parent vaccine was approved, the quality control technique for the variant vaccine was updated.

The same storage conditions and shelf life are applied to variant vaccine based on the assumption that the qualitative qualities of variant vaccination are the same as those of parent vaccine. The applicant must justify the storage conditions and shelf life by demonstrating the similarity of the parent and variant vaccines using active substance and end product stability data (long-term stability data). Following approval, stability testing of the active component and final product of the variant vaccination should be completed as soon as feasible, and study results covering the allowed shelf life should be submitted to the Pharmaceutical and Medical Devices Agency (PMDA). (15)

Nonclinical Study Data

In general, non-clinical pharmacology, toxicology, and pharmacokinetic studies are not required in the development of variant vaccines, and necessity is determined based on documents containing data on parent vaccines or vaccines developed on the same platform as parent vaccines (such as lipid nanoparticles (LNP), DNA plasmid vectors, and recombinant proteins). The proliferative qualities of attenuated live vaccines may differ between parent and variant vaccines due to antigen modification, hence the principles stated above may not be applicable.

The use of a challenge test with an animal model of a variant vaccination could aid in the interpretation of clinical trial data. The findings are particularly beneficial when it is difficult to enrol patients in clinical trials who have not yet developed immunity to SARS-CoV-2, and when it is difficult to interpret clinical trial immunogenicity data that is ambiguous. (16)

Clinical Trial Data on the Efficacy

In terms of the clinical trial, depending on the expected uses of the variant vaccine, both or one of the following designs should be used: in the case where the variant vaccine is administered to someone who has never received any SARS-CoV-2 vaccines, including the parent vaccine, and has never been infected with SARS-CoV-2; in the case where the variant vaccine is administered to someone who has never received any SARS-CoV-2 vaccines, including the parent vaccine, and has never been infected with SARS .

When enough serum samples from a parent vaccine clinical trial are available, they can be used as a control group in the clinical trial below, provided the population to compare is sufficiently similar, the same assay is used to investigate neutralising antibody titer for both the parent and variant vaccines, and the dosage and administration investigated in the clinical trial of parent vaccine is the same as those of variant vaccine. (14)

Administration of Variant Vaccine as Initial Immunization

In clinical trials, subjects are randomly assigned to one of two vaccine groups: variant vaccine or parent vaccine. Each vaccine is given the same dosage and dosing interval as the parent vaccine, and the schedule for taking serum is determined using data from clinical trials conducted for the development of the parent

vaccine. Non-inferiority of immunogenicity against variant in variant vaccination group to immunogenicity against wild strain in parent vaccine group should be statistically examined for measuring efficacy, and clinical trials should be ensured to have enough power for this assessment. The geometric mean titer (hereinafter, "GMT") of neutralising antibody and seroconversion rate of neutralising antibody (defined as the fraction of participants whose neutralising antibody titer increases by more than 4 times following vaccination) are the primary objectives.

In theory, the non-inferiority margin is defined as the difference between the seroconversion rate of neutralising antibody and the GMT ratio, which is measured against the lower bound of the 95% confidence interval. If a different value is utilised as the non-inferiority margin, a case-by-case justification should be provided.

When the parent vaccine's efficacy is less than 60%, a stricter non-inferiority margin may be necessary. In addition, secondary analysis should include neutralising antibody titers against wild strain in the serum of variant vaccine receivers and neutralising antibody titers against variant in the serum of parent vaccine recipients. (15)

Administration of Variant Vaccine as Booster Immunization

Immunogenicity of booster immunisation against variants is compared to that of first immunisation against wild strains in clinical trials that provide variant vaccine as a booster immunisation. Subjects to be vaccinated with variant vaccine should have participated in a parent vaccine clinical study, received parent vaccination according to approved dosage and administration, and had neutralising antibody titer data recorded at the time of initial immunisation. If this is not practicable, careful measures should be made to improve comparability, such as collecting data on neutralising antibody titer at the time of initial vaccination from a group with similar age, gender, and underlying disease to the variant vaccine group, among other criteria.

Considerations in conducting Clinical Trial

The aforementioned clinical trial was carried out in a single age group (for example, 18-65 years of age, which was the age group employed in the parent vaccination clinical trial), and the results can be generalised to other age groups that are approved for parent vaccine.

In the case of a clinical trial to assess a variant vaccine as an initial immunisation, if it is difficult to conduct a clinical trial in people who are not immune to SARS-CoV-2 due to the rise in SARS-CoV-2 vaccine recipients and SARS-CoV-2 ex-infected people, it must be explained that the clinical trial results can be interpreted by also considering how immune status of subjects may affect the outcome.

If overseas trials, such as the one mentioned above, showed that the immunogenicity and immunogenicity profile of the variant vaccine were similar to those of the parent vaccine, and Additional Japanese clinical trials for the parent vaccine could be done if no special concern about efficacy and safety of the parent vaccine was detected in a Japanese clinical study for the parent vaccine that assessed immunogenicity and safety in the Japanese population.

When asking for licensure of a variant vaccination without conducting Japanese clinical trials, the explanation for invoking outside trials for immunogenicity in Japanese should be included. (2)

Clinical Trial data on the Safety

In terms of safety, adverse events (AEs) of solicited local reactions and solicited systemic reactions noticed during the first at least 7 days after immunisation, significant AEs observed during the immunogenicity confirmation period, and additional AEs must be collected. (16)

If any safety signals are found during the clinical trial, additional safety evaluations based on pharmacovigilance data for the parent vaccine, and, depending on the situation, a substantial safety study of the variant vaccine may be required.

A long-term safety data collecting plan should be necessary for every variant vaccination being produced, including data gathering of Japanese and overseas AEs beyond the market introduction. Scientific guidance from PMDA is needed as soon as feasible in relation to this plan, as well as clinical trial protocols. (17)

Table 3. Basic differences between Europe and Japan

Content	Europe	Japan
Approval process	National procedure Decentralized procedure Centralized procedure Mutual recognition procedure	a clinical trial notification (CNT) submit to PMDA
Regulatory agency	EMA	PMDA
Emerging vaccine data	1. Clinical trial 2. Non clinical 3. Pharmaceutical quality study 4. Risk management plan	1. Clinical trial data on efficacy 2. Non clinical study data 3. Quality data 4. Considerations In Conducting Clinical Trial
Example	1. Vaxchora 2. mosquirix 3. M.M Rvaspro 4. B C G vaccine A50	1. Prntacel and vaxcel 2. PPSV23 3. DTP 4. DTaP

11. Conclusions

Through our study, we clarified some differences in current regulatory condition in each region like Japan and Europe as for the vaccines i.e. recently provided an early approval system (a conditional, time-limited approval system), undeveloped condition in guideline development is found in particular in Japan and Europe

Various different Marketing authorization procedures, Overview Over the Regulatory Landscape with Approval Development and Monitoring of vaccine Overview study of different type of vaccination taken in particularly Japan and Europe as well as emerging vaccines like SARS-CoV-2 vaccine clinical data was studied.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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