International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 1026-1036 www.ijprajournal.com ISSN: 2249-7781

Marketing Authorization and Pharmacovigilance Plan of the Eu Regulatory Network for Covid-19 Vaccines

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Date of Submission: 15-10-2021 Date of Acceptance: 27-10-2021

ABSTRACT: An internal single market has been developed by the EU through a standardized system of laws that apply in all member states in those matters, and only those matters, where members have agreed to act as one. This article discusses about the marketing authorization procedures of European Union (EU) and the ways, procedures, criteria and conditions for marketing authorization of Covid-19 vaccines in EU. It also states about the requirements for applying for Conditional marketing authorization. This article also describes about the Pharmacovigilance plan of the EU regulatory network for Covid-19 vaccines.

KEY WORDS: European Union, Marketing Authorization, Authorization procedures, Conditional Marketing Authorization, Pharmacovigilance plan.

I.INTRODUCTION:

The European Union (EU) highly regulates the Medicinal products which are subjected to a separate and complex system of approvals that administers how, when, where, and in what form such products will be permitted to be sold within the boundaries of the EU.

The European Union (EU) is a political and economic union which consists of 27 member states that are found fundamentally in Europe. An internal single market through a standardized system of laws has been developed by The EU in all member states in those matters, and only those matters, where individuals have consented to act as one.

A network of around 50 regulatory authorities from the 31 EEA countries (28 EU Member States plus Iceland, Liechtenstein and Norway), the European Commission and EMA is the base for The European medicines regulatory system. This network is the thing that makes the EU regulatory system extraordinary.

The European Medicines Agency (EMA) is an organization of the European Union (EU) responsible for the assessment, supervision and oversight of the medicinal products. Preceding 2004, it was known as the European Agency for the Evaluation of Medicinal Products or European Medicines Evaluation Agency (EMEA)

The regulation of medicinal products is administered in the EU/EEA by Directive 2001/83/EC

A firm or organization proposed to market their medicinal products within the European Economic Area should first get the marketing authorization from a competent authority of a Member State of European Union (EU) or European Economic Area (EEA country) or when an authorisation has been allowed as per Regulation (EC) No 726/2004.

In the centralized procedure the scientific evaluation of applications for European Union marketing authorizations for human and veterinary medicines are carried out by the European Medicines Agency [EMA]. The pharmaceutical companies submit a single marketing – authorization application to the EMA under the centralized procedure. A centralised marketing authorization once granted by the European commission is valid in all European Union (EU) member states, as well as in the European Economic Area (EEA) countries.

Scientific committees, which are made up of members from EEA countries, as well as representatives of patient, consumer and healthcare – professional organizations carry out the majority of the EMA'S scientific evaluation work.

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The scientific work of the European Medicines Agency (EMA) is conducted by seven scientific committees and a number of working parties and related groups.

The 7 scientific committees of EMA are:

- Committee for Medicinal Products for Human Use (CHMP)
- Pharmacovigilance Risk Assessment Committee (PRAC)
- Committee for Medicinal Products for Veterinary Use (CVMP)
- Committee for Orphan Medicinal Products (COMP)
- Committee on Herbal Medicinal Products (HMPC)
- Committee for Advanced Therapies (CAT)
- Pediatric Committee (PDCO)

II. DISCUSSION:

Marketing Authorization:

To market a medicinal product in the EU member states an application called Marketing Authorization Application (MAA) is submitted to the European Medicines Agency (EMA).

Applicant should notify the European Medicines Agency (EMA) of their intention to submit an application and give a realistic estimate of month of submission at least seven months before submission.

MAA can be filled in four ways:

- Centralised procedure
- National procedure
- Mutual recognition procedure
- Decentralised procedure

The authorization of these procedures is done by different member states which is shown in the below figure (1).

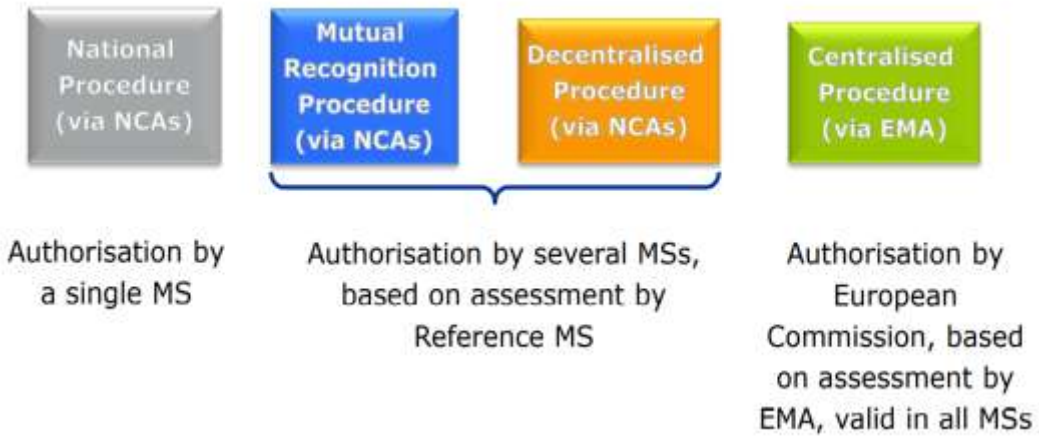

Figure (1)

Requirements for Marketing Authorization:

A comprehensive dossier called as common technical document (CTD) must be submitted by the regulatory team to the appropriate competent authority(s) (CAs) in order to make a marketing authorisation application (MAA). The requirements for marketing authorization i.e., the CTD triangle is described in the below figure (2).

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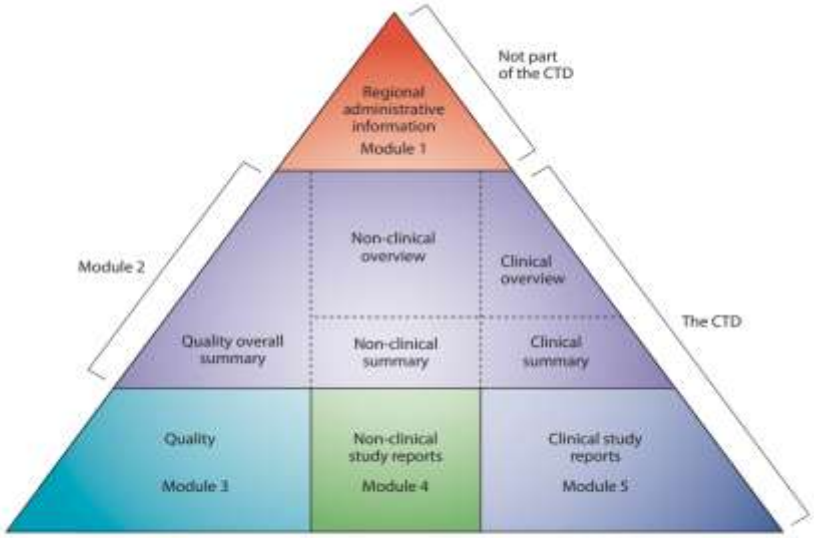

The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

Figure (2)-CTD Triangle

EU: MAA Regulatory Submissions-General process flow:

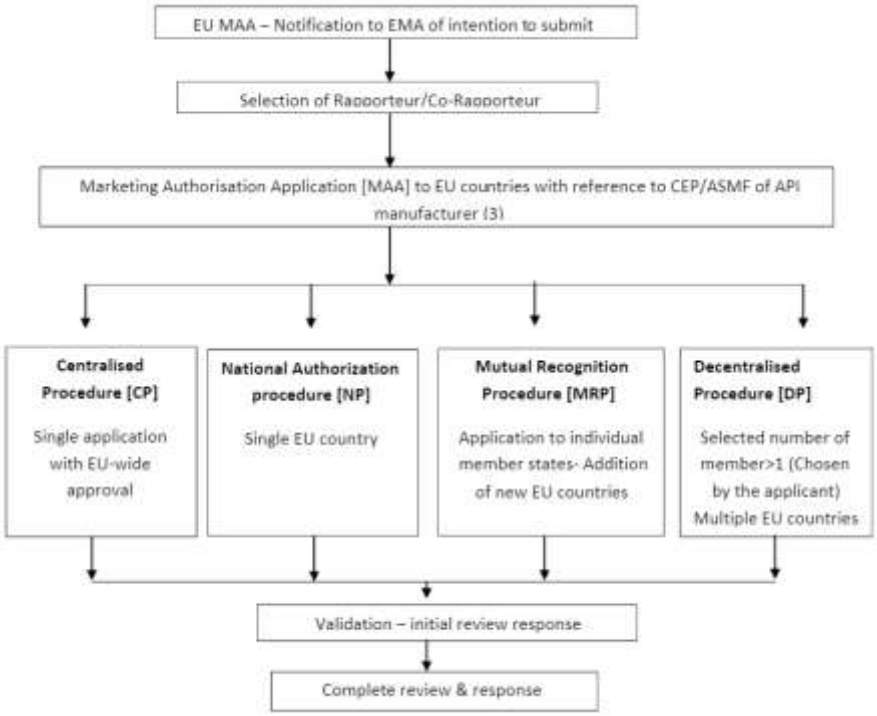

Figure (3)-MAA Regulatory submissions general process

Marketing authorization for covid-19 vaccines:

The European Medicines Agency (EMA) operates rapid procedures to support the development and evaluation of treatments and vaccines for COVID-19 together with the responsible scientific committees and their working parties, and in collaboration with the European Commission.

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The applications for COVID-19 medicines are assessed by the European Medicines Agency (EMA) which is essential for a thorough evaluation of the medicine's benefits and risks under the minimum timeframe.

The COVID-19 EMA pandemic Task Force (COVID-ETF) coordinates and enables fast regulatory action on the development of vaccines, authorisation of treatments and vaccines and safety monitoring of treatments and vaccines intended for the treatment and prevention of COVID-19.

Rapid procedures:

- Every step of the regulatory pathway can be accelerated by EMA"s rapid procedures while ensuring that robust evidence on efficacy, safety and quality is generated which is necessary to support scientific and regulatory decisions.

- There are no pre-specified submission deadlines for developers to submit their submission dossier.
- There is flexibility regarding the type and extent of the briefing dossier, which needs to be discussed on a case-by-case basis.
- This scientific advice is free of charge in accordance with the EMA Executive Director Decision (EMA/133106/2021).
- The total review time from the start to the final advice letter is reduced to 20 days, compared to the regular 40/70 days' timeframe which is achieved through accelerating all stages of process such as validation, assessment report circulation, peer review, adoption. The timelines could be shortened even further depending on the nature of the request.

To plan for such rapid scientific advice, developers should make the initial contact through the 2019- ncov@ema.europa.eu mailbox in order to allow review of suitability and maturity of the planned request for the rapid scientific advice procedure.

Applying for conditional marketing authorisation:

Conditional marketing authorisation:

- Is a regulatory tool for granting marketing authorisationto fast track medicines for use in emergency situations as soon as sufficient data becomes available to demonstrate that the benefits outweigh the risks.
- It ensures that the medicine is manufactured and controlled according to high pharmaceutical standards that are compatible with large scale commercialisation.
- Companies must provide further data from ongoing or new studies within pre-defined deadlines Once conditional marketing authorization has been granted, to confirm that the benefits continue to outweigh the risks.
- Conditional marketing authorization is valid for one year and it is renewable.
- For the treatment or prevention of COVID-19, rapid procedures are available for initial marketing-authorisation applications.
- These Rapid procedures are also available for applications to 'repurpose' medicines that are already authorised for other conditions, by extending their indications to include COVID-19.

Rapid scientific advice:

In support of evidence generation, rapid scientific advice is provided for planning for treatments and vaccines for COVID-19. It is an ad hoc procedure. This procedure follows the general principles of the regular scientific advice but with certain adaptations in order to facilitate acceleration. The advice will be adopted by the CHMP, but the process will also involve the COVID-ETF.

The following are the key features of rapid scientific advice:

Conditional marketing authorization is also intended for use during a public health emergency (e.g., a pandemic). Less comprehensive pharmaceutical and non-clinical data may also be accepted for these types of medicines. Article 14(7) of Regulation (EC) No 726/2004 is the legal basis. Regulation (EC) No 507/2006 further elaborates the provisions for granting a conditional marketing authorisation.

Requests or proposals:

The applicant together with an application may submit a request for a conditional marketing authorisation in accordance with Article 6 of Regulation (EC) No 726/2004. The request shall be accompanied by details showing that the product falls within the scope of this Regulation and satisfies the requirements laid down in Article 4(1). The Agency shall immediately inform the Commission of applications containing a request for a conditional marketing authorization.

The Committee for Medicinal Products for Human Use, hereinafter 'the Committee', may, in its opinion on an application submitted in accordance with Article 6 of Regulation (EC) No 726/2004,

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propose a conditional marketing authorisation, after having consulted the applicant.

Criteria and conditions:

if EMA's CHMP finds that all of the following criteria are met then it may grant a conditional marketing authorisation for a medicine if:

- the medicine's benefit-risk balance is positive;
- it is likely that the applicant will be able to provide comprehensive data post-authorisation;
- the medicine fulfils an unmet medical need;
- the benefit of the medicine's immediate availability to patients is greater than the risk inherent in the fact that additional data are still required.

Specific obligations:

specific obligations must be fulfilled within the defined timelines by the marketing authorisation holder, once a conditional marketing authorisation has been granted.

with a view to confirming that the risk-benefit balance is positive the holder of a conditional marketing authorisation shall be required to complete ongoing studies, or to conduct new studies and should provide the additional data that is referred to in Article 4(1).

Renewal:

The conditional marketing authorisation may be renewed annually After its period of validity of one year.

At least six months before the expiry of theconditional marketing authorisation the application for renewal together with an interim report on the fulfilment of the specific obligations to which it is subject shall be submitted to the Agency.

The Agency shall make sure that within 90 days the opinion of the Committee is given following receipt of a valid renewal application. The opinion of the committee shall be made publicly available.

Until a decision is adopted by the Commission in accordance with Article 10 of Regulation (EC) No 726/2004 the conditional marketing authorisation shall remain valid.

Use during COVID-19 pandemic:

EMA's conditional marketing authorisation is being used to facilitate the approval of safe and effective COVID-19 treatments and vaccines in the European Union during the COVID-19 pandemic.

To speed up the approval process and to save lives during public health emergencies the conditional marketing authorisation is used as the fast-track authorisation procedure which is in line with EU legislation.

As soon as sufficient data becomes available to demonstrate that the medicine's benefits outweigh its risks it allows regulators to grant a marketing authorisation with robust safeguards and controls in place post-authorisation.

It is the most appropriate tool to grant access to COVID-19 vaccines to all EU citizens at a time. It is the most appropriate tool to support mass vaccination campaigns also.

Guidance for applicants:

Applications for a marketing authorisation for products intended for prevention or treatment of COVID-19 will be treated in an expedited manner. The applicants are advised to contact EMA via email to 2019-ncov@ema.europa.eu early in the development to discuss scientific and regulatory aspects of their planned application. The guidance for the applicants is described in detail in below figure (4).

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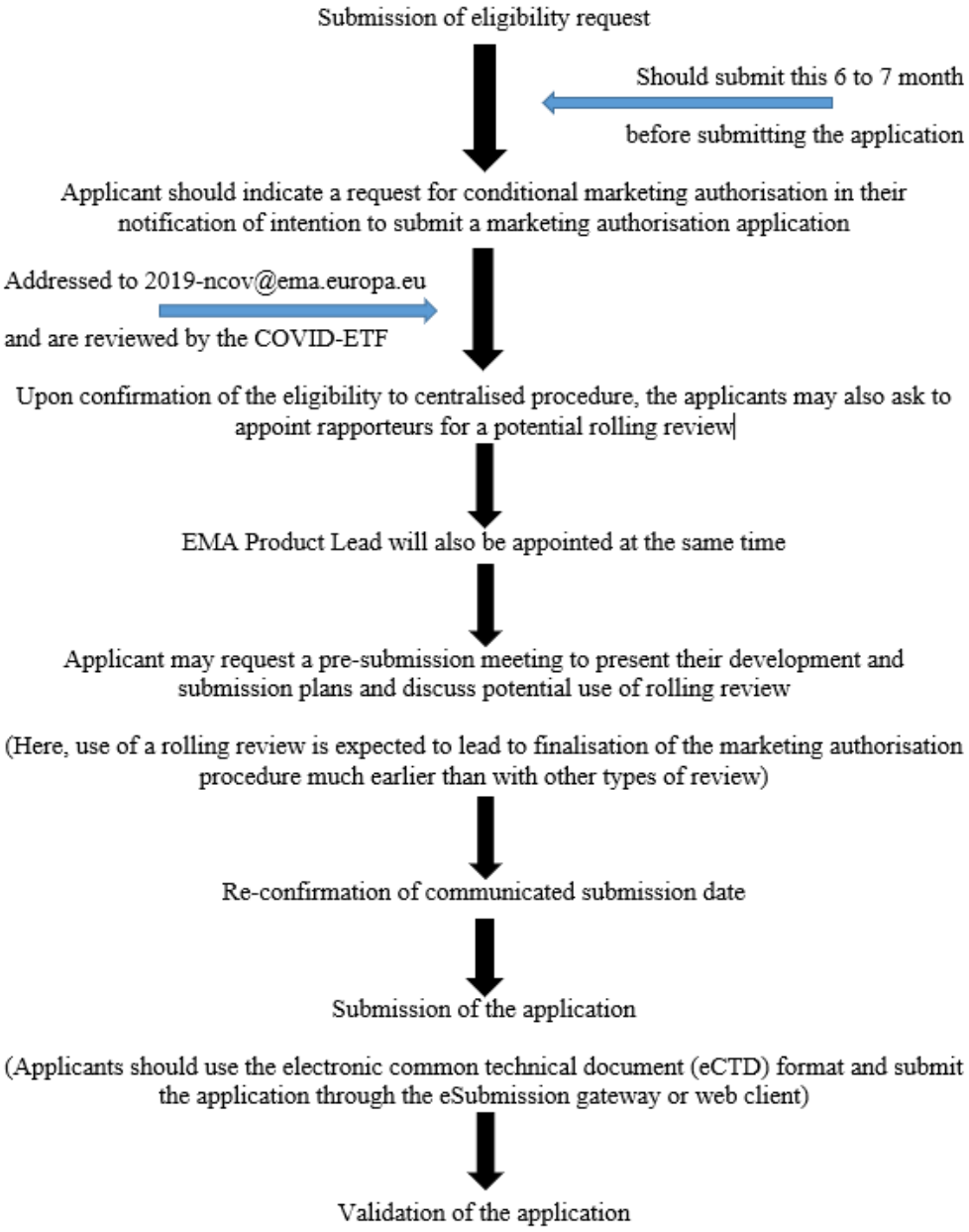

Should the applicant not wish to use rolling review or in case the application has not been accepted for such review, the applicant may still apply for accelerated assessment. In such case, after validation of a complete application only the review of the application is started, but the maximum active review time which is 210 days is reduced to 150 days, which in practice may even be shorter.

A conditional marketing authorisation request should be included by applicants in their MA application. The CHMP will assess this request together with the application.

EMA will work closely with the European Commission, keeping them informed about such applications, to facilitate the acceleration of the decision-making process and also accelerates the linguistic review process for products intended for prevention or treatment of COVID-19.

Accelerated assessment:

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In order to review a marketing-authorisation application, accelerated assessment procedure reduces the timeframe for the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP). if the CHMP decides the product is of major interest for public health and therapeutic innovation then the applications may be eligible for accelerated assessment. This Can be considered for medicines and vaccines not undergoing a rolling review. unlike a rolling review it Requires a complete application to be available at the time of submission.

It can take up to 210 days for evaluating a marketing-authorisation application under the centralised procedure, not counting clock stops when the applicants have to provide additional information. If the applicant provides sufficient justification for an accelerated assessment, then the CHMP can reduce the timeframe to 150 days on request of the applicant.

The CHMP issues a scientific opinion on whether the medicine may be authorised or not after the evaluation of the application. European Medicines Agency sends the opinion of the CHMP to the European Commission, which issues the marketing authorisation.

Pharmacovigilance plan for COVID-19 vaccines:

The EMA in association with NCAs fostered an extensive guidance and the legal provisions on pharmacovigilance that are applicable to all medicinal products authorized in the EU, including COVID-19 vaccines which are set out in the good pharmacovigilance practices (GVP).

The pharmacovigilance plan for COVID-19 vaccines sets out how EMA and the National competent authorities in the EU Member States distinguish and assess any new relevant data that emerges immediately, including any safety signals for the benefit-risk balance of these vaccines.

The regulators can take any appropriate regulatory actions according to this pharmacovigilance plan and communicate these to the public as quickly as possible.

The monitoring activities in the plan apply to all vaccines, but they take place on a bigger scale during this pandemic:

- Collecting exposure data to COVID-19 vaccines

Collection of exposure data:

- specific safety signal detection and management measures are adopted
- For monitoring COVID-19 treatments and vaccines a European infrastructure is established
- Using real-world data from clinical practice
- Exceptional transparency measures are applied

Marketing authorisation applicants develop risk management plans for COVID-19 vaccines based on EMA's guidance which set out how the company will monitor and report on safety and following authorisation of a COVID-19 vaccine how the company will characterise and manage risks.

Risk management plan:

The detailed requirements and guidance on the principles of risk management (GVP Module V) and the format of the risk management plan (RMP template) along with the pharmacovigilance requirements for vaccines (GVP P.I) are included in the good pharmacovigilance practices.

Also, core RMP necessities for COVID-19 immunizations have been created to work with and blend the planning of RMPs by organizations and their assessment by assessors. The 'coreRMP19' addresses the planning of the post-authorization safety follow-up of COVID-19 immunizations by MAHs, while recognizing vulnerabilities in the pandemic setting and prescribing approaches to prepare for pharmacovigilance activities.

Periodic safety reports:

Marketing authorization holders (MAHs) submit the Periodic safety update reports (PSURs) at 6 months intervals in the first years of authorisation for evaluation by regulatory authorities for any medicinal product and with a decreasing frequency thereafter.

The monthly summary safety reports should be submitted to the agency by MAHs in addition to regular PSURs for COVID-19 vaccines. The information on reported suspected adverse reactions, including adverse events of special interest (AESIs), and sales data will be included in these summary safety reports along with other data. The coreRMP19 lists out the minimum elements that are needed to be addressed in these safety reports.

For each COVID-19 vaccine a timely availability of aggregated exposure data will be

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fundamental for several pharmacovigilance activities including observed-to-anticipated analyses. By implementing national health data registers the Member states will be gathering the data and collect information on individual vaccinations. The EMA will collect this data from Member States and compiles this data.

In the EU during clinical use the need for product and batch traceability is an important requirement for the safety monitoring of all biological medicines. The release by the manufacturer, the entire distribution chain and the actual vaccination comes under the traceability requirements. The RMP should describe the use of traceability tools such as stickers and their executionshould be agreed at national level.

Observational research:

MAHs voluntarily or upon request from the regulatory authorities conducts post-authorization safety studies (PASS). The need for observational PASS studies will be carefully considered as routine activities and to provide adequate data ongoing or planned clinical trials may not be sufficient to further characterise identified and potential risks and investigate missing information for COVID-19 vaccines. To support the readiness of research networks and to perform observational research EMA has contracts in place with academic and private partners including on COVID-19 treatments and vaccines.

To monitor the safety, effectiveness and coverage of COVID-19 vaccines the ACCESS project ('vACCine Covid-19 monitoring readinESS') focuses on data sources and epidemiological methods. This project involves 22 research centres in Europe. EMA Advisory Group composed of members of the ECDC, PRAC and CHMP supports the ACCESS project.

Spontaneous reporting of suspected adverse reactions:

The GVP Module VI addresses the regulatory requirements for the collection, data management and submission of individual reports of suspected adverse reactions associated with medicinal products. GVP P.I also contains specific recommendations for vaccines.

In the context of COVID-19 a detailed guidance on individual case safety reports (ICSRs) are published by the Agency, which takes into account, the guidance regarding COVID-19 related terms which are published by the Maintenance and Support Services Organization of the Medical Dictionary for Regulatory Activities (MedDRA MSSO) and the implementation of the updated MedDRA 23.0 containing additional COVID-19 related terms.

COVID-19 vaccines will be subjected to additional monitoring, upon authorisation, which aims at enhancing the reporting of suspected adverse reactions.

Signal management:

In EU the GVP Module IX describes the roles and responsibilities, processes and requirements for signal management.

Provisions for emerging safety issues (ESIs) i.e., those safety issues that require urgent attention by the competent authorities which are considered by MAHs are also included in the module. The module's addendum also discusses about the methodological aspects of signal detection from various spontaneous reports. The Agency has also published scientific guidance on screening for adverse reactions in EudraVigilance.

Exchange of information:

To communicate on signals the European Pharmacovigilance Issues Tracking Tool (EPITT) is the tool that is established within the EU regulatory network which may warrant evaluation by Pharmacovigilance Risk Assessment committee (PRAC) and through the Rapid Alert (RA) and Non-Urgent Information (NUI) System, it is used to support rapid exchange of the data on other safety concerns. RAs and NUIs will be the preferred channels in the context of the pandemic, for the timely exchange of further data on batch related issues, national communications, or that of any concern that may not warrant a regulatory action yet could affect the vaccination programmes because of public perception.

Through EMA's Patients' and Consumers' Working Party (PCWP) and the Healthcare Professionals' Working Party (HCPWP), the European Medicines Agency will engage with EU networks of patients, consumers and healthcare professionals and the agency will distribute any relevant information on COVID-19 vaccines to their organisations. National Competent Authorities (NCAs) may also interact at national level with patients' and healthcare professionals' organisations.

In countries outside the EU, e.g., US FDA and Health Canada, and international public health organisations, such as WHO the Agency has regular interactions with the regulators. In

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compliance with that of the confidentiality agreements discussions on specific safety topics will take place as necessary.

Communication and transparency:

For all the medicines that are authorised in the European Economic Area (EEA), certain descriptive information on suspected adverse reactionsis reported to EudraVigilance which is published by the agency. The Early Notification System isoperated by the agency and it circulates this information to National Competent Authorities (NCAs) and international partners safety communications agreed at EMA Committees under prohibition ahead of publication. Lines-to-take are additionally developed to address expected media questions.

Capacity building:

In order to continuously achieve a high quality and fit-for-purpose safety monitoring and risk management of the COVID-19 vaccines, NCAs and supporting EMA staff should have the necessary expertise at their disposal. To support and reinforce the knowledge of assessors and staff who will be involved in these activities, the Agency, in collaboration with NCAs, have set up a dedicated training program. The training builds on the scientific and regulatory experience gained by EMA and NCA experts through procedures for, COVID-19 related products where a pharmacovigilance assessment was performed. The training recordings and presentations will be made available on the EU Network Training Centre (EU NTC) Learning Management System platform.

III. CONCLUSION:

The guidelines for the development, evaluation and marketing authorization of vaccines differs from one country to other countries. Each country has certain set of standards established by its regulatory body or agency and every manufacturer should follow these standard guidelines in order to market their drugs or biologics in that country.

As COVID-19 is declared as a pandemic by World Health Organization (WHO) there is an urgent constant need for the manufacturers and developers to manufacture a drug or vaccine for the treatment of COVID-19, which enabled the manufacturers for accelerated development of various vaccine technologies which in turn enabled the regulatory authorities of various countries to grant the Emergency use authorization for these vaccines.

In order to accelerate the process of medicine and vaccine development and to accelerate the approval process for COVID-19 vaccines, the European Medicines Agency (EMA) is providing guidance for medicine developers and pharmaceutical companies and is also providing guidance on how they should address the regulatory challenges arising from the COVID-19 pandemic.

EMA uses its rolling review procedure for promising medicines for COVID-19. As the data becomes available during the development process, this allows EMA to begin assessing data to assist the subsequent formal marketing authorisation application assessment even further.

EMA's conditional marketing authorisation is being used during the COVID-19 pandemic, in order to assist the approval of safe and effective COVID-19 treatments and vaccines in the EU.

The European Medicines Agency (EMA) is assessing potential COVID-19 vaccines to enable the distribution of vaccines in the European Union (EU) as soon as possible.

The COVID-19 vaccines that are under the rolling review and that has been authorized to use in EU are described below.

The following COVID-19 vaccinesare being evaluated by the EMA's Committee for Medicinal Products for Human Use (CHMP):

TABLE 1:COVID-19 vaccines under rolling review

SL. NO	BRAND NAME	COMPANY	VACCINE TYPE	VACCINE
1.	COVID-19 Vaccine (Vero Cell)	Sinovac Life Sciences Co., Ltd	Inactivated	

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2.	CVnCoV	CureVac AG	mRNA-based vaccine	
3.	NVX-CoV2373	Novavax CZ AS	subunit	
4.	Sputnik V (Gam-COVID-Vac)	Russia's Gamaleya National Centre of Epidemiology and Microbiology	adenovirus viral vector vaccine	
5.	Vidprevtyn	Sanofi Pasteur	Protein-based vaccine	

TABLE 2:Authorised COVID-19 vaccines

SL. NO	BRAND NAME	COMPANY	VACCINE TYPE	VACCINE
1.	Comirnaty	Pfizer–BioNTech	mRNA-based vaccine (nucleoside-modified)	
2.	COVID-19 Vaccine Janssen	Johnson & Johnson	viral vector vaccine based on a human adenovirus	
3.	Spikevax (previously COVID-19 Vaccine Moderna)	Moderna	mRNA-based vaccine	

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4.	Vaxzevria (previously COVID-19 Vaccine AstraZeneca)	Oxford–AstraZeneca	Viral vector (adenovirus)	

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