EMA/333964/2020

Pharmacovigilance Plan of the EU Regulatory Network for COVID-19 Vaccines

1. Background

Since its emergence in 2019, the SARS-Cov2 virus has spread to almost every country making the COVID-19 pandemic a global health crisis.

COVID-19 vaccines once available are expected to play a major role in the control of the pandemic. While developed at unprecedented speed, they will only be authorised by European Union (EU) authorities if their benefits outweigh their risks based on data on efficacy, safety and quality.

During the development phase of any medicine, a limited number of selected participants are included in clinical trials and followed up for a relatively short duration under controlled conditions. As a result, certain side effects, particularly rare or very rare ones, only emerge during real life use in many different people. It is therefore essential to closely monitor the safety and effectiveness of any medicine after it is authorised.

The uptake of COVID-19 vaccines once authorised is anticipated to be very high which may lead to a high volume of suspected adverse reaction reports and other safety data. Thus, the prompt detection and evaluation of new information on the benefit-risk balance of these vaccines, timely communication and a high level of transparency will be key to protect public health and ensure the public's trust in the vaccines and in the regulatory system.

In view of the public health urgency and the extensive vaccination campaigns foreseen worldwide, the European Medicines Agency (EMA) and the national competent authorities (NCAs) in EU member states have prepared themselves for the expected high data volume by putting in place this pharmacovigilance plan specific for COVID-19 vaccines. This is to ensure that all new information collected post-marketing will be promptly reviewed and any emerging new information will be shared with the public in a timely manner. The plan builds on the well-established pharmacovigilance system of the EU regulatory network and the experience gained during the 2009 (H1N1) flu pandemic while taking into account the current specificities of the COVID-19 pandemic.

2. Scope

The present document provides an overview of the activities the EU regulatory network (EMA and NCAs) will conduct once COVID-19 vaccines are authorised.

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The legal provisions on pharmacovigilance[1] and the extensive guidance developed by EMA in collaboration with NCAs set out in the good pharmacovigilance practices (GVP), apply to all medicinal products authorised in the EU, including COVID-19 vaccines.

This document focusses on the activities planned specifically for COVID-19 vaccines. The established processes and requirements for pharmacovigilance in general are briefly noted where relevant to provide context.

3. Objectives

The main objectives of this plan include:

- Active collection of data on rare potential risks;
- Rapid detection, prioritisation and assessment of emerging safety information derived from spontaneous reporting systems, observational studies and other data sources;
- Prompt evaluation of the impact of detected safety issues on the benefit-risk balance of the vaccines, taking into account exposure and effectiveness data;
- Active surveillance of vulnerable populations, such as pregnant women and older vaccinees;
- Engagement and collaboration with stakeholders including vaccinees and healthcare professionals, marketing authorisation holders (MAHs) and international partners;
- Prompt and effective communication of new information arising from the above activities.

4. Roles and responsibilities

The respective roles and responsibilities of MAHs, NCAs, the EMA and its scientific committees, including the Pharmacovigilance Risk Assessment Committee (PRAC) and the Committee for Medicinal Products for Human Use (CHMP), in the conduct of pharmacovigilance activities for medicinal products authorised in the EU are defined in the legislation and detailed in the respective GVP modules.

As part of its response to the COVID-19 pandemic, the Agency has established a COVID-19 EMA pandemic Task Force (COVID-ETF), whose main purpose is to draw on the expertise of the EU medicines regulatory network and ensure a fast and coordinated response to the COVID-19 pandemic. Amongst other activities, the task force will support the regulatory activities of member states and the European Commission and contribute to the PRAC activities on emerging safety concerns related to COVID-19 vaccines. The COVID-ETF includes experts from the Agency and its scientific committees.

Patients and healthcare professionals are regularly involved in EU pharmacovigilance processes and have representatives in the PRAC. They will also have representatives in the COVID-ETF meetings, to provide input and bring views from their community on specific aspects of EMA's work during the pandemic.

[1] Directive 2001/83/EC, Regulation (EC) No 726/2004, Commission Implementing Regulation (EU) No 520/2012

5. Activities

5.1. Risk management plan

The good pharmacovigilance practices include 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 requirements for vaccines (GVP P.I).

In addition, core RMP requirements for COVID-19 vaccines have been developed to facilitate and harmonise the preparation of RMPs by companies and their evaluation by assessors. The 'coreRMP19' addresses the planning of the post-authorisation safety follow-up of COVID-19 vaccines by MAHs, while acknowledging uncertainties in the pandemic setting and recommending ways to prepare for pharmacovigilance activities.

5.2. Periodic safety reports

Periodic safety update reports (PSURs) are submitted by MAHs for evaluation by regulatory authorities at 6 months intervals in the first years of authorisation of any medicinal product and with a decreasing frequency thereafter (see GVP Module VII).

For COVID-19 vaccines, MAHs will be expected to submit to the Agency monthly summary safety reports in addition to regular PSURs. These will include, among others, information on reported suspected adverse reactions, including adverse events of special interest (AESIs), and sales data. The minimum elements to be addressed in these reports are listed in the coreRMP19.

5.3. Collection of exposure data

A timely availability of aggregated exposure data for each COVID-19 vaccine will be essential for several pharmacovigilance activities including observed-to-expected analyses. Member states will be gathering this data in various manners, for instance by implementing national health data registers to collect information on individual vaccinations. EMA will collect and compile this data from Member States.

An important requirement for the safety monitoring of all biological medicines in the EU (see GVP P.II: Biological medicinal products) is the need for product and batch traceability during clinical use. The traceability requirement covers the release by the manufacturer, the entire distribution chain and the actual vaccination. The use of traceability tools such as stickers should be described in the RMP (see coreRMP19). Their implementation is to be agreed at national level.

5.4. Observational research

Post-authorisation safety studies (PASS) are conducted by MAHs voluntarily or upon request from the regulatory authorities (see GVP Modules V and VIII). For COVID-19 vaccines, the need for observational PASS studies will be carefully considered as routine activities and ongoing or planned clinical trials may not be sufficient to provide adequate data to further characterise identified and potential risks and investigate missing information. Further recommendations are outlined in the coreRMP19.

EMA has contracts in place with academic and private partners to support the readiness of research networks to perform observational research, including on COVID-19 treatments and vaccines.

The ACCESS project ('vACCine Covid-19 monitoring readinESS') focuses on data sources and epidemiological methods to monitor the safety, effectiveness and coverage of COVID-19 vaccines. The project involves 22 research centres in Europe and its main objectives are to:

- Identify and characterise a Europe-wide network of data sources that could provide a continuous monitoring of the coverage, safety and effectiveness of COVID-19 vaccines and be used to investigate specific research questions on COVID-19 vaccines;
- Provide background rates of AESIs and other relevant conditions;
- Set up a network for the timely monitoring of coverage, safety and effectiveness of COVID-19 vaccines and the investigation of specific research questions including feasibility analyses.

The ACCESS project is supported by an EMA Advisory Group composed of members of the ECDC, PRAC and CHMP. The common protocols for safety studies and the network of data sources developed by ACCESS will be available to MAHs and other stakeholders for joint PASS studies. Vaccine-specific protocols submitted by applicants/MAHs will have to be endorsed PRAC and CHMP.

The CONSIGN ('COVID-19 infectiOn aNd medicineS In preGNancy') project will collect data on the impact of COVID-19 in pregnancy in order to guide decision-making about vaccine indications, vaccination policies and treatment options for COVID-19 in pregnant women. The project will be carried out in collaboration with the ConcePTION consortium, which was established under the EU Innovative Medicines Initiative (IMI), the International COVID-19 and pregnancy registry (COVI-PREG) project and the International Network of Obstetric Survey Systems (INOSS) network.

In addition to these initiatives, the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) may support the development and dissemination of good methodological practices for COVID-19 studies. The ENCePP Guide on Methodological Standards in Pharmacoepidemiology highlights relevant aspects for COVID-19 observational studies. Researchers should register their pharmacoepidemiological studies and make study protocols and reports public in the European Union electronic register of post-authorisation studies (EU PAS Register), to ensure transparency on the various research efforts.

Several NCAs will also conduct pharmacoepidemiological studies on COVID-19 vaccines at national level and will register these in the EU PAS Register.

EMA, ECDC and many national governments are working to secure public funding for vaccine safety monitoring studies. Information on studies that are initiated will be available on the EU PAS Register.

5.5. Spontaneous reporting of suspected adverse reactions

The regulatory requirements for the collection, data management and submission of individual reports of suspected adverse reactions associated with medicinal products are addressed in GVP Module VI. With respect to vaccines, there are also specific recommendations in GVP P.I.

The Agency has also published detailed guidance on individual case safety reports (ICSRs) in the context of COVID-19, which takes into account the guidance regarding COVID-19 related terms 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.

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

The quality and completeness of the information in ICSRs are important for any meaningful causality assessment and will be crucial in this context of mass vaccination. Beyond the minimum criteria required for ICSR validation (see GVP VI.B.2), reports should ideally contain precise information on demographics, vaccine brand, batch number, vaccination and reaction dates, outcome, concomitant drugs etc.

EMA and NCAs will encourage timely submission of ICSRs.

The submission of ICSRs with AESIs, or fatal or life-threatening reactions in a shorter timeframe than 15 days should be considered when feasible.

5.6. Signal management

The roles and responsibilities, processes and requirements for signal management in the EU are described in GVP Module IX. The module also includes provisions for emerging safety issues (ESIs) i.e. those safety issues considered by MAHs to require urgent attention by the competent authorities. Methodological aspects of signal detection from spontaneous reports are discussed in the module's addendum. The Agency has also published scientific guidance on screening for adverse reactions in EudraVigilance.

GVP P.I outlines specific considerations for signal detection in mass vaccination campaigns, with a discussion on the caveats of traditional disproportionality methods and on observed-to-expected analyses. It is anticipated that a high volume of ICSRs related to COVID-19 vaccines will be sent to spontaneous reporting systems, including EudraVigilance, with a relatively short lag after the vaccination campaigns start. Routine signal detection methods may be insufficient to screen such a volume of data efficiently and effectively. EMA and NCAs, within PRAC's signal management review technical working group (SMART WG), are testing several methodologies to address these challenges.

In line with the prioritisation principles outlined in GVP Module IX, timelines should be expedited as much as possible throughout the management of potential signals for COVID-19 vaccines, although this should not be at the expense of a thorough evaluation. For instance, the 30-day timeframe for the confirmation of a validated signal may need to be shortened to allow for discussion of the signal at the forthcoming PRAC meeting. Similarly, shorter than usual timetables for assessment by PRAC (e.g. 30 days) may be warranted for some signals. The COVID-ETF will support the PRAC by providing rapid advice on new safety issues related to COVID-19 vaccines.

5.7. Exchange of information

Within the EU regulatory network, the European Pharmacovigilance Issues Tracking Tool (EPITT) is the established tool to communicate on signals that may warrant evaluation by PRAC (see GVP Module IX) and to support rapid exchange of information on other safety concerns through the Rapid Alert (RA) and Non-Urgent Information (NUI) System (see EU regulatory network incident management plan). In the context of the pandemic, RAs and NUIs will be the preferred channels to timely exchange of further information on batch related issues, national communications, or any concern that may not warrant a regulatory action but could have an impact on the vaccination programmes due to public perception.

The Agency will engage with EU networks of patients, consumers and healthcare professionals, for example through EMA's Patients' and Consumers' Working Party (PCWP) and the Healthcare Professionals' Working Party (HCPWP), and will disseminate any relevant information on COVID-19 vaccines to their organisations. NCAs may also interact at national level with patients' and healthcare professionals' organisations.

The Agency has regular interactions with regulators in countries outside the EU, e.g. US FDA and Health Canada, and international public health organisations, such as WHO. Discussions on specific safety topics will take place as necessary and in compliance with the confidentiality agreements in place. In addition, the International Coalition of Medicines Regulatory Agencies (ICMRA) provides a framework for exchanging information on COVID-19 related initiatives and best practices across worldwide stakeholders. Its vaccines and surveillance working group has developed a COVID-19 pharmacovigilance network to share knowledge, experience and communication on pharmacovigilance planning activities, as well as emerging data on the safety and effectiveness of vaccines, once deployed.

Exchanges between MAHs, Rapporteurs at EMA committee level and EMA will take place whenever warranted to discuss any emerging information on the benefit-risk balance of the vaccines.

5.8. Communication and transparency

A detailed overview of established EMA transparency practices in relation to medicinal products is provided in the Guide to information on human medicines evaluated by EMA. The Agency also publishes descriptive information on suspected adverse reactions reported to EudraVigilance for all medicines authorised in the European Economic Area (EEA). The Agency operates the Early Notification System and circulates to NCAs and international partners safety communications agreed at EMA Committees under embargo ahead of publication. Lines-to-take are also developed to address anticipated media queries.

In addition to these, the Agency has put in place Exceptional transparency measures in relation to COVID-19 vaccines and treatments approved or under evaluation. These include the publication of the full RMPs for these products.

The scope of the meeting Highlights from the PRAC, has also been extended to include information on other safety procedures involving COVID-19 treatments and vaccines, including signals, PSURs, PASS and RMPs.

The Agency will publish regular pharmacovigilance updates on the approved COVID-19 vaccines, with the latest information. The format and contents will be developed in collaboration with NCAs through PRAC.

Patients', consumers' and healthcare professionals' organisations will be consulted during the preparation of some of these communication materials and pre-user testing will be considered.

NCAs may have webpages or websites dedicated to the pandemic, with information on suspected adverse reactions reported for COVID-19 vaccines in their territories.

5.9. 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 programme. 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.

List of abbreviations

ACCESS: vACCine Covid-19 monitoring readinESS

AESI: adverse event of special interest

CHMP: Committee for Medicinal Products for Human Use

CONSIGN: COVID-19 infectiOn aNd medicineS In preGNancy

COVID-19: Coronavirus disease 2019

COVID-ETF: COVID-19 EMA pandemic Task Force

COVI-PREG: International COVID-19 and pregnancy registry

ECDC: European Centre for Disease Prevention and Control

EEA: European Economic Area

EMA: European Medicines Agency

ENCePP: European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

EPITT: European Pharmacovigilance Issues Tracking Tool

ESI: emerging safety issue

EU: European Union

EU NTC: EU Network Training Centre

EU PAS Register: European Union electronic register of post-authorisation studies

FDA: Food and Drug Administration

GVP: Good pharmacovigilance practices

HCPWP: Healthcare Professionals' Working Party

HRA: health regulatory authority

ICMRA: International Coalition of Medicines Regulatory Authorities

ICSR: individual case safety report

IMI: Innovative Medicines Initiative

INOSS: International Network of Obstetric Survey Systems

MAH: marketing authorisation holder

MedDRA: Medical Dictionary for Regulatory Activities

MSSO: Maintenance and Support Services Organization

MS: Member State

NCA: national competent authority

NUI: non-urgent information

PASS: post-authorisation safety study

PCWP: Patients' and Consumers' Working Parties

PRAC: Pharmacovigilance Risk Assessment Committee

PSUR: periodic safety update report

RA: rapid alert

RMP: risk management plan

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

SMART WG: Signal Management Review Technical Working Group

US: United States

WHO: World Health Organization