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The Role of EudraVigilance in Protecting and Promoting Public Health in the European Economic Area in the Context of the SARS-CoV-2 Pandemic

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ABSTRACT: The EudraVigilance database is the central pillar for pharmacovigilance activities in the European Economic Area. The reporting of adverse reactions in the EEA through the EudraVigilance system enables the management of reported data and the analysis of adverse medicine reactions, with the information being available anywhere in the EEA. This article aims to analyze, on the one hand, the EU legislation on pharmacovigilance, the key activities and developments that will take place through the implementation of the EudraVigilance Operational Plan 2020–2022, a document launched by the European Medicines Agency to ensure the sustainability of EudraVigilance and the associated actions in support of EU pharmacovigilance and public health protection activities. On the other hand, the article aims to analyze how, in accordance with a specific pharmacovigilance plan and using the EudraVigilance system, the EMA and the national competent authorities (NCA) of the EU member states have monitored suspected adverse reactions to the COVID-19 vaccines, thereby contributing to the protection of the health of European citizens.

KEYWORDS: EU pharmacovigilance legislation, EudraVigilance, public health, European Economic Area, COVID-19 vaccines

Introduction

EudraVigilance is the central pillar for pharmacovigilance activities in the European Economic Area (EEA). In February and April 2017, the improved EudraVigilance system successfully passed an independent audit in accordance with Article 24 of Regulation (EC) 726/2004. The EMA Management Board confirmed on 22 May 2017 that the full functionality of the EudraVigilance database was achieved and that the system met the defined functional specifications (EMA 2017). The new EudraVigilance system was launched on 22 November 2017, providing improved functionality to national competent authorities, the European Medicines Agency (EMA), the Commission and the marketing authorization holders for the effective reporting and monitoring of suspected adverse reactions and the detection of suspected adverse reactions and medicine safety risks, thus contributing to the protection and promotion of public health. In addition, EudraVigilance facilitates the safety reporting of suspected unexpected serious adverse reactions (SUSARs) to experimental medicines which occur during clinical trials.

By the end of 2019, EudraVigilance held information on more than 16.5 million safety reports, covering 7.95 million cases, as well as information on 744,219 medicines on the EU market. EudraVigilance is used for signal detection by EMA and national authorities and in support of other pharmacovigilance procedures in terms of data analysis.

In addition, making available all individual case safety reports (ICSRs) from the European Economic Area to the Uppsala Monitoring Centre (UMC) of the World Health Organization (WHO) directly from EudraVigilance facilitates global pharmacovigilance activities.

The reporting of adverse reactions in the EEA through the EudraVigilance system allows the management of reported data and the analysis of adverse reactions to medicines, the information being available anywhere in the European Economic Area.

Theory

The EudraVigilance system is operated by the European Medicines Agency through the Pharmacovigilance Risk Assessment Committee (PRAC). EMA launched in May 2020 the EudraVigilance 2020–2022 Operational Plan (EMA 2020a), document that describes the key activities and the developments that will take place, as well as their estimated impact on the stakeholders. The pharmacovigilance risk assessment committee evaluates the alerts registered in the EudraVigilance system and can recommend regulatory actions for reported situations.

The objective of the plan is to outline technical and operational activities with anticipated timelines and highlight how EudraVigilance and the stakeholders interacting with the system will be affected. This should facilitate planning by EMA, which operates EudraVigilance on behalf of the network, and ensure the timely preparation of national competent authorities, marketing authorization holders, commercial and non-commercial sponsors of clinical trials and the WHO Uppsala Monitoring Centre.

The aim is to ensure the sustainability of EudraVigilance and of associated actions in support of EU pharmacovigilance activities and public health protection. In addition, interaction with stakeholders as part of training and support, as well as of communication and engagement, are covered to ensure that a platform for learning, cooperation, dialogue, and alignment is provided throughout the evolution and operation of the EudraVigilance system.

The operational plan is regularly updated regarding timetables and new activities/developments. Enhanced access to EudraVigilance data is also provided for healthcare professionals, the public and academia. By simplifying the reporting of suspected adverse reactions and improving the tools for their analysis and monitoring, EudraVigilance contributes to the optimization of the risk-to-benefit ratio of medicines and thus to the protection and promotion of public health. The key areas supported by EudraVigilance are:

- Collection and processing of adverse drug reaction reports.
- Maintaining and updating the Extended EudraVigilance Medicinal Product Dictionary, based on information on all medicines authorized in the EU.
- Ongoing activities on data quality, detection and management of duplicate reports and categorization of reported information on medicines.
- Producing and providing drug safety data analysis reports to the EU network (electronic reaction monitoring reports - eRMR) and providing data analysis to support assessments in pharmacovigilance procedures.
- Supporting the central role of the Pharmacovigilance Risk Assessment Committee in evaluating and monitoring the safety of medicines for human use in the EU, including prioritization and evaluation of safety signals.
- Signal management and data monitoring available in EudraVigilance by marketing authorization holders.
- Continuation of public access to aggregated EudraVigilance data (www.adrreports.eu).
- Making adverse reaction reports originating in the EEA available to the WHO Uppsala Observatory.

Article 26 of the Implementing Regulation (EC) 520/2012 of the Commission emphasizes the use of internationally agreed formats and standards in the context of pharmacovigilance.

In accordance with Article 24 paragraph (2) third point of Regulation (EC) no. 726/2004, the Pharmacovigilance Risk Assessment Committee recommended, on October 2, 2019, that the use of the ISO ICSR standard based on the ICH E2B(R3) modalities, and the related ISO standard terminology should become mandatory as of June 30, 2022 with regard to reporting obligations to EudraVigilance.

The set of five ISO standards for medicinal product identification defines the rules and data elements that uniquely identify drugs and related concepts, such as pharmaceutical products, substances, pharmaceutical forms, units of presentation, routes of administration,

and units of measurement. Implementing Regulation (EU) no. 520/2012 of the Commission (Articles 25 and 26) defines the use of ISO standards in the context of pharmacovigilance.

EudraVigilance Clinical Trial Module (EVCTM) and the reporting of suspected unexpected serious adverse reactions (SUSARs) to investigational medicinal products during clinical trials will undergo a major change when the Clinical Trials Regulation becomes applicable. The Regulation enables the harmonization of the evaluation and supervision processes for clinical trials across the EU, through a Clinical Trial Information System (CTIS), formerly the EU Clinical Trials Portal and Database. The Regulation simplifies the rules on safety reporting, introducing the possibility of a risk-proportionate approach, in particular, but not limited to, low-intervention clinical trials. It also simplifies safety reporting by sponsors, in accordance with Article 40 of the Regulation.

In addition, several documents in EudraLex Volume 10 are revised and updated to bring them in line with the changes required by the Clinical Trials Regulation (EU) no. 536/2014. In addition, new documents have been prepared to cover new aspects introduced by the same regulation.

Medical literature is an important source of information for identifying suspected adverse reactions to authorized medicinal products. The EMA is responsible for monitoring several substances and selected medical literature to identify suspected adverse reactions to medicinal products authorized in the Union and for entering the relevant information into the EudraVigilance database, the service being fully operational since 1 September 2015.

Marketing authorization holders in the European Economic Area are usually responsible for monitoring the medical literature on their medicines and reporting individual cases of suspected adverse reactions to EudraVigilance and national safety databases.

Results and discussions

The Commission publishes at set intervals a report on the activities of the Member States and the EMA, to monitor the safety of medicinal products throughout their life cycle, as provided for by pharmacovigilance legislation. The report describes the activities of the EU collaborative system for monitoring and controlling the safety of medicinal products for human use.

The Commission's last report (European Commission 2019) focused on the experience of the European Medicines Agency, at the national and European levels, regarding the list of medicinal products for human use subject to additional monitoring.

The outbreak of novel coronavirus type 2 (SARS-CoV-2) infection, which began in late December 2019 in China and rapidly escalated into a COVID-19 pandemic, has spurred the development of preventive measures and treatment options, including vaccines. New production platforms and molecular biology tools have enabled the rapid design of COVID-19 vaccine candidates, classified into two broad categories (Graham 2020), gene-based vaccines and protein-based vaccines. In December 2020, the UK, US and European Union authorized the first vaccines.

As of 28 May 2021, four gene-based COVID-19 vaccines have received conditional marketing authorization in the EU following evaluation by the European Medicines Agency and are part of the EU portfolio of coronavirus vaccine strategy. Two belong to the type of modified mRNA vaccines: Comirnaty developed by BioNTech/Pfizer (European Commission 11 March 2021) and Moderna's COVID-19 Vaccine. The other two are non-replicating vaccines based on recombinant viral vector: Vaxzevria from AstraZeneca (European Commission 23 March 2021) and the COVID-19 vaccine developed by Janssen (European Commission 15 March 2021).

The commission also signed contracts with two other developers of COVID-19 vaccines: CureVac and Sanofi-GSK. In addition, the EMA initiated ongoing reviews for the vaccines developed by Novavax, CureVac, Sinovac Life Sciences Co., Ltd, and for the Sputnik V vaccine developed by Gamaleya (EMA 2021a; 2021b; 2021c; 2021d). According

to the World Health Organization summary information of April 16, 2021, 88 vaccine products are in clinical trials, and 184 in preclinical development worldwide (WHO 2020).

Due to the limited administration of vaccines in the development and clinical testing phase, some side effects - especially those that are very rare - occur only during widespread use. Therefore, EMA and national competent authorities of EU Member States monitor suspected adverse reactions to COVID-19 vaccines according to a specific pharmacovigilance plan and using the EudraVigilance system, which includes the electronic reporting and analysis of suspected adverse drug reactions (EMA 2020b).

Following the widespread use of vaccines across the EU, new data on suspected adverse reactions to vaccination against COVID-19 have become available, allowing further assessment of vaccine safety in the post-vaccination period.

The European Centre for Disease Prevention and Control (ECDC) aims to strengthen Europe's defence systems against infectious diseases, its beneficiary being the public health sector in Europe, in particular: sub-national and national public bodies in the EU/EEA, EU institutions, as well as other decision-makers in Europe. The European Centre for Disease Prevention and Control, taking into account the pre-approval safety data for the use of COVID-19 vaccines, in its June 2021 technical report (ECDC 2021), published data on suspected adverse reactions to vaccination against COVID-19.

Thus, according to the ECDC, from the start of vaccination in the EU/EEA until April 28, 2021, a total of 133,739,633 doses of the EU-approved COVID-19 Vaccine Tracker vaccine were administered in the EU/EEA countries.

During the same period, 354 177 (0.2%) cases of suspected adverse reactions after vaccination were reported to EudraVigilance. Most reports of suspected adverse reactions thus far relate to general and administration site reactions (e.g., "flu-like" illness, headache, application site pain, chills, fatigue, nausea, fever, dizziness, weakness, myalgia, and tachycardia.) Generally, these reactions are not associated with more serious illnesses. Data monitoring conducted as part of the US vaccination program indicates that most non-serious adverse reactions occur within two days of vaccination and almost all within seven days (Gee 2021). Serious reactions, such as allergic and anaphylactic reactions, are very rare and usually occur shortly after vaccination with a sudden onset.

Thrombotic and thromboembolic events, including TTS, have been reported following the administration of non-replicating COVID-19 vaccines based on viral vectors. Adverse events of this type after vaccination with Vaxzevria have triggered the suspension of some batches and even of the use of the vaccine in several EU/EEA countries (EMA 2021). As of May 12, 2021, some countries have resumed age-restricted Vaxzevria vaccination (reserved for those over 55 or 60), while others have discontinued its use (Denmark, Norway) (ECDC 2021b).

The EMA's safety committee, the Pharmacovigilance Risk Assessment Committee (PRAC), performed a signal assessment on "embolic and thrombotic events" after vaccination with Vaxzevria in March 2021 (EMA/PRAC 2021). A total of 269 cases (258 serious and 45 fatal) reported to EudraVigilance were analyzed. At the time of assessment, 28 February 2021, more than 5.5 million doses of AstraZeneca vaccine had been administered in EU/EEA countries and approximately 9.7 million doses in the UK. The reported cases were healthy individuals at the time of vaccination who developed moderate to severe thrombocytopenia and thrombotic complications at unusual sites, such as cerebral venous sinus thrombosis or thrombosis in the portal, splanchnic, or hepatic veins, one to two weeks after vaccination. Some patients developed deep vein thrombosis, pulmonary embolism, or acute arterial thrombosis.

On a national level, according to the National Institute of Public Health (INSP) (INSP 2021), following vaccination with vaccines against SARS-CoV-2, in the period 27.12.2021-

03.10.2021, a number of 18,471 suspicions were reported of adverse events following immunization (AEFI), and of these 17,307 (93.7%) were classified as AEFI.

The main source of data for the cases of adverse events following immunization reported in the period 27.12.2020-03.10.2021 was represented by the online system of the competent national authority, National Agency for Medicines and Medical Devices (ANMDMR), and over 80% of AEFI had general manifestations. Thus:

- 15,857 had the ANMDMR website as their reporting source, of which 93% were confirmed;
- 1,810 had as their reporting source the National Electronic Register of Vaccination (RENV), of which 99% of reactions were confirmed;
- 804 had as their reporting source the reporting files received from the County Public Health Directorates/of the municipality of Bucharest, of which 97% of the reactions were confirmed.

A higher percentage of adverse events following immunization was recorded with Astra Zeneca and Moderna among males in the age groups between 20-59 years old.

From the INSP data, it is found that the rate of AEFI cases per 10,000 administered doses is elevated in the age groups of 25-29 years, 30-34 years, 35-39 years for all types of vaccine administered, with the highest rate in the Astra Zeneca vaccine, followed by Moderna, Comirnaty and Johnson & Johnson.

In the reported period, 9 cases of anaphylactic shock were confirmed, classified as AEFI associated with vaccine components. All cases showed anaphylactic shock after the administration of the first dose of a vaccine, and the distribution of cases, depending on the vaccine product administered, was as follows:

- 7 cases of anaphylactic shock after administration of the Comirnaty vaccine product;
- 1 case of anaphylactic shock after administration of the Moderna vaccine product;
- 1 case of anaphylactic shock after the administration of the Astra Zeneca vaccine product.

Of the 9 people who experienced anaphylactic shock, 3 were known to have allergies to medicinal products.

The purpose of EU pharmacovigilance rules is to monitor the safety of medicines so that regulatory authorities can take action to reduce the risks and increase the benefits of medicines for human use. The role of individual EU countries is to monitor drug safety data, assess signals of possible emerging side effects and analyze the data when a European-wide safety problem is identified. The EMA has a central role in the EU pharmacovigilance system – it coordinates the activities of an EU regulatory network of over 30 national competent authorities and provides technical, regulatory and scientific support.

Given the important role of EudraVigilance in monitoring the safety of medicines and evaluating signals of possible emerging side effects, the benefits of the system will be reflected in the context of the overall EU pharmacovigilance activities addressed in the next report expected for 2022.

To ensure a coordinated EEA approach to pharmacovigilance, technical and procedural aspects of the operation of EudraVigilance that require further discussion and clarification are being addressed by national competent authorities, marketing authorization holders and clinical trial sponsors.

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