EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Report on pharmacovigilance tasks

From EU Member States and the European Medicines Agency (EMA)
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Chapter 2

Executive summary

This report summarises the work carried out by the EU pharmacovigilance Network between January 2019 and December 2022 to ensure the safety of all medicines authorised in the EU, including COVID 19 vaccines and therapeutics. The report also describes the main enhancements to the EU pharmacovigilance system introduced during this period and reflects critically on the main areas that will need further strengthening in the forthcoming period.

Responding to the public health emergency

Enhanced safety monitoring during the pandemic

The response to the COVID 19 pandemic dominated a significant part of the period covered by this report. Over this period, the EU Network took concerted action to ensure that vaccines and treatments for COVID-19 were closely monitored and used in the safest possible way.

This started with preparation for intensified safety monitoring of COVID-19 vaccines. In November 2020, before the first vaccines were authorised, EMA and the national competent authorities (NCAs) in EU Member States published a dedicated safety monitoring plan for COVID-19 vaccines. This created the framework for rapidly collecting and reviewing the high volume of safety data anticipated from the planned vaccination campaigns.

As outlined in the plan, dedicated guidance on risk management plans (RMPs) and periodic safety update reports (PSURs) was provided to COVID-19 vaccines developers with specific and minimum requirements for data collection and reporting. Marketing authorisation holders (MAHs) were also required to provide monthly summary safety reports (SSRs) for at least 6 months after authorisation of a COVID-19 vaccine to ensure frequent scrutiny of new safety information both from published literature and the use of the vaccines in the real world; the frequency of SSR submissions was subsequently reduced once more data were available. In total, 56 SSRs were assessed for all the authorised COVID-19 vaccines up until December 2022.

The Network carried out intensified safety monitoring of COVID-19 vaccines throughout the pandemic. A process for a more frequent screening of suspected adverse drug reactions (ADRs), including near real-time monitoring of adverse events of special interest (AESIs), was implemented. During 2021 and 2022, the EU database of suspected ADRs, EudraVigilance, received 2.8 million individual case safety reports (ICSRs) related to COVID-19 vaccines, close to 4,000 every day. In addition, as a result of an agreement with the

World Health Organization (WHO) Uppsala Monitoring Centre (UMC), the Network gained access to ADR reports from WHO member states as an additional source of safety information.

As part of the intensified safety monitoring, refined methodologies for analysing safety data were used, including observed-versus-expected analyses to support the detection and characterisation of signals. A Standardised MedDRA Query was developed for COVID-19 and ad-hoc dashboards were integrated in the EudraVigilance data analysis system to support the visualisation of serious or fatal cases in specific populations.

In addition, extraordinary committee meetings and ad-hoc expert groups were convened to discuss safety topics, signals procedures were accelerated, and an extraordinary update of MedDRA (beyond the biannual standard releases) was released to support safety reviews.

These activities enabled the rapid expansion of the knowledge on vaccines safety. Safety monitoring confirmed that the vast majority of the side effects of COVID-19 vaccines are mild or moderate, appear soon after vaccination and are short-lived. Rare or very rare side effects that had not emerged during the clinical development due to their rarity, were quickly detected, assessed and promptly acted upon.

One example is thrombosis with thrombocytopenia syndrome (TTS), a very rare but serious new clinical entity associated with adenoviral vector COVID-19 vaccines (Vaxzevria and Jcovden). The Network rapidly identified, evaluated, and contextualized the risk of TTS and took appropriate measures to protect public health.

Observational research

Additionally, real-world evidence (RWE) from pharmacoepidemiological studies complemented the intensified safety monitoring of COVID-19 vaccines, helping to further characterise emerging safety issues.

Between 2019 and 2022, the Network contracted out 11 COVID-19 research projects to consortia specialising in observational research. One such project, ACCESS (vACcine Covid-19 monitoring readinESS) commissioned in May 2020, collected data on background incidence rates for AESIs, which were important for monitoring the safety of COVID-19 vaccines as soon as they were authorised in the EU. The ACCESS consortium also developed template protocols for different types of research questions and real-world data sources.

Studies were also commissioned to provide RWE on certain side effects, such as myocarditis, pericarditis and TTS. Other studies assessed the impact of treatments for COVID-19 in pregnant women.

These studies contributed to the collective body of evidence on the benefits and risks of COVID-19 vaccines, confirming their favourable benefit-risk profile.

Public health advice on emerging issues

EMA's Emergency Task Force (ETF), an advisory body that supports EMA's scientific committees during public health emergencies, played a key role in the review of the literature and provision of public health recommendations on emerging issues. For example, the task force evaluated data on the off-label use of chloroquine, ivermectin and inhaled corticosteroids to treat COVID-19 and warned about the potential harm they may cause and their lack of effectiveness. ETF also concluded that angiotensin converting enzyme inhibitors and angiotensin receptor blockers, which are critical hypertensive medicines, did not affect the outcome of the COVID-19 infection and should continue to be used as advised by the treating doctor. Throughout the pandemic, the task force also played an important advisory role for emerging safety issues as well as safety aspects arising during the evaluation of new medicines, supporting EMA committees decision making.

Enhanced transparency, communication, and stakeholder engagement

EMA implemented exceptional measures to maximise transparency before, during and after the evaluation of COVID-19 vaccines and treatments. The aim was to provide the public with as much information as possible about its assessments, including its safety monitoring processes. For instance, the full RMPs of COVID-19 vaccines and therapeutics were published and the policy on publication of clinical data supporting marketing authorisations, which EMA had paused, was resumed for COVID-19 medicines. The exceptional transparency measures devised for the COVID-19 pandemic were subsequently adopted at the end of 2022 for all future public health emergencies.

To inform the public about its safety assessments, in 2021 and 2022 EMA also published over 50 monthly safety updates on COVID-19 vaccines. These highlighted changes to the product information of the vaccines and recommendations for patients and healthcare professionals to minimise certain risks.

In addition, engagement with the public increased substantially, with EMA organising 30 press briefings (once every fortnight at the peak of the pandemic) and four public meetings, where journalists and members of the public could ask EU experts questions about COVID-19 vaccines and medicines.

International collaboration

Collaboration and exchange of information with international regulators played an important role in safety monitoring activities and significantly increased during the pandemic through the use of existing confidentiality agreements as well as ad-hoc and time-limited new agreements established to increase collaboration with other regulatory authorities.

For example EMA could enrich its review of myocarditis and pericarditis in association with mRNA vaccines, thanks to exchange of information with the medicine regulatory authority in Israel, where the vaccination campaign was more advanced. EMA also worked closely with the US FDA during the review of

TTS with Jcovden which started on the basis of a case reported in the United States while the vaccine had not yet been used in the EU.

EMA collaborated with WHO through various fora, including a COVID-19 subcommittee of WHO Advisory Committee on Safety of Medicinal Products (ACSoMP), which reviewed safety data on new COVID-19 medicines, and the WHO Global Advisory Committee on Vaccine Safety (GACVS) subcommittee on COVID-19 vaccine safety, which provided independent scientific advice to WHO on vaccine safety issues.

As Chair of the International Coalition of Medicines Regulatory Authorities (ICMRA), EMA led the efforts to streamline and align regulatory requirements for medicine development and approval among global medicines regulatory authorities. It was also part of various working groups on COVID-19 that aimed to align monitoring activities across the globe.

All of the actions noted above were only possible due to an unprecedented collaborative effort and the commitment, dedication and flexibility of the EU Network and all the stakeholders involved.

Measuring the impact of pharmacovigilance activities

Ensuring that regulatory actions taken to minimise risks are effective and have the expected impact on public health is an essential part of pharmacovigilance. As part of the implementation of the PRAC Impact Strategy, the EU network has developed guidance for stakeholders on robust methods underpinning good pharmacovigilance practice for conducting studies measuring the impact of pharmacovigilance activities and the effectiveness of risk minimisation measures (RMMs).

As more than 10 studies have been launched to measure the impact of RMMs during the reporting period, the recognition of the importance of systematically tracking their results and evaluating the need for further regulatory actions has translated into the strengthening of related processes.

Some of these impact studies underlined challenges with implementing RMMs, particularly with regard to changes in clinical practice and prescribing behaviour. Initiatives were therefore undertaken to help improving the implementation of RMMs.

For instance, a forum with regulators, patients, and healthcare professionals, the PRAC Risk Minimisation Alliance (PRISMA), was established as a pilot in 2022 to better understand the barriers and enablers of RMM implementation and to proactively advise on RMM options for specific medicines. In addition, a study looking at how specific RMMs in five disease areas were integrated into national clinical guidelines was initiated to better understand the role of clinical guidelines in the implementation of RMMs in clinical practice.

Leveraging real-world evidence

Although RWE has long been used to support the authorisation and safety evaluation of medicines after their authorisation, EMA and the NCAs took steps as part of the Big Data Steering Group work plan to build a sustainable platform to access, analyse and incorporate into the decision-making process a wide range of healthcare data from across the EU.

A notable achievement during the reporting period was the establishment of the Data Analysis and Real-World Interrogation Network (DARWIN EU®), a network that widened the geographical coverage and the types of real-world data available for safety evaluations. The Erasmus University Medical Centre Rotterdam was appointed as the Coordination Centre of DARWIN EU® in February 2022. By the end of 2022, 10 data partners – public and private institutions with access to real-world healthcare data from sources such as hospitals, primary care, health insurance, biobanks, or disease-specific patient registries – had been onboarded and more databases will be added in the forthcoming years. Four studies coordinated by DARWIN EU® were initiated in 2022 and it is expected that over 100 studies will be conducted annually from 2025.

Another key development was the establishment of the EU Vaccine Monitoring Platform, a joint initiative of EMA and the European Centre for Disease Prevention and Control (ECDC) that aims to strengthen the continuous monitoring of the safety and effectiveness of vaccines in the EU. Through the VMP, the two agencies will define a research agenda and oversee EU-funded, independent post-authorisation studies on vaccines use, safety and effectiveness to be conducted in EU countries.

Simplifying processes

EMA continuously strives to simplify and automate its processes to improve efficiency. The notable changes introduced during the reporting period to simplify its pharmacovigilance processes include:

- the migration of pharmacovigilance inspections into IRIS, a secure online platform for handling product-related scientific and regulatory procedures;
- the development, during the pandemic, of a new hybrid (in person/remote) pharmacovigilance inspection model that will now also be considered in other contexts with a view to improving efficiency while maintaining high standards;
- the publication of the full body of RMPs (plus annex 4 and 6) based on set criteria, reducing the administrative burden for generic companies;
- the simplification of the assessment process for RMPs of generic medicines during the marketing authorisation phase (now carried out by the PRAC only);
- the development of a statistical tool to help determine PSUR submission frequency, based on data from different electronic sources.

Managing workload across procedures

The work of the EU Network continued to grow during the reporting period, with the bulk of work relating to the assessment of PSURs, signals and RMPs impacting significantly on the PRAC workload. Around 2,400 RMPs were on the PRAC agenda; the Committee assessed 273 signals and issued recommendations for more than 3,300 PSURs.

A striking fact was the massive increase in the number of suspected ADRs collected in EudraVigilance, which was mainly linked to COVID-19 vaccines: 3.5 and 2.9 million ICSRs were received in 2021 and 2022, respectively, compared with 1.8 million in 2020. About one in two of those were related to COVID-19 vaccines. The great majority of the signals reviewed during the reporting period originated from screening EudraVigilance.

In terms of safety referrals, 17 procedures were finalised during the reporting period, of which 13 led to variations to marketing authorisations. For the other 4, the PRAC concluded that the medicines had a negative benefit-risk balance and they are now withdrawn from the market.

Hundreds of inspections were carried out during the reporting period, most of them under national pharmacovigilance inspection programmes. Inspections continued to be carried out even when travel was restricted. Examples of actions taken when issues were identified are provided in the report.

This report includes a number of case studies that illustrate how the different tools provided by the EU pharmacovigilance system have been used to minimise risks in different contexts. These examples also show how these tools (for example PSURs and safety referrals) can be combined to allow for an in-depth review of the safety issue at stake.

Next steps

At a time of extreme pressure, the EU Network was able to act swiftly to protect public health, using the tools provided for by the EU pharmacovigilance legislation to harness the unprecedented volume of data on vaccines generated by the large vaccination campaigns.

Experience during the public health emergency has highlighted a number of areas for improvements. An upgrade of EudraVigilance data analysis system is underway to achieve a higher level of automation, increased flexibility and enhanced data extraction and query functionalities, which are critical at times of high demand.

To better leverage real-world data for decision-making and rapidly generate evidence on the safety and effectiveness of medicines, in particular in times of crisis, the range of available tools needs to be widened and the collection and analysis of health data across the EU harmonised. The establishment of DARWIN EU® is expected to be transformative in these regards.

Earlier and strengthened engagement with healthcare professionals through for example PRISMA will help identify the barriers and enablers of RMM implementation in clinical practice.

Further engagement with national immunisation technical advisory groups (NITAGs), the national expert bodies advising on vaccination programmes coordinated by the European Centre for Disease Prevention and Control (ECDC), is also envisaged to harmonise public health recommendations at time of crisis.

Finally, as the pandemic put considerable strain on resources, reflection has started with NCAs to further rationalise the use of resources and possibly build capacity across the Network.

Introduction

This third multi-annual report describes pharmacovigilance activities carried out between 2019 and 2022 by the national competent authorities of the European Union (EU) Member States, Norway and Iceland and by the European Medicines Agency (EMA) which also acts as the coordinating body of the EU pharmacovigilance system.

The current EU pharmacovigilance legislation became operational in 2012, and this report aims to support the European Commission's ongoing obligation to report on those activities and the overall impact of the legislation. It describes the qualitative and quantitative impact of the tools provided for by the legislation and gives an overview of progress made 10 years since its implementation.

The European system of pharmacovigilance is a strong and adaptable system and is built on the principle of collaboration. The EMA, national competent authorities (NCAs) and marketing authorisation holders (MAHs) for medicines have their own systems which interconnect to build this strong European system.

The European medicines regulatory network

Responsibility for pharmacovigilance in the EU is distributed via a unique collaborative network that promotes and protects human health via a proactive, risk-proportionate, transparent and patient-centred approach.

The European Commission oversees the entire system and supplies the legal authority that underpins it. EMA, Member States and the European Commission work together in a setup called the European medicines regulatory network (hereafter referred to as the EU Network).

The Member States are key pillars in the EU pharmacovigilance system. They conduct a wide range of activities, particularly supervising the collection of information on suspected side effects; assessing signals, periodic safety update reports (PSURs), post-authorisation safety studies (PASS) and risk management plans (RMPs); providing rapporteurs for the evaluation and analysis of safety issues in referrals; communicating suitably tailored safety messages to their citizens; and maintaining the inspectorates that check that the elements of the system are functioning correctly.

Experts from each Member State also contribute at the European level through their membership of EMA's scientific committees, notably the Pharmacovigilance Risk Assessment Committee (PRAC), which is primarily responsible for questions of pharmacovigilance and risk management, and the Committee for Medicinal Products for Human Use (CHMP), which is responsible for the overall evaluation and approval of marketing authorisation applications for centrally authorised products (CAPs). In addition, the EU Member States plus Iceland, Liechtenstein and Norway work together through the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which is responsible for ensuring harmonised safety standards for medicines authorised via national procedures.

In the EU pharmacovigilance system, the assessment activity is performed by the appointed national competent authority on behalf of the EU network. EMA coordinates the resources made available by the Member States and the network activities, providing technical, regulatory and scientific support to Member States and industry as well as essential infrastructure and expertise for various pharmacovigilance tasks. EMA also leads on detecting signals for CAPs and coordinating safety communication at EU level.

Sources of information

This report covers pharmacovigilance activities carried out by the EU Network during the period from 1 January 2019 to 31 December 2022. The NCAs of the different Member States have provided information mainly about national pharmacovigilance activities, while EMA, in its co-ordinating role within the EU network, has provided information on centralised activities that fall under the mandate of the PRAC.

Other sources of information, including published studies, are cited throughout the report.

Chapter 1

Focus areas of the EU network in 2019-2022

Response to the COVID-19 pandemic

The COVID-19 pandemic posed unprecedented challenges to the scientific community and society as a whole. Despite these challenges, the mobilisation of scientists, industry, regulators, healthcare professionals and public health bodies around the globe led to the development and authorisation of vaccines, new therapeutics and repurposed medicines in record time, with all the products adhering to EU standards for quality, safety and efficacy. Before the rollout of these new medicines, EMA and the NCAs played a critical role in preparing for intensified safety monitoring and for any actions that would be necessary in the event of emerging safety issues. Building on the provisions of the EU pharmacovigilance system, the EU Network implemented specific monitoring activities to assess emerging data promptly and to take rapid action when needed to minimise risks. It developed and made use of a number of tools and methods to harness the unprecedented volume of safety data generated for the vaccines. This has enabled the rapid expansion of knowledge on vaccines safety and allowed the swift identification of very rare side effects. Complementing this enhanced monitoring system, several independent observational studies were commissioned to help further characterise emerging safety issues.

The EU was at the forefront of detecting and managing emerging safety issues. One example is the detection of a very rare but serious new clinical entity associated with adenoviral vector COVID-19 vaccines, thrombosis with thrombocytopenia syndrome (TTS). This risk was rapidly identified, evaluated, contextualized, and minimized for Vaxzevria (formerly COVID-19 Vaccine AstraZeneca) and the EU Network was proactive in dealing with the same risk for another adenoviral vector COVID-19 vaccine, Jcovden (formerly COVID-19 Vaccine Janssen), acting before the vaccine was rolled out within the EU (see case stories on pages 49 and 68).

Enhanced safety monitoring and public health advice provision

Dedicated safety monitoring plan for COVID-19 vaccines

When medicines are first approved, information on safety comes mainly from clinical trials and is therefore limited as regards rare side effects or side effects with long latency; to fill the knowledge gaps, more information on safety is collected from real-world use and follow-up studies after authorisation.

In November 2020, shortly before the authorisation of the first COVID-19 vaccine in the EU, EMA and the NCAs in EU Member States published a dedicated safety monitoring plan for COVID-19 vaccines. This plan created the framework for rapidly collecting and reviewing emerging safety data in view of the exceptionally large vaccination campaigns to be rolled out and the high number of adverse drug reaction (ADRs) reports expected. It also emphasised the importance of timely communication and a high level of transparency.

New guidance for RMPs

Based on this safety monitoring plan, EMA published new guidance to support pharmaceutical companies in their preparation of the RMPs for COVID-19 vaccines. RMPs, which are put in place for every medicine ahead of marketing authorisation, describe the medicine's safety profile and all the safety concerns that need to be managed proactively or further studied. They also describe planned pharmacovigilance activities to characterise and quantify clinically relevant risks and to identify new adverse reactions, as well as the implementation of RMMs and evaluation of their effectiveness. RMPs ensure that relevant knowledge gaps will be filled and uncertainties on potential safety issues reduced.

The RMP guidance for COVID-19 vaccines was developed on the basis of lessons learned from the H1N1 influenza pandemic (2009-2010) and adapted to the evidence emerging from the COVID-19 pandemic. It addresses core requirements for data collection on vaccine safety, including in special populations (i.e., pregnant women, the elderly and patients with

co-morbidities), and methods for detecting and following up safety signals. It also covers the monitoring of adverse events of special interest (AESIs).

AESIs are events that could be causally associated with a specific medicine based on the evidence from the literature and what is already known about the medicine or the class it belongs to. For this reason, they need to be closely monitored. For COVID-19 vaccines, for instance, anaphylaxis and Guillain Barré syndrome, two side effects previously linked to certain vaccines (see GVP module on Vaccines for prophylaxis against infectious diseases for further information) were amongst the over 30 AESIs identified and therefore subject to intensive monitoring from the moment COVID-19 vaccines were being used (see further information on AESIs in the box on page 17).

Summary safety reports

The RMP guidance also foresaw specific measures for an intensified safety monitoring of COVID-19 vaccines as soon as they started being used. Among those measures was one requiring MAHs to submit Summary Safety Reports (SSRs). MAHs were requested to submit these reports in addition to the regular PSURs submitted for all medicines, the first of which is usually expected 6 months after authorisation. SSRs were initially required every month for at least 6 months following authorisation after which EMA requested them less frequently depending on the information available on each vaccine.

SSRs enhanced the efficient use of regulatory tools by the EU Network. SSRs enabled the intense monitoring of new safety data and provided a framework for promptly assessing them and taking the actions needed to protect public health.

Certain emerging issues were followed up in the context of SSRs on a monthly basis with companies required to provide cumulative reviews for the following report. In some cases, the SSR assessment could lead directly to changes to the product information through a variation procedure.

In other cases, the PRAC decided that a more comprehensive review of an issue was needed in the context of the upcoming PSUR or that a formal signal procedure was needed to look into the issue in more depth, as was the case when the PRAC evaluated data on capillary leak syndrome with Vaxzevria.

As of the end of 2022, 13 SSRs had been submitted and assessed for Comirnaty, 8 for Vaxzevria, 10 for Jcovden, 13 for Spikevax, 7 for Nuvaxovid and 5 for Valneva, with the differences reflecting the different approval times and the change in frequency along the product life-cycle.

As an example of how SSRs supported safety monitoring, during the initial evaluation of Jcovden (formerly COVID-19 Vaccine Janssen), the CHMP and PRAC noted a slight numerical imbalance with regard to venous thromboembolic events in clinical trials. Although the majority of the participants had underlying medical conditions (such as obesity, hypothyroidism and diabetes) that could have contributed to these events, venous thromboembolism (VTE) was listed in the first version of the RMP as an important potential risk for further investigation. After authorisation of the vaccine, these events were closely monitored and new data, including data from spontaneous reports, were promptly reviewed in the context of SSRs. These actions allowed the PRAC to gather sufficient evidence to conclude in September 2021 that there was a reasonable possibility that VTE was causally related to Jcovden. VTE was therefore added as a rare side effect in the vaccine's product information, together with a warning to raise awareness among healthcare professionals and people taking the vaccine, especially those who may have an increased risk of VTE. A Direct Healthcare Professional Communication (DHPC) was also sent out to healthcare professionals.

Dedicated guidance for PSURs

In July 2021 dedicated guidance was provided to companies on core requirements for PSURs of COVID-19 vaccines. The guidance aimed to ensure that all relevant information would be included in the PSUR and presented in such a way that PRAC could conclude on the vaccine's safety. The guidance highlighted specific requirements, such as the inclusion of cumulative and interval vaccine exposure data (based on administered doses rather than distributed doses and stratified by region, age group, gender and dose) and, in view of the large vaccination campaigns, the prioritisation of the review of specific information, e.g., medication errors with harm, new scientific literature and data on specific populations such as pregnant women or immunocompromised patients.

How the network intensified safety monitoring

The EU network was able to intensify the monitoring of safety data for COVID-19 vaccines and therapeutics. This objective was achieved in a number of ways described below.

Intensifying and expanding surveillance
The number of ADR reports received in EudraVigilance surged following the start of the vaccination campaigns in 2021. About 2.8 million ICSRs reports related to COVID-19 vaccines were submitted to EudraVigilance over the period 2021-2022, meaning close to 4,000 every day. To ensure a prompt review of these emerging data a specific monitoring strategy was developed for COVID-19 vaccines. EMA monitored AESIs for COVID-19 vaccines in a near real-time manner right after authorisation (see further information in the box below). Other ADRs reports were monitored weekly, instead of bi-monthly as was the case at that point in time for other products.
To ensure that the ADR reports received by NCAs were available in EudraVigilance in a timely manner to support signal detection activities, EMA supported Member States with a semi-automated classification of reported reaction terms and exceptionally processed some reports for a limited period. Relevant medical literature was screened daily to ensure comprehensive evidence on safety was available for analysis.

Furthermore, exchange of information with international regulators across the globe was enhanced (see section on international collaboration starting on page 28) and an agreement with the World Health Organization (WHO) Uppsala Monitoring Centre (UMC) was signed to get access to ADR reports from WHO Member States. This provided an additional source of information for safety monitoring.

Tools to facilitate monitoring

Various tools were developed to support every aspect of safety monitoring.

Listing adverse events of special interest
In preparation for the huge influx of spontaneous ADRs expected as a result of the large vaccination campaigns, EMA defined a list of vaccine targeted medical events (vTMEs) to facilitate safety monitoring. The list included events to be monitored with a higher frequency (up to 2-3 times per week) for a short period of time after authorisation.

The vTME list consists of a dedicated list of MedDRA preferred terms which have been mapped from AESIs identified for COVID-19 vaccines. Two main criteria were used to identify relevant AESIs for inclusion within the vTME list:

- AESIs associated with immunisation in general (e.g. anaphylaxis, Guillain Barre syndrome and Bell's palsy). These were identified via the Brighton/Safety Platform for Emergency Vaccines (SPEAC) collaboration guidance documents.[1]

- AESIs related to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. These AESIs were included on the principle that a vaccine targeting a pathogen may induce an adverse event with a similar immunopathogenic mechanism. These AESIs were identified following review of an initial list of 19 AESIs proposed by the ACCESS consortium for SARS-CoV-2 (see section on observational research starting on page 19).

As it was anticipated that administration errors might increase during a large vaccination campaign, a specific AESI was created for vaccination error. This was to ensure prompt identification of any trends regarding administration errors or product quality issues, particularly at the start of the vaccination campaign.

1 Black et al. The critical role of background rates of possible adverse events in the assessment of COVID-19 vaccine safety.

Within the first version of the list a total of 33 AESIs were mapped to 227 MedDRA preferred terms.

The list of vTMEs was shared with the EU network to support the safety monitoring activities at national level. It helped prioritise intensive monitoring of spontaneous reports, leading to a rational use of resources and a quicker detection of serious ADRs.

Development of Standardised MedDRA Query on COVID-19
A Standardised MedDRA Query (SMQ) on COVID-19 was developed in September 2020. SMQs are a tool consisting of validated, pre-determined sets of MedDRA terms grouped together after extensive review and expert discussion. They are meant to facilitate retrieval of MedDRA-coded data and support safety analyses in pharmacovigilance and clinical development.

The COVID-19 SMQ could be used in a variety of scenarios, e.g., to support the identification and recording of COVID-19 cases, to capture information about other aspects of the pandemic (e.g., testing and exposures), as well as to record instances of off-label use of medicines to treat or prevent COVID-19.

Development of EVDAS dashboard for COVID-19
In March 2021, EMA created a dedicated COVID-19 dashboard in the EudraVigilance data analysis system (EVDAS) to ensure the prompt, automated extraction of data. The dashboard facilitated the continuous monitoring of special populations (such as pregnant women and children) and specific safety concerns (e.g., Guillain Barré syndrome, myocarditis and TTS), with the benefit of containing all the relevant information in one place. The dashboard made it easier to promptly ascertain and visualise reporting patterns over time according to parameters such as age, gender and country. It also allowed visualisation of the most frequently reported adverse events and the number of fatalities. It has been used extensively by EMA and the Member States as a monitoring tool and to support communication, complementing other more focused signal detection tools.

Refining methodologies for data analysis
Processes and methodologies for signal detection were refined and tested with the EU Member States prior to implementation thanks to the work of the Signal Management Review Technical Working Groups. These groups represent a collaboration between the Member States and EMA to establish, disseminate and periodically review tools and methodologies to facilitate and support the signal management process in the EU. One of the groups worked for instance on testing machine-learning to support the adjudication of cases of TTS (see 2021 EudraVigilance report for further information) and on methodologies for observed versus expected (O/E) analysis. O/E analyses were used to either support signal detection or to further characterise previously detected signals for vaccines (see section 15.2.1.2 of the ENCePP Guide for Methodological Standards in Pharmacoepidemiology). Together with the Member States, EMA refined the O/E methodology based on past experience with the 2009-2010 H1N1 influenza pandemic. It defined methods and created a team of experts in pharmacovigilance, pharmacoepidemiology and data analysis to inform the selection of parameters and interpretation of the results. Ad-hoc O/E analyses were conducted to investigate and evaluate 4 safety signals. Additionally, O/E analyses were used to investigate safety concerns in the context of other procedures, e.g. SSRs or PSURs. Lastly, routine O/E analyses were also embedded into the safety monitoring tools to better characterise identified risks (e.g. fortnightly analyses stratified by age group and gender for selected AESIs).

Enhancing consistency and quality of safety data
EMA proactively issued new guidance to promote consistent coding of the ADRs reported to EudraVigilance in consultation with the NCAs and MAHs of the respective vaccines. This aimed to

reduce the need for manual correction by EMA after receipt and ensured that good quality data were available to the Member States, signal detection assessors and the PRAC as early as possible. EMA also put in place processes to swiftly correct reports with a misnamed COVID-19 vaccine and delete duplicated reports.

Expanding the evidence base
From the start of the pandemic, a variety of EU-wide studies were contracted out by EMA to address safety concerns for each COVID-19 vaccine, including pharmacoepidemiological studies using large EU electronic healthcare databases and patient-reported information from vaccinees. Vaccine effectiveness studies were also conducted. See section on observational research further down.

Displaying flexibility
The EU Network demonstrated flexibility and the capacity to promptly respond to new emerging evidence. This took several shapes, for instance, the convening of ad-hoc PRAC and CHMP extraordinary meetings at very short notice or the mobilisation of EU experts to participate in ad-hoc expert meetings to discuss TTS in association with Vaxzevria (see case story on page 49).

In April 2020, the EU network agreed to release an update to the Medical Dictionary for Regulatory Activities (MedDRA) even though a new version had been released a month earlier, in March. Although this exceptional measure required significant effort by all those involved, it was essential to include new COVID-19 terminology and ensure that scientific and medical information could be promptly captured, shared and analysed appropriately. Additionally, detailed guidance was released to assist with the processing and submission of individual case safety reports (ICSRs) in the context of COVID-19, including specific MedDRA coding guidance.

To facilitate the authorisation of COVID-19 vaccines in children, studies agreed in paediatric investigation plans (PIPs) were designed and continuously updated on the basis of safety data emerging from real-world use in adults. This flexibility and rapid adoption of PIPs facilitated the generation of safety data to support the authorisation of vaccines in children.

Accelerating signal evaluation
The EU network accelerated procedures for confirming and assessing signals. Owing toan unprecedented collaborative effort and the commitment of EU experts, the timetables were often accelerated and time frames reduced to a minimum while still ensuring a robust evaluation. The publication of updated product information was also accelerated. Publication in English was done immediately after the procedures concluded and in all other EU languages within days. This ensured that conclusions of evaluations of new safety issues were reached as early as possible and EU citizens swiftly informed.

The close monitoring of the safety of COVID-19 vaccines confirmed that the vast majority of side effects observed are mild or moderate, appear soon after vaccination and are short-lived. The EU Network was able to promptly assess the fast growing amount of safety data, identify a few rare but serious side effects associated with COVID-19 vaccines and issue recommendations in a timely manner to mitigate these risks. Examples of these side effects are TTS (which is described on page 49), capillary leak syndrome, immune thrombocytopenia, Guillain-Barré syndrome, venous thromboembolism, myocarditis and pericarditis (see case story on page 22). A full list of signal procedures related to COVID-19 vaccines and therapeutics can be found in the Annex 4B.

Observational research

During the pandemic, the EU Network took steps to leverage real-world data (RWD) from vaccination campaigns to monitor the safety and effectiveness of COVID-19 therapeutics and vaccines. Real-world monitoring through pharmacoepidemiological studies complemented regular pharmacovigilance activities, supporting the characterisation of new safety issues and enriching PRAC's assessments.[2] As EMA's mandate was extended in 2022 to strengthen EMA's role in crisis preparedness, the role of EMA-funded independent studies to support the safety monitoring of COVID-19 vaccines was

2 Durand et al. Safety monitoring of COVID-19 vaccines: perspective from the European Medicines Agency

further reinforced and the scope was expanded to include vaccine effectiveness studies, partly through the EU Vaccine Monitoring Platform established in May 2022 in collaboration with ECDC.

Between 2019-2022, 11 studies were contracted out to consortia specialising in observational research, of which 6 were completed and 5 were ongoing as of December 2022. The full list of studies, together with links to the EU PAS Register, can be found in Annex 2.

Preparedness to monitor vaccine safety

One of the first EMA-funded studies aimed to prepare for intensified monitoring by proactively generating background incidence rates for AESIs (see section 15.2.1.2 of the ENCePP Guide for Methodological Standards in Pharmacoepidemiology) and developing study protocol templates to support the prompt design of vaccine safety and effectiveness studies. This project is described in the box below.

ACCESS (vACcine Covid-19 monitoring readinESS): Importance of preparedness to provide epidemiological evidence and monitoring tools during crisis management

As early as May 2020, EMA engaged with researchers to ensure that a European infrastructure would be in place to effectively monitor COVID-19 vaccines. The project, which ran from April to December 2020, was led by Utrecht University (Netherlands), in collaboration with the Vaccine Monitoring Collaboration for Europe (VAC4EU).

The main aim was to generate background incidence rates for 41 AESIs using 10 healthcare databases from 7 European countries over the period 2017 to 2020.[3]

Preparedness proved useful as the first vaccines became available in December 2020 and the first set of background rates were delivered mid-December 2020. Similarly, EMA requested the establishment of study protocol templates for vaccine coverage, safety and effectiveness studies, which were made publicly available in the EU catalogue of observational studies (EU PAS Register). These templates were used by MAHs and research organisations when the investigation of the first safety signals became necessary.[4] These tools were used by both EMA and vaccine developers to support O/E analyses and for safety studies in the context of signal assessments.

Beyond this readiness phase, these background rates remained extremely useful throughout the pandemic as vaccination campaigns continued and further vaccines using different technologies were authorised. While the benefit-risk profile of authorised COVID-19 vaccines was favourable, post-authorisation use saw the emergence of unexpected safety signals (i.e. not captured or fully captured by the predefined list of AESIs), which sometimes involved complex syndromes such as TTS. The responsiveness of vaccine safety research networks, such as the Brighton collaboration, coupled with the output of the ACCESS project and the readiness of other consortia[5] collaborating with EMA through its framework contracts, allowed the rapid generation and update of case definitions and the provision of background rates for specific adverse events following immunisation.

3 Willame et al. Background rates of 41 adverse events of special interest for COVID-19 vaccines in 10 European healthcare databases - an ACCESS cohort study

4 EUPAS37273 (background rates); EUPAS39370 (vaccine coverage); EUPAS39361 (template for safety studies); EUPAS39289 (template for effectiveness studies)

5 Li et al. Characterizing the incidence of adverse events of special interest for COVID-19 vaccines across eight countries: a multinational network cohort study - PubMed (nih.gov)

As soon as the vaccination campaigns started, an early safety study was coordinated by the same research consortium as for ACCESS with a view to:

- updating some of the background rates for AESIs provided by ACCESS, e.g., with additional stratification by age group to align with the populations affected by a given safety signal;
- generating background rates for new signals, e.g., TTS;
- generating evidence on the incidence of COVID-19 infections.

This early study was initially set up to prospectively collect solicited and unsolicited ADRs in vaccinated people.[6] It was then expanded into a larger 2-year safety study to also monitor the safety of COVID-19 vaccines in special populations (e.g. pregnant women, immunocompromised people, previously infected people and those with a history of allergies). The final report of this study will be published in the course of 2023, but interim results based on self-reported information from vaccinees suggested that serious ADRs and AESIs in special populations were uncommon, in line with the study data in the general population. A second component of the study was to set up a framework for rapid evaluation of new safety concerns through access to large healthcare databases in several EU countries.[7] The results on myocarditis and pericarditis are presented in the box on the next page.

EMA also commissioned several aetiological studies through its framework contracts to further address emerging safety concerns, leveraging access to 59 data sources of data from more than 380 million persons from 21 EU countries, via different academic organisations and large consortia.

Studies on myocarditis/pericarditis and on TTS

Studies were commissioned to better characterise some side effects that emerged with COVID-19 vaccines.

For example, a study on the association between TTS or thromboembolic events (arterial thromboembolism [ATE]/VTE) and COVID-19 vaccines was initiated in Q3 2021 to further support the evaluation of the signals that emerged for these events and the quantification of their risk. The study also examined risk factors for VTE, ATE or TTS in people receiving COVID-19 vaccines and characterised the treatment for patients with VTE, ATE or TTS, including the use of anticoagulants and other therapeutic products.[8] The study outcome provided further knowledge on the new TTS clinical entity. An additional aim of the study was to explore the impact of genetic predisposition on adverse safety outcomes, using VTE as an example.[9] The results suggested that there is no difference in terms of genetic susceptibility between people who have conventional VTE and those with VTE associated with COVID-19 vaccination. This will serve as a proof-of-concept for future pharmacogenomic analyses using biobanks to potentially support safety monitoring of COVID-19 and other vaccines.

Observational studies also helped better characterise the occurrence of cases of myocarditis and pericarditis after vaccination with mRNA vaccines. The box below describes how a combination of tools and data gathered through collaboration supported the management of these side effects.

6 Sturkenboom et al. Cohort monitoring of 29 Adverse Events of Special Interest prior to and after COVID-19 vaccination in four large European electronic healthcare data sources. See also EUPAS39798

7 EUPAS42467

8 Li et al. Comparative risk of thrombosis with thrombocytopenia syndrome or thromboembolic events associated with different covid-19 vaccines: international network cohort study from five European countries and the US; see also EUPAS44469

9 Xie et al. Genetic risk and incident venous thromboembolism in middle-aged and older adults following COVID-19 vaccination

Myocarditis and pericarditis with mRNA vaccines

Myocarditis and pericarditis have been reported in association with COVID-19 infection and were therefore included in the AESI list developed by the Brighton/SPEAC collaboration. In early 2021, a signal of myocarditis emerged in Israel for Comirnaty. The cases occurred predominantly in young (16- to 19-year-old) males after the second dose. This triggered a review of myocarditis and pericarditis for both mRNA vaccines at EU level.

Data from various sources were used to characterise these side effects. Cases reported in EudraVigilance from countries of the European Economic Area (EEA) suggested a temporal association with vaccination and a possible causal association with the vaccines. O/E analyses of myocarditis could be conducted using background rates calculated by ACCESS and exposure data stratified by age and gendter provided by the European Centre for Disease Prevention and Control (ECDC) and the EU Member States. These analyses showed a higher occurrence of this side effect in 18- to 24-year-old males for both vaccines. The occurrence of cases of myocarditis and pericarditis was reflected in the product information for each vaccine and communicated to healthcare professionals and the public.

In the months that followed, two large European pharmacoepidemiological studies including children and adolescents provided further evidence on the risk of myocarditis and pericarditis following administration of mRNA vaccines (a cohort study based on Nordic registry data,[10] and a case-control study based on French national health data).[11] The two studies provided estimates of the number of excess cases of myocarditis after the second dose of mRNA vaccine in young vaccinees compared to unexposed people. These findings were reflected in the product information. In addition, the consortium coordinated by University Medical Center Utrecht in partnership with VAC4EU carried out a pharmacoepidemiological study using a large amount of healthcare data from four European countries (Netherlands, United Kingdom, Italy and Spain).[12] The results confirmed the findings observed from the independent research in France and Nordic countries and also showed that COVID-19 disease itself increased the incidence rates of these events.

Studies to better understand COVID-19 disease to support signal evaluation

Other studies were commissioned to better understand the impact on health outcomes of COVID-19 infection itself, including the impact of medication on COVID-19 disease. One example is a study of the natural history of coagulopathy and use of antithrombotic agents in COVID-19 patients. The study was initiated in the spring of 2020 to better understand the risks of thromboembolic events among patients with COVID-19, the impact of these events on prognosis, the risk factors for such events and whether individual risk can be predicted based on demographic characteristics and medical history. When the TTS signal emerged with Vaxzevria, a cohort of vaccinated subjects was added to this study, taking advantage of the study being ongoing. The study used databases from the United Kingdom and Spain to estimate incidence rates for coagulopathies and TTS in the following 4 cohorts: the general population in the pre-pandemic period (background incidence); unvaccinated people with a recent positive

10 Karlstad et al. SARS-CoV-2 Vaccination and Myocarditis in a Nordic Cohort Study of 23 Million Residents
11 Le Vu et al. Age and sex-specific risks of myocarditis and pericarditis following Covid-19 messenger RNA vaccines
12 Bots et al. Myocarditis and pericarditis associated with SARS-CoV-2 vaccines: A population-based descriptive cohort and a nested self-controlled risk interval study using electronic health care data from four European countries

polymerase chain reaction test for SARS-CoV-2; people vaccinated with a first dose of Vaxzevria; and people with a first dose of Comirnaty. This was the largest analysis at the time of VTE, ATE and TTS following vaccination or infection with SARS-CoV-2.[13] The background rates from this study were used to carry out O/E analyses in the context of pharmacovigilance activities.

Studies in pregnant women and children

The CONSIGN study[14] (COVID-19 infectiOn aNd medicineS In preGNancy), which was still ongoing at the end of 2022, aims to provide data on medicines used in pregnant women with COVID-19, describe severity and clinical outcomes of COVID-19 according to treatments received during pregnancy, and assess the rate of pregnancy-related and neonatal outcomes by different treatments. Preliminary results in 2021 showed an increase in use of antibiotics, steroids and anti-thrombotic agents in pregnant women with COVID-19. The final study results are expected in 2023. Ultimately, this project is expected to serve as a global framework for studying medicines in pregnancy, also beyond the context of COVID-19.

To expand knowledge in this area, the safety and effectiveness of vaccines in pregnant women will be included in the research agenda of the newly established EU Vaccine Monitoring Platform (see further information on page 40).

In addition, following the authorisation of the first COVID-19 vaccines in children, to further expand the evidence base in younger people and ensure continued monitoring in real-life settings, EMA procured a study to assess the safety of the vaccines in children. This study, which started at the end of 2022 in Nordic countries, aims to evaluate safety for a series of outcomes including thromboembolic events, myocarditis, and immune-mediated diseases, with results expected in early 2023.[15]

RWE supporting use of COVID-19 vaccines during pregnancy

At the time of the authorisation of the first COVID-19 vaccines, there was limited experience on their use during pregnancy, since initial clinical trials do not generally include pregnant women. The recommendation was therefore that vaccination in this population should only be considered when the potential benefits outweighed any potential risks for the mother and fetus. At the beginning of 2022, EMA's Emergency Task force (ETF; initially called COVID-19 EMA pandemic Task Force) conducted a detailed review of all the available data that had been generated in order to provide more precise recommendations. This review included several studies involving around 65,000 pregnancies at different stages. The review did not find any sign of an increased risk of pregnancy complications, miscarriage, preterm birth or adverse effects in unborn babies following mRNA COVID-19 vaccination. Despite some limitations in the data, the results appeared consistent across studies looking at these outcomes. Studies also showed that COVID-19 vaccines are as effective at reducing the risk of hospitalisation and deaths in pregnant women as they are in non-pregnant women. The most common side effects of the vaccines in pregnant women were mild or moderate and also matched those in the overall vaccinated population. Given that pregnancy had been associated with a higher risk of severe COVID-19, particularly in the second and third trimesters, EMA recommended that women who were pregnant or might become pregnant in the near future should be encouraged to get vaccinated in line with national recommendations.

13 Burn et al. Background rates of five thrombosis with thrombocytopenia syndromes of special interest for COVID-19 vaccine safety surveillance: Incidence between 2017 and 2019 and patient profiles from 38.6 million people in six European countries

14 Work packages of CONSIGN: WP1 (EHRs): EUPAS39438; WP2 (COVI-PREG): EUPAS39226; Favre et al. COVID-19-related medicine utilization study in pregnancy: The COVI-PREG cohort; WP3 (INOSS): EUPAS40489; Meta-analysis: EUPAS40317

15 EUPAS48979

RWE generation as part of international collaborations

Some studies were also initiated through collaborations with the US Food and Drug Administration (FDA) and other regulatory agencies. This was the case for the E-CORE project (Evidence for COVID-19 Observational Research Europe) launched in June 2020 to address the initial need for RWE on COVID-19 drug use patterns, safety and effectiveness. It established cohorts of patients in a number of countries, using a common protocol or an established common data model. The feasibility of this collaboration, which involved several regulatory agencies, was demonstrated with a proof-of-concept study on patterns of use, risks and disease outcomes associated with systemic glucocorticoids in hospital and primary care settings. This pilot showed that the network of databases established in the E-CORE project can be used as a resource to address public health questions and can allow large association studies to be performed rapidly.

Guidance update to support high-quality data

High-quality RWE is important to support pharmacovigilance activities. Based on lessons learnt from the studies conducted during the pandemic, the ENCePP Guide on Methodological Standards in Pharmacoepidemiology was revised (revisions 8, 9 and 10) to promote best practices and provide methodological guidance for COVID-19 safety and effectiveness research. This guide, which is updated annually, constitutes an important resource to help generate high-quality evidence in pharmacoepidemiology and pharmacovigilance to support regulatory actions.

All these RWE studies contributed to the collective body of evidence supporting the favourable benefit-risk profile of COVID-19 vaccines. They also contributed to the characterisation of important safety concerns under close monitoring by the EU Network and MAHs, as well as to a better understanding of the COVID-19 disease itself and its therapeutic options.

Public health advice on emerging issues

Beyond monitoring the safety of newly authorised medicines for treating COVID-19, the need arose to provide objective, neutral information about the off-label use of certain medicines to treat COVID-19 and the safety of certain critical medicines in people infected with SARS-CoV-2. The inappropriate use of certain medicines, often stemming from the misinterpretation of unvalidated research findings and the exploration of unconfirmed hypotheses or academic speculation, raised concerns. An extensive review of literature was carried out, with EMA's ETF playing a key role in this review and the issuance of public health recommendations (see box below on ETF).

Establishment of ETF

As part of its response to the COVID-19 pandemic, EMA established a COVID-19 EMA pandemic Task Force. Its 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. The task force has provided support to EMA's scientific committees throughout the pandemic on the development, authorisation and safety monitoring of treatments and vaccines for COVID-19. As part of EMA's extended mandate[16] to reinforce the Agency's role in crisis preparedness and management for medicines and medical devices, the role of ETF in supporting the Network's response to an emergency was formalised and reinforced. It is now named Emergency Task Force.

16 EMA established the ETF in accordance with Regulation (EU) 2022/123 of the European Parliament and of the Council of 25 January 2022 on a reinforced role for the European Medicines Agency in crisis preparedness and management for medicinal products and medical devices.

For example, supported by ETF, EMA advised against using chloroquine or hydroxychloroquine to treat patients with COVID-19. It confirmed early on that these medicines, alone or with other medicines such as azithromycin, did not show any beneficial effects in treating COVID-19 in large randomised clinical trials and, most importantly, that they may cause serious side effects, including cardiac and psychiatric problems, when used in higher doses than recommended for the medicines'authorised indications.

With ETF's support, EMA also advised the public that there was not enough evidence that inhaled corticosteroids such as budesonide or ciclesonide were beneficial for people with COVID-19 and warned that it could not exclude the possibility of harm in people with normal levels of oxygen who use inhaled corticosteroids to treat COVID-19. Similar recommendations were issued on the use of ivermectin.

At the beginning of the pandemic, a review was undertaken on the use of non-steroidal anti-inflammatory medicines such as ibuprofen because reports (especially on social media) raised questions about whether these medicines could worsen COVID-19. EMA reviewed the available data and issued a public health statement confirming that patients with COVID-19 could safely use these medicines.

Throughout the pandemic EMA and ETF carried out critical reviews of protocols and results from the scientific literature (both peer-reviewed and not peer-reviewed), as soon as they became available. This evidence was used to inform a number of public health recommendations, such as those on heterologous vaccination schedules, touching both on vaccine effectiveness and safety.

Public health advice on use of critical medicines

In March and June 2020, EMA issued two public health statements following media articles and publications that raised concerns about the effects of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) medicines in patients with COVID-19.

ACE inhibitors and ARBs are commonly used for treating patients with high blood pressure, heart failure or kidney disease.

After reviewing relevant studies on the use of ACE inhibitors and ARBs published early in the pandemic, the ETF concluded that there was no evidence that those medicines had an effect on the risk of becoming infected with SARS-CoV-2, nor did they have an impact on the outcome of the infection.

EMA confirmed that patients should continue to use ACE inhibitors or ARBs as advised by their doctors, since there was no clinical evidence against their use in COVID-19 patients. This advice was important to prevent EU citizens from stopping life-saving treatment (such as antihypertensives) based on misinformation and anecdotal evidence.

Throughout the COVID-19 pandemic, EMA, supported by the ETF, continued to provide impartial and evidence-based advice to patients and healthcare professionals on the safe use of medicines.

Enhanced transparency, communication and stakeholder engagement

Transparency, communication and stakeholder engagement are embedded in the EU Network's activities. For example, with regard to pharmacovigilance activities, PRAC's agendas and minutes are routinely published, as is information on safety signals, PSURs and RMPs. For emerging safety issues, EMA publishes information when a safety review starts and immediately after it has concluded.

Representatives of patients, consumers and healthcare professionals are members of EMA's management board, scientific committees such as PRAC, and working parties, and of expert groups convened to give scientific or protocol advice. This ensures that their input is considered not only in the context of pharmacovigilance but during all phases of a medicine's lifecycle.

During the pandemic, many of these activities were enhanced to respond to the public's demand for information. These are described below.

Transparency

EMA considers maximum transparency as a precondition for fostering trust and confidence in the EU regulatory system. During the COVID-19 pandemic, EMA implemented exceptional measures to maximise the transparency of its regulatory activities related to COVID-19 treatments and vaccines that have been approved or are under evaluation.

Notably, for COVID-19 medicines EMA resumed its policy on the publication of clinical data supporting marketing authorisations. This resource-intensive programme had been suspended at the end of 2018 as a result of the business continuity plan linked initially to EMA's relocation from London to Amsterdam, and later to the COVID-19 pandemic, due to the impact of these events on human resources. However, EMA decided to exceptionally publish clinical data for COVID-19 medicines, given the unprecedented public interest in this information.

These exceptional measures also included the publication of the RMP (full body of the RMP plus annex 4-Specific Adverse Drug Reaction Follow-up Forms) for authorised COVID-19 medicines instead of the summary. During the reporting period, initial RMPs and RMP updates following a major post-authorisation change were published for 6 vaccines and 8 therapeutics, providing useful resource for the public.

Communication activities and engagement

One of EMA's top priorities has been to provide the general public with factual, complete and up-to-date information about its activities to fight the pandemic, in a timely manner. EMA's approach has been to communicate proactively on any safety issues, acknowledging uncertainties and unknowns. Between 2019 and 2022, over 200 PRAC-related communication materials were developed, many of them relating to COVID-19; about two thirds were lines to take that were sent to the EU Network to help respond to media queries on emerging issues.

To further inform the public about ongoing and concluded safety assessments, EMA published monthly safety updates for authorised COVID-19 vaccines, highlighting any label changes and specific recommendations for patients and healthcare professionals to minimise certain risks. Between 2021 and 2022, over 50 safety updates were published.

In addition, when significant safety issues emerged, such as the risk of TTS with Vaxzevria, EMA issued regular communications and organised dedicated press briefings to keep the public up to date about its ongoing investigations: 9 public health communications and 4 press briefings on TTS were issued or organised between March and April 2021.

EMA also strengthened its engagement with the media, which serve as an important emergency information system during a crisis, through press briefings, interviews with experts to explain complex concepts and the dissemination of factual information on social media. The number of media queries increased more than 4-fold on average during the pandemic and the number of individual queries from the public saw a similar surge. From May 2021, press briefings were conducted on a fortnightly basis to provide updates on ongoing activities, and then on a monthly basis from April 2022. In total between 2020 and 2022, more than 30 press briefings were organised on COVID-19,

including 4 on the emerging issue of TTS reported with Vaxzevria and Jcovden.

More than ever, EMA reached out to the public to respond to their questions and concerns. It engaged with patient and healthcare professional organisations and the general public at large through information sessions, public meetings as well as consultations to increase the effectiveness of public health communications. During the reporting period, 4 public stakeholder meetings on COVID-19 were organised to explain how the Agency assesses and monitors COVID-19 vaccines and to hear directly from European citizens about their needs and concerns. The meetings were held virtually and broadcast live. They were attended by thousands of people who had the opportunity to ask EMA experts questions in real time, in particular on safety issues. In addition, regular updates on the ongoing pandemic activities, including safety monitoring, were given to EMA's patients and consumers working party and healthcare professionals working party.

During the pandemic, there was a high demand from the public for access to data on adverse reactions reported to regulatory authorities. The number of consultations of the public EU ADR website (www.adrreports.eu) surged (from around 2.4 million hits in 2019 to more than 10.5 million hits in 2022) and a large amount of information derived from this public website circulated online and on social media.

This surge confirmed the utility of the website in informing the public about the suspected ADRs received by regulators; however, it also highlighted a possible risk of misinterpretation of the data leading to false claims about the number of deaths linked to vaccination.

To address this, EMA developed new guidance to help the public make best use of the public database. The guidance further explained what these data mean and how EU regulators use them to reach robust conclusions on the safety of a vaccine, putting the overall number of ADR reports into context. In addition, information about the number of deaths reported post-vaccination was included in the monthly safety updates and contextualised to help the public understand how to interpret these data.

Examples of enhanced communication materials

Video: how authorised COVID-19 vaccines are monitored for safety in the EU?
This video on safety monitoring was distributed mainly on Twitter via a paid ads campaign and was available in 15 EU official languages. The campaign generated over 3 million video views and reached almost 1.2 million users.

Visual risk contextualisation: benefits and risks in context
EMA published a graphic representation of the risk of TTS with Vaxzevria in the context of the vaccine's benefits for different age groups and different rates of infection. This was to inform national decisions on the roll-out of the vaccine, taking into account the evolving pandemic situation and other factors such as vaccine availability.

Infocards on the importance of reporting suspected side effects
Infocards were published on the EMA website and advertised on social media to remind the public of the importance of reporting any suspected side effects experienced with their medicines. They provided clear instructions on what information should be reported, supporting robust safety monitoring activities.

EMA's enhanced transparency measures and communication during the pandemic gave the public prompt insight into its assessment and safety-monitoring activities. The publication of clinical data supporting marketing authorisations allowed further independent scrutiny within the scientific community.

International collaboration

International collaboration plays an important role in safety monitoring activities as it provides invaluable insights into emerging safety issues.

Exchange of information with international regulators significantly increased in recent years due the COVID-19 pandemic but also due to the issue of nitrosamine impurities in human medicines. Such exchange of information usually takes place under confidentiality arrangements. In recent years, to facilitate cooperation on specific health crisis, EMA has established *ad hoc* confidentiality arrangements with international regulators with limited scope (e.g., COVID-19 or nitrosamines) and duration.

Through these arrangements, a number of international regulators or health organisations such as Health Canada, MHLW/PMDA Japan, Swissmedic, the UK's Medicines & Healthcare products Regulatory Agency (MHRA) and WHO attended certain PRAC meetings on an *ad hoc* basis as observers, in particular those where important safety signals were discussed. Their participation was beneficial in guiding discussions within their respective regulatory agencies and to facilitate alignment of decisions, resulting in turn into a benefit for public health.

EMA worked closely with the Israeli health authorities on the issue of myocarditis and pericarditis with mRNA vaccines. As the first cases were reported in Israel, where the vaccination campaign was ahead of the EU campaigns, EMA invited the Israeli medicine authority to its scientific meetings to exchange further information and views on this emerging issue. This collaboration enriched PRAC's assessment and supported further decision making.

EU regulators also worked closely with the US FDA and the Centre for Disease Control and Prevention (CDC), sharing information in a timely manner about emerging safety issues and cases reported in their respective territories. This was the case, for instance, for reports of TTS with Jcovden, an adenoviral vector vaccine like Vaxzevria. Jcovden was deployed in the US territory before it was used in the EU; as a result, cases of TTS first emerged from the United States. The exchange of information and enhanced collaboration with the US FDA and CDC allowed EU regulators to proactively manage the risk of TTS for Jcovden – ensuring risk minimisation measures could be put in place before the vaccine was deployed in the EU. Some of these discussions took place in the context of the pharmacovigilance cluster (further information on clusters can be found on page 68).

OPEN Initiative

EMA launched the 'OPEN' pilot initiative in December 2020. OPEN is an international collaboration framework of parallel or near-concurrent review among international regulators. OPEN allowed non-EU regulators (from Australia, Canada, Japan and Switzerland) as well as WHO to collaborate on the CHMP scientific evaluation of COVID-19 vaccines and therapeutics. While maintaining their scientific and regulatory independence, these non-EU regulators could also participate in the ETF's discussions, where many important safety signals were discussed. The initiative aimed to facilitate sharing of scientific expertise, tackle common challenges, enhance transparency on regulatory decisions and support the assessment of vaccines and therapeutics for COVID-19. All the COVID-19 vaccines and therapeutics evaluated since the launch of the pilot were assessed under the OPEN framework, from the moment the rolling review started. This collaboration facilitated the assessment of similar data by multiple authorities, thus reducing duplication of work and allowing the release and redeployment of some resources to other critical areas. It also accelerated the assessment of COVID-19 vaccines and therapeutics, and therefore patients' access outside the EU, and promoted alignment of the labels. Considering the positive experience within the OPEN initiative, frameworks for systematic collaboration with non-EU regulators may be considered in the future including in the context of PRAC safety evaluations.

ICMRA

As Chair of the International Coalition of Medicines Regulatory Authorities (ICMRA), EMA led the global efforts to streamline and align regulatory requirements for medicine development and approval. ICMRA is a voluntary, executive-level entity of worldwide medicines regulatory authorities set up to provide strategic coordination, advocacy and leadership. The EMA Executive

Director has been the chair of ICMRA since 1 October 2019.

EMA chaired a series of workshops and strategic meetings to exchange information, develop joint approaches and provide recommendations on key aspects of medicine development and benefit-risk evaluation during the pandemic. In terms of pharmacovigilance, these workshops covered for instance:

- the need to address the theoretical risk that vaccines against COVID-19 might enhance the disease prior to starting first-in-human clinical trials;

- how to address knowledge gaps with regard to the use of COVID-19 vaccines and therapies during pregnancy and breastfeeding.

ICMRA also has a dedicated working group on vaccine pharmacovigilance composed of 20 regulatory authorities across the globe, including EMA and WHO as observers. This group has operated as part of the COVID-19 response and focused on pharmacovigilance of COVID-19 vaccines. The initial purpose of the group was to share information on vaccines pharmacovigilance, emerging safety profiles and ongoing reviews. Later in the pandemic, discussions focussed on post-marketing pharmacovigilance experience and ongoing deployment of boosters and paediatric vaccines.

EMA has also co-chaired with Health Canada the ICMRA COVID-19 Real-World Evidence and Observational Studies Working Group to discuss observational studies to characterise COVID-19, links between clinical outcomes and concomitant medication use, and the safety and effectiveness of vaccines and treatments; exchange information on research questions, protocols and results; and explore the feasibility of global collaboration on specific research questions. Seven meetings were held during the reporting period.

ICMRA members and the WHO jointly developed a statement to inform and help healthcare professionals answer questions about the role of regulators in the oversight of COVID-19 vaccines. The statement was developed to explain how vaccines undergo robust evaluation to determine their safety, efficacy and quality and how safety is monitored closely after approval. The statement was last updated in May 2022 to include information on clinical trial data (effectiveness studies), variants, commonly reported adverse events for each vaccine type as well as the latest advice on boosters and vaccination safety in children and during pregnancy.

Based on experience gained through the COVID-19 pandemic, EMA co-chairs with UK MHRA an ICMRA working group that aims to develop core elements for clinical trial protocols for public health emergencies. This in particular includes alignment on the generation of robust and actionable data for regulators and public health authorities.

Learnings from this collaboration were discussed in June 2022 during a workshop on RWE co-organised by EMA, FDA and Health Canada, which led to an ICMRA statement on RWE, which among other things called for collaboration to enhance readiness for emerging health threats building on the COVID-19 experience.

Collaboration with WHO

EMA also worked closely with WHO through various formats and fora. EMA collaborates with the WHO on medicines safety as a permanent member at the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP). A COVID-19 subcommittee of the ACSoMP was established in January 2022 with the specific mission to review, evaluate and interpret post-authorisation safety data with new COVID-19 medicines and provide advice on safety of COVID-19 treatments and risk communication material. The group met 8 times in 2022 and provided advice to the WHO on the safety of different COVID-19 medicines.

In addition, in the context of COVID-19, EMA participated in the WHO Global Advisory Committee on Vaccine Safety (GACVS) subcommittee on COVID-19 vaccine safety, a group that provides independent, authoritative, scientific advice to WHO on vaccine safety issues. Members of EMA's pharmacovigilance office attended 19 such meetings between 2021 and 2022, providing input and advice on safety data on COVID-19 vaccines which were subsequently reflected in WHO's and other regulatory authorities' safety guidelines on COVID-19 vaccines.

As of February 2021, EMA's pharmacovigilance office set up regular meetings with the pharmacovigilance office at WHO headquarter and

the UMC to allow for faster, real-time exchange of new safety information on COVID-19 vaccines and therapeutics. EMA signed an agreement with UMC to have access to their signal detection and management tool, Vigylize, and therefore to ADRs reported into the WHO's global ADR database and, to signals published by UMC. This exchange of safety information, in particular on potential signals, aimed to better support signal assessment at EU level and bring relevant information to WHO for the benefit of the world population.

Finally, the partnership with WHO as part of the OPEN initiative (see page 28) also meant that OPEN contributed to global health by breaking down regulatory barriers and facilitating access and equity for COVID-19 vaccines and therapeutics. The WHO Prequalification team, leveraging its participation in OPEN, uses the EMA assessments for the WHO Emergency Use Listing (EUL) of the vaccines and therapeutics authorised in the EU. WHO then encourages the recognition of the WHO EUL and prequalification list for national authorisation or other regulatory actions concerning the safety of the COVID-19 vaccines or therapeutics in low-and middle-income countries.

International collaboration was taken to a higher level during the pandemic. In addition to sharing knowledge to facilitate and enrich safety assessments, enhanced international collaboration helped regulators align research questions and methods and provide consistent information to healthcare professionals and the public.

Prioritisation due to the pandemic

During the COVID-19 pandemic a business continuity plan (BCP) was put in place to cover procedures related to medicines for COVID-19, as well as core procedures for all other human and veterinary medicines, irrespective of their authorisation route. The plan makes clear that the assessment of COVID-19 treatments and vaccines cannot be delayed under any circumstances. It also sets out how to handle possible delays for non-COVID-19-related assessments, and how Member States can deal with the inevitable disruptions arising from the pandemic. The general principles of BCP are as follows:

- always prioritise COVID-19 related procedures;
- for non-COVID-19 related procedures: flexibility within the overall timetable should be applied and if not possible, the overall timetable may be extended taking into account the potential impact of the delay on public health and the benefit-risk balance;
- MAHs' requests for delay to respond to questions should not be accepted for COVID-19 related procedures.

In addition to these general principles, the PRAC agreed on rules for prioritisation of pharmacovigilance activities to further optimise the use of resources and to continue to deliver high quality assessment of the data and science-driven decision making despite the workload increase due to COVID-19. For the assessment of PSURs/PSUSAs and signals, the possibility for another Member State to support the Rapporteur during the assessment was introduced.

Finally, guidance was provided to companies on adaptations to the regulatory framework to address challenges arising from the pandemic. In terms of pharmacovigilance activities, the guidance sets out priorities for the reporting of ICSRs, with serious ICSRs related to COVID-19 medicines, and serious ICSRs related to other products to be processed first, within the 15 days set out in EU law. Specific measures were also introduced in relation to the conduct of on-site pharmacovigilance inspections, to the planning and conduct of pharmacovigilance system audits and to the standard management of corrective and preventive actions.

Prioritisation of activities was key to allow EMA, the EU Member States and the European Commission continue carrying out their core regulatory activities to protect public and animal health despite the multiple challenges posed by the pandemic.

Measuring and increasing the impact of pharmacovigilance activities

Pharmacovigilance activities and the regulatory actions taken by competent authorities based on emerging safety data are designed to ensure the safe and effective use of medicines through changes in knowledge and behaviour of individuals (i.e., patients, consumers, caregivers and healthcare professionals). As interventions are recommended to minimise certain risks, monitoring whether those interventions are effective and have the expected impact on public health is an essential part of pharmacovigilance activities.

The PRAC Strategy on Measuring the Impact of Pharmacovigilance Activities ('PRAC Impact Strategy') was launched in 2016 with the aim to create a framework for systematically measuring patient-relevant health outcomes of major regulatory interventions, shifting the focus of pharmacovigilance to those activities and regulatory tools that make a difference in daily healthcare.

This strategy was first revised in December 2017 and again in 2022. The revised version includes, among other topics, guidance on how to conduct impact research, lessons learnt and an outline of the frameworks for the conduct of such research.

The strategy comprises 4 key activity areas for measuring impact. The progress made in these different areas is described below.

Evaluating effectiveness of risk minimisation activities

When PRAC issues recommendations for regulatory actions, studies are frequently put in place to examine if the additional risk minimisation measures (RMMs) work in practice or fail to achieve their intended objectives, and whether unintended consequences may have occurred.

In line with the legislation and EU good pharmacovigilance practice (GVP Modules VIII and XVI) MAHs conduct PASS that evaluate the effectiveness of certain RMMs for authorised medicines. In some cases, PASS may be imposed on MAHs in the context of regulatory procedures, such as a referral.

This activity undertaken by MAHs may be complemented with research initiated by regulators, like the EU Network, to assess the impact of regulatory actions of major public health importance. On PRAC request, impact research may be commissioned under EMA's framework contract with research organisations. Alternatively, competent authorities in the Member States may conduct impact studies on their own initiative or establish research collaborations within the EU Network. For instance, research collaboration was set up for impact studies on use of codeine and of alternative treatments for pain and cough in children.[17]

While MAH-sponsored PASS would typically look at product-specific targeted effects and assess patient and healthcare professional awareness, knowledge, behaviour or patterns of use in clinical practice, EMA-commissioned studies would complement these PASS by looking for instance at health outcomes (e.g., reduction of harm from adverse reactions, prevention of medication errors etc.) and potential unintended consequences of regulatory actions in routine healthcare setting (e.g. unintended switching patterns etc.).

Since 2019 PRAC has established a process for prioritisation and regulatory follow-up of impact research. In 2021 a revised process was implemented with a view to focus on regulatory actions of major public health importance where a

17 Hedenmalm et al. A European multicentre drug utilisation study of the impact of regulatory measures on prescribing of codeine for pain in children

significant impact is expected on clinical practice. Prioritisation also allows regulators to direct resources to regulatory actions that require additional evidence beyond data generated by routine pharmacovigilance processes (such as expedited and periodic safety reporting, or studies included in the RMP).

Between 2019 and 2022 a total of 169 PRAC-led procedures were considered for impact research. Six of these were confirmed by PRAC Rapporteurs for follow-up discussion by the PRAC Interest Group on Impact, a group set up by PRAC to oversee the implementation of the strategy.

During the reporting period, 11 impact studies commissioned to research organisations through EMA tenders were ongoing.[18]

Among these, a study on the impact of EU label changes and communication concerning the association between TTS and SARS-CoV-2 adenovirus vector vaccines was set up in late 2021,[19] with results expected in Q1 2023. This study looks at the level of awareness and knowledge of this risk by healthcare professionals, the extent of attitude changes in healthcare professionals and patients towards national vaccination programmes and the extent of change of national vaccination policies in 6 EU Member States.

Eight studies were finalised during the reporting period. A few examples are presented below, focusing on different types of regulatory actions and intended objectives of RMMs.

The first example presents two studies that were conducted separately but had similar objectives and outcomes. In both cases, the aim of the research was to measure whether a reduction in the use of the medicines was achieved without leading to a switch to alternative medicines with less favourable safety profile.

Diclofenac

Diclofenac-containing medicines are authorised for the relief of pain and inflammation in a wide range of conditions, including arthritic conditions and acute musculoskeletal disorders. In 2013, new measures, including restricting use in patients who have had certain heart or blood circulation-related issues, were implemented to reduce the risk of acute cardiovascular events.

During the reporting period, a study was conducted in several EU countries to assess the impact of the regulatory changes in clinical practice. The results showed that in most countries the regulatory action was associated with significant and immediate reductions in the initiation of treatments with diclofenac. Most importantly, although geographical variations in terms of use of ternative medicines were noted, no switch to opioids was observed.[20]

Hydroxyzine

Hydroxyzine medicines are available in most EU countries. Their approved uses vary between countries and include treatment of anxiety disorders, relief of pruritus (itching), premedication before surgery, and treatment of sleep disorders. In 2015, measures including restricting use of hydroxyzine in patients at high risk of heart rhythm problems and using the medicine at the lowest effective dose for as short a time as possible, were introduced to minimise the risk of

18 Overview of studies commissioned under the PRAC impact strategy that collect and analyse real-world data from clinical practice to help monitor the safety and effectiveness of medicines: https://www.ema.europa.eu/en/about-us/how-we-work/big-data#research-projects-section
19 EUPAS44970
20 Morales et al. Impact of EMA regulatory label changes on systemic diclofenac initiation, discontinuation, and switching to other pain medicines in Scotland, England, Denmark, and The Netherlands.

effects on heart rhythm. During the reporting period, a study looking at the impact of these regulatory actions on clinical practice in several EU countries showed that treatment initiation with hydroxyzine medicines was overall reduced and these reductions varied across countries. The regulatory action was not associated with switching to other antihistamines, benzodiazepines or antidepressants following discontinuation in any country.[21]

In both cases, PRAC concluded that the objectives of the RMMs were achieved, and no further regulatory action was warranted.

In 2018, EMA organised public hearings for valproate and fluoroquinolones to allow PRAC to listen to the views and experiences of stakeholders and to gather perspectives, knowledge and insights into the way these medicines are used before issuing major public health recommendations.

In the case of valproate medicines, the new RMMs introduced important changes to the way these medicines should be prescribed and used in order to reduce serious risks that commonly affect unborn babies during pregnancy. These measures targeted a broad group of healthcare professionals, as well as patients. Studies were commissioned to look at the awareness of the risks as well as the implementation of the new measures in clinical practice. The results are presented below.

Valproate

Valproate and related substances are used in the EU for the treatment of epilepsy, bipolar disorder and, in some Member States, to prevent migraine attacks. For some patients with serious epilepsy, valproate may be the best or only treatment option. However, it has long been known that if taken during pregnancy valproate can damage the unborn baby and cause certain abnormalities. More than 10% of children exposed to valproate in utero have congenital malformations, and between 30-40% of children exposed in utero show neurodevelopmental or behavioural disorders at an older age. Although steps had been taken previously to better inform women about these risks and prevent use of valproate during pregnancy, the evidence showed that the measures in place had not been sufficiently effective.

In 2018, PRAC established a new pregnancy prevention programme (PPP) aimed at ensuring that patients are made fully aware of the risks and the need to avoid becoming pregnant while using the medicine. With these new measures, girls and women able to have children would not be prescribed valproate for epilepsy, bipolar disorder or migraine prophylaxis unless the conditions of the PPP are met, which include getting counselling on the risks, using effective contraception, having pregnancy tests before starting and during treatment as needed, and seeing a specialist at least annually to review treatment. Additionally, a visual warning was placed on the packaging of the medicines, a new risk acknowledgement form was created, guides for patients and healthcare professionals were revised and a patient alert card was attached to the packaging.

Measuring the impact of the new measures

Two studies were commissioned by EMA to assess the impact of these new measures.

The first study[22] was conducted to assess patients and healthcare professionals' awareness of teratogenic and neurodevelopment effects of valproate and gauge their knowledge, attitudes and practices through surveys across 8 European countries. The study showed that awareness

21 Morales et al. Impact of EMA regulatory label changes on hydroxyzine initiation, discontinuation and switching to other medicines in Denmark, Scotland, England and the Netherlands: An interrupted time series regression analysis.
22 EUPAS32405

of the teratogenic risks of valproate was high among patients (71%), prescribers (94%) and pharmacists (95%); however, the knowledge and uptake of the PPP measures, in particular the use of the new guides for patients and doctors was low. Healthcare professionals indicated that the print-format in which most of the information tools were offered was difficult to integrate in the electronic prescribing and dispensing systems which is essential to fit into daily clinical practice.

The second study[23] investigated changes in utilisation and prescribing trends before and after implementation of the 2018 RMMs in 5 European countries. Although a significant reduction in valproate use in women who can become pregnant was observed in all countries across the study period (January 2010 to December 2020), there was no further significant decrease after the 2018 PPP compared to the period before. An increasing trend in use of alternative medicines for epilepsy and bipolar disorder indications across the study period in most databases was observed, while valproate use for migraine was mostly steady.

Although the available data on contraceptives use were limited, no increase in use was seen after the 2018 measures across the studied databases. There were reductions in the rates of pregnancies while using valproate after the 2018 measures, but pregnancies still occurred in all but one country (The Netherlands).

Conclusion

The overall impact of the 2018 additional risk minimisation measures (aRMMs) on valproate use and prescribing was small. Despite the declining rates of pregnancies after the 2018 intervention in most countries/regions, the number of pregnancies while using valproate is still a matter of concern.

Several study limitations should be noted, including limited or lack of data on pregnancy testing or contraceptive use in the included databases and the limited information on the reasons for valproate discontinuation.

It should also be noted that the PPP measures were not fully implemented in all countries at the time of these studies. In addition, the period studied after the 2018 intervention was rather short to measure changes in behaviour of patients and prescribers. Therefore these results had to be analysed in the light of other ongoing studies.

Additional studies were ongoing by the end of 2022 to complement these results and have helped to get a clearer picture of the effectiveness of the 2018 measures in the EU.

A consortium of MAHs of valproate medicines is conducting a drug utilisation study with a longer duration than the one described above and a slightly different focus in terms of the countries and PPP elements studied. Interim results were under review by PRAC at the end of 2022.

In addition, EMA commissioned another study on prescriptions of valproate, making use of the newly established DARWIN EU® platform (see section on DARWIN EU® starting on page 39). This study collected further information on valproate use in 6 European countries, in particular in women between 12 and 55 years who are initiating treatment.[24] The results showed that the use of valproate decreased during the study period between 2010 and 2021 and remained stable at a lower level afterwards. The decrease in use was generally more pronounced in younger age groups.

While further data will be analysed on the medicine use, one important learning so far is the need for more qualitative studies to understand why awareness of the risks amongst healthcare professionals does not necessarily translate into a

23 EUPAS31001
24 EUPAS50789

change in behaviour and higher compliance with the recommendations. As a follow-up action, the PRAC requested that MAHs conduct a PASS to investigate the barriers and reasons why certain measures are not followed in clinical practice. Innovative approaches have been discussed to help understand the reasons behind the behaviours observed in the various surveys.

In addition, a multistakeholder meeting was planned to take place on 1 February 2023 to further discuss with healthcare professional and patient representatives which non-regulatory tools could facilitate RMMs implementation in clinical practice (e.g. alerts in electronic prescribing/dispensing software, inclusion in medical curriculum, additional communication channels) and how NCAs can support professional organisations and key actors at national level.

In 2018, the PRAC issued another set of major public health recommendations, this time in relation to rare but serious side effects occurring with widely used medicines, the fluoroquinolone antibiotics. These measures introduced important changes to the way these medicines are prescribed, restricting their use so that they are no longer used in milder infections. Because of the large number of medicines concerned and the impact on public health, a study was commissioned to assess the impact of the measures on prescribing.

Fluoroquinolones

Fluoroquinolone antibiotics (used orally, by injection or inhalation) can, very rarely, cause long-lasting and disabling side effects, mainly involving muscles, tendons, bones and the nervous system.

In November 2018, EMA recommended that fluoroquinolones should no longer be prescribed for milder, non-severe or self-limiting infections (such as pharyngitis, tonsillitis and acute bronchitis) or for preventing travellers' diarrhoea, recurrent lower urinary tract infections or non-bacterial infections (e.g. non-bacterial chronic prostatitis). Other indications were restricted to last-line therapy in patients in whom other therapeutic options are not effective or not tolerated. Additional warnings also aimed at protecting people at a higher risk of tendon injury.

Measuring the impact of the new measures

To measure the impact of these RMMs, a study[25] based on electronic health care records from 6 European countries between 2016 and 2021 was commissioned to determine changes in prescription patterns over time, prescriber's compliance with revised warnings for use in patients at increased risk of harm, and use of alternative antibiotics for infections where fluoroquinolones should no longer be used.

At the start of the study and throughout the study period, there were important differences in the incidence of fluoroquinolones use across the countries included, ranging from a very low incidence (0.7/1,000 persons per month) in the United Kingdom to a high incidence (8/1,000 persons per month) in Spain.

The findings of the study indicated that fluoroquinolone prescribing in the primary care setting decreased over time in the 6 countries included in the study. This reduction coincided with the implementation of the RMMs in 2 countries, while in the others a decrease had already started before the introduction of the restrictions. Overall, the extent of the decrease observed in these 6 countries was limited.

The study also suggested that fluoroquinolones may still be used outside the revised indications, as recommended within the 2018 referral, with respiratory tract infections, (uncomplicated) urinary tract infections and ear infections being the most frequent indications.

25 EUPAS37856

Conclusion
The regulatory action seems to have had only a modest impact on fluoroquinolones prescribing in primary care setting.

However, these results need to be interpreted taking into account the study limitations including lack of prescribing data from secondary care (hospitals) and limited information on indications as well as potential misclassification (i.e. incorrect categorisation) of cases concerning on- and off-label use in the electronic health care data sources included in this study.

This study also brought to light a decrease in fluoroquinolone prescribing that started before the implementation of 2018 measures. This positive trend, which may be attributed to increased awareness and media attention on the safety of this class of antibiotics as well as increased antibiotic stewardship overall and local changes in clinical guidance, goes in the direction of the overall objective of the measures put in place.

In the context of the fight against antimicrobial resistance, a study coordinated by DARWIN EU® was commissioned to investigate prescription patterns of antibiotics on the WHO 'Watch' list, which includes fluoroquinolones.[26] The results showed that the use of the fluoroquinolones included in the study (among others, ciprofloxacin, levofloxacin and ofloxacin) largely decreased or was similar compared to the earlier time periods beginning in 2012. The study also showed different trends in use of Watch list antibiotics between primary care and hospital settings.

As foreseen in the process for prioritisation and regulatory follow-up put in place in 2019, the findings of the impact study were to be reviewed by the PRAC at the beginning of 2023 with a discussion on any further actions needed, including further engagement with relevant healthcare professionals to support behavioural change.

As some of these impact studies underlined challenges with implementing RMMs, particularly with regard to changing clinical practice and prescribing behaviour, initiatives were undertaken to facilitate change, although some of these go beyond the regulatory scope. Clinical guidelines, for instance, play an important role in the implementation of RMMs in clinical practice. EMA commissioned a study in 2022 to better understand how specific RMMs in 5 disease areas were integrated in national clinical guidelines, and the role of healthcare professionals' associations and public bodies in the production of such guidelines as well as in the dissemination of emergent safety concerns. The study will include fluoroquinolones as a case study, amongst others. The outcome, which is expected in 2023, will provide recommendations for engagement with relevant bodies with a view to strengthen the role of clinical guidelines in the implementation of RMMs in daily healthcare.[27]

Enablers of effective pharmacovigilance and stakeholder engagement

The effectiveness of RMMs depends on 'enablers' for their implementation in daily healthcare, in particular on engaging patients and healthcare professionals in the implementation of these measures.

During the reporting period, EMA collaborated with the University of Amsterdam to 'conceptionalise' pharmacovigilance engagement for regulatory purposes,[28] reviewed the evolution of EMA's stakeholder interactions from a risk governance perspective[29], and performed an in-depth analysis of the public hearing and other interactions in 2017 for managing the risks of in-utero exposure to valproate.[30] These studies have provided

26 EUPAS103381
27 EUPAS47588
28 Brown et al. Engagement of patients and healthcare professionals in regulatory pharmacovigilance: establishing a conceptual and methodological framework
29 Bahri et al. Systematising Pharmacovigilance Engagement of Patients, Healthcare Professionals and Regulators: A Practical Decision Guide Derived from the International Risk Governance Framework for Engagement Events and Discourse
30 Bahri et al. Proposals for Engaging Patients and Healthcare Professionals in Risk Minimisation from an Analysis of Stakeholder Input to the EU Valproate Assessment Using the Novel Analysing Stakeholder Safety Engagement Tool (ASSET)

recommendations for a future PRAC process for stakeholder engagement, including development of a decision guide that regulators may use for selecting engagement mechanisms in different typical scenarios of safety concerns.

To pilot some of these recommendations, PRAC established in July 2022 a working group with patients, healthcare professional representatives and regulators called PRISMA (PRAC Risk Minimisation Alliance) with the aim to better understand the barriers and enablers of RMM implementation. This initiative offers a forum outside PRAC plenary meetings to discuss, early in the regulatory procedure, options for additional RMMs for specific medicines, as well as to advise PRAC on their 'implementability' in healthcare and on the need for further engagement (such as public hearings). For example, in 2022 the group provided questions to be discussed at the 2023 multistakeholder meeting on the effectiveness of RMMs for valproate mentioned on page 35. It also started working on information requests to Member States to map implementation processes and identify opportunities for improving collaboration with stakeholders.

Effectiveness of specific pharmacovigilance processes

Since 2012 a significant number of PASS evaluating the effectiveness of RMMs have been imposed or requested by PRAC to MAHs. The systematic collection and review of the results of MAH-sponsored PASS contributes to a better understanding of the requirements for data collection, study designs and analytical methods, as well as the interpretation of study results, factors associated with success or failure of RMMs and impact of individual regulatory tools in clinical practice.

A systematic review of the PASS assessed by PRAC between 2016 and 2019[31] highlighted a marked heterogeneity in quality and methodology across the studies and showed that 40% of the studies were unable to conclude whether the RMMs were effective or not. The review suggests that inconclusive PASS used more often survey methodology while conclusive PASS used prospective observational studies and interviews to assess RMM effectiveness and often included pre-defined criteria to measure success. In addition, conclusive PASS showed more variety in the data sources used, with primary data less frequently used. This work continued with a follow-up review including additional PASS assessed in 2020 and 2021 that identified limitations related to survey methodology, secondary use of data and general study design as key factors leading to inconclusive PASS.[32] Recommendations to improve the quality of these studies were being reviewed by PRAC at the end of 2022.

Analytical methods for impact research

There is no single commonly accepted method for measuring the impact of pharmacovigilance activities or to evaluate the effectiveness of RMMs. In 2017, a systematic review of methodologies for measuring the impact of regulatory interventions showed significant heterogeneity and highlighted the need for scientific guidance for stakeholders on methods for impact research.[33] The development of methodological guidance continued to be a priority during the reporting period and revision 9 of the ENCePP Guide on Methodological Standards in Pharmacoepidemiology includes a specific topic on methods for pharmacovigilance impact research.[34] For pharmaceutical industry and regulators revision 3 of GVP Module XVI[35] includes guidance on the principles, objectives and assessment of RMM effectiveness, and a new Addendum II on methods for effectiveness evaluation. The final version is expected to be published in 2023.

31 EUPAS45978
32 EUPAS47563
33 Goedecke et al. Measuring the impact of medicines regulatory interventions – systematic review and methodological considerations
34 ENCePP Guide on Methodological Standards in Pharmacoepidemiology https://www.encepp.eu/standards_and_guidances/methodologicalGuides.html
35 GVP Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 3), under public consultation: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-xvi-risk-minimisation-measures-selection-tools_en.pdf

Use of real-world evidence (RWE)

Although RWE has been used for a long time both in support of the authorisation of medicines[36] and in safety monitoring, EMA and the NCAs have taken steps to build a more sustainable platform to access, analyse and incorporate into the decision making process a wide range of healthcare data from across the EU, in line with the European medicines agencies network strategy to 2025 and the EMA Regulatory Science to 2025, as part of the Big Data Steering Group work plan.[37] Leveraging use of high-quality RWE in medicine regulation will benefit public health by accelerating medicine development, improving treatment outcomes and facilitating earlier patient access to new treatments.

Expanding access to healthcare databases

Between November 2019 and January 2021, EMA coordinated a pilot on rapid data analytics to support the PRAC activities. The aim was to test the feasibility and usefulness of a process for rapid identification, analysis and reporting of results of epidemiological questions that may arise in the context of regulatory assessments. It focussed on questions for which RWD and RWE can support regulatory decisions by filling knowledge gaps identified during a procedure. The experience gained from the pilot has revealed several important aspects to be considered for EMA support to the PRAC. The recommendations drawn from the pilot will help optimise usage of RWD and RWE by the PRAC and facilitate their integration into regulatory procedures. They also pave the way for similar pilots with the other EMA committees.

The data sources available to EMA in 2019-2021 to generate RWE for PRAC included large electronic healthcare databases from France, Germany and the United Kingdom available in-house and studies procured through EMA framework contracts with research organisations. To increase the number and scope of studies that could be performed through these sources, EMA published in 2021 a call for tenders for additional in-house data sources from Eastern and Southern European countries and from hospital settings. Subsequently, in 2022, additional databases from Italy, Spain, and Romania became available to EMA. A tender for new framework contractors was also published resulting in the availability of 8 contractors with expertise in pharmacoepidemiology with access to 59 databases in 21 EU Member States. These additional data sources will help EMA increase its support to PRAC and other scientific committees by broadening the geographical coverage and the available data types.

During the reporting period, EMA initiated 28 studies to gather RWE in support of ongoing or upcoming procedures at PRAC. These were being conducted using EMA's in-house databases. A couple of examples are presented on the next page.

36 Flynn et al. Marketing Authorization Applications Made to the European Medicines Agency in 2018–2019: What was the Contribution of Real-World Evidence?

37 Big Data Steering Group Workplan 2021-2023 https://www.ema.europa.eu/en/documents/work-programme/workplan-2021-2023-hma/ema-joint-big-data-steering-group_en.pdf

Aflibercept and retinal artery occlusion

A concern over an increased risk of central retinal artery occlusion (cRAO) following exposure to intravitreal aflibercept, for which neovascular (wet) age-related macular degeneration (nAMD) is the main indication, was raised during the assessment of the PSUR. A request was made to EMA for additional data on the incidence of RAO in the nAMD population to support the regulatory decision-making process and a study (EUPAS34826) was performed using electronic health care records databases in the United Kingdom, France and Germany. The analyses suggested that the incidence of cRAO in the nAMD population to be in the region of 10 to 20 cases per 100,000 patient year. This was comparable to the rate that was expected of cRAO in the general population.

These results supported the regulatory decision by contextualising the increased risk observed in the PSUR.

Based on all the available evidence, including literature, EudraVigilance case reports and epidemiological data, the PRAC concluded that no labelling change was warranted.

Fluoroquinolones and thrombotic thrombocytopenic purpura

Fluoroquinolone antibiotics are widely used for the treatment of certain types of microbial infection. In June 2021, a review of cases in the EudraVigilance database led to the suspicion of a possible association between this class of antibiotics and the onset of thrombotic thrombocytopenic purpura, a rare disorder that causes blood clots (thrombi) to form in small blood vessels throughout the body. This signal has been evaluated by the PRAC. In order to support this evaluation, EMA performed a study of data from databases in the United Kingdom and Germany to determine how often thrombotic thrombocytopenic purpura occurs after patients are prescribed fluoroquinolones. To allow contextualisation of the results, the same analysis was conducted on data from two other groups of patients prescribed other antibiotic medicines, broad spectrum penicillins and azithromycin. The results were published in the EU register of post-authorisation studies, the EU PAS Register (EUPAS42641). Based on these data, it was concluded that there was insufficient evidence at present to confirm a causal association between systemic fluroquinolones and thrombotic thrombocytopenia purpura.

Launch of DARWIN EU®

In order to increase the Network's capacity to deliver valid and timely evidence to support regulatory decisions using RWD, in 2022 EMA started setting up DARWIN EU®, the Data Analysis and Real-World Interrogation Network, in line with the objectives of the European medicines agencies network strategy to 2025. DARWIN EU® is a federated network of data, expertise and services to support EMA and the EU Network with evidence on diseases, patient populations and the use, safety and performance of medicines. Following a call for tenders launched in 2021, the Erasmus University Medical Centre Rotterdam was appointed as the Coordination Centre of DARWIN EU® in February 2022. It will run scientific studies to answer research questions that may come up during the development, evaluation and supervision of medicines in the EU, and alsomaintain a catalogue of RWD sources for use in medicine regulatory activities. All studies will be published in the EU register of post-authorisation studies (EU PAS Register).

In 2022, DARWIN EU® onboarded the first 10 data partners. The selected partners include both public and private institutions and have access to real-world healthcare data from one or more sources such as hospitals, primary care, health

insurance, biobanks and disease-specific patient registries. Additional databases are foreseen to be added each year from 2023 to 2025, increasing the capacity for generating RWE to support EMA's Committees and the EU Network. It is planned that, by year 2025, DARWIN EU® will have the capacity to perform at least 60 routine repeated analyses, 60 off-the-shelf studies, 24 complex studies and 1 very complex study every year. In 2022,[38] four studies were initiated by DARWIN EU®, one of which will support the PRAC in its assessment of the use of valproate-containing medicines; another will look at trends in antibiotics use, including fluoroquinolones, as mentioned on page 36.

New catalogue of data sources

The use of high-quality RWE for regulatory decision-making requires the ability to identify and characterise existing data sources in the EU. For this purpose, a project aimed at building a new catalogue of data sources enhancing the current ENCePP Resources Database was initiated. A list of metadata describing RWD sources and studies that will feed into the catalogue was published in 2022. The catalogue will be searchable and will include metadata describing the main characteristics of each data source, e.g. population size, demographics, type of care covered, diseases of interest covered, as well as information on data quality. A new catalogue for studies based on the EU PAS Register will also be delivered and linked to the catalogue of data sources, with improved functionalities like search and export functions.

DARWIN EU® and the catalogue of data sources and studies will be useful tools to generate RWE, and adequate expertise will be needed not only to contribute to study design, data collection, analysis and reporting, but also to critically review study protocols and study reports required by regulatory authorities and developed by pharmaceutical companies. The content of a big data training curriculum covering the domains of data science, pharmacoepidemiology, biostatistics and clinical trials has been developed since 2019. Following a call for tenders, service providers were selected for the pharmacoepidemiology and data science curriculum, with trainings expected to be released starting from 2023.

Patient registries

The field of RWD sources is very diverse. Patient registries are increasingly used as a source of data for RWE studies but when compared to population-based electronic health care data sources they may present with specific issues related to availability of data elements, data quality and data sharing. From 2019 to 2021, the Cross-Committee Task Force on Patient Registries developed a guideline providing recommendations to marketing authorisation applicants (MAAs) and MAHs, as well as to other stakeholders using patient registries as a data source for regulatory studies. Following extensive consultations, the CHMP Guideline on Registry-based studies was published in October 2021. An important recommendation from the guideline is the early discussion between MAAs/MAHs and EMA scientific committees and the Scientific Advice Working Party about the suitability of a patient registry for the research questions at stake. This early discussion should be supported by a feasibility analysis performed by the MAA/MAH with the registry holder and structured as recommended in the guideline.

EU Vaccine Monitoring Platform

In May 2022, EMA and ECDC launched the EU Vaccine Monitoring Platform, a joint initiative for strengthening the continuous monitoring of the safety and effectiveness of vaccines in the EU. Through this platform, the two agencies will coordinate and oversee EU-funded, independent post-authorisation studies on vaccines' use, safety and effectiveness in EU countries. Such large studies aim to meet the needs of medicines regulators, national institutes for health and vaccination recommendation bodies. The Immunisation and Vaccine Monitoring Advisory Board (IVMAB), a multidisciplinary panel with representatives of the European Commission, ECDC's National Focal Points, EMA's ETF, CHMP and PRAC, was set up to advise EMA and ECDC on the VMP research agenda. An important achievement in 2022 was the coordination of an EU-funded study to assess the effectiveness and safety of Imvanex (mpox / monkeypox vaccine).[39] The VMP is an important milestone of the European Commission's initiative to support the European Health Union.

38 EUPAS50800; EUPAS50789; EUPAS103381; EUPAS103936
39 EUPAS50093

Simplification of processes

The EU pharmacovigilance system encompasses a wide range of activities, all carried out across the EEA, and sometimes beyond; the complexity of this task across a diverse population of nearly 500 million people, accessing varied healthcare systems, should not be underestimated.

During the reporting period, as in the previous years, efforts were made to simplify processes to make them more efficient. Examples are provided below.

Publication of full RMPs and further process simplification

RMPs of medicines are one of the documents most requested by stakeholders. EMA routinely publishes summaries of the RMP for each authorised medicine. However, to increase transparency during the COVID-19 pandemic, the Agency decided to publish the full RMP body plus Annex 4-*Specific Adverse Drug Reaction Follow-up Forms* of all medicines intended for COVID-19, instead of summaries.

In 2022 EMA extended this initiative (now also including the publication of Annex 6 of the RMP-*Details of proposed additional risk minimisation activities)* to any medicine that contains a new active substance granted a CHMP positive opinion from July 2022 onwards. In addition, the Agency decided that the most requested RMPs would also be published. As a result, 13 of those RMPs were published by the end of 2022.

The publication of RMPs (main body + Annexes 4 and 6) is expected to have several benefits. First, it will further increase transparency and provide even more safety information to patients, healthcare professionals, researchers, and the public as a whole. Second, it will support the development of generic medicines as companies will now have direct access to the RMP of reference medicines; lastly, it will reduce administrative burden for both EMA and medicines developers.

In addition, to further simplify the RMP process, since September 2021 the PRAC has been assessing the entire RMP of generic products during the MAA phase without the involvement of the CHMP assessors. In the past, the two committees used to share the assessment of these documents, with each committee focusing on different parts. The objective is to streamline the assessment process, speed up the procedure and free up time for the CHMP assessment team to focus on other aspects of the dossier.

Migration of inspections to IRIS

In 2021 and 2022, the coordination of inspections requested by EMA's committees for human and veterinary medicines under the centralised procedure was transferred to IRIS, a secure online

platform for handling product-related scientific and regulatory procedures. This started with GMP (Good Manufacturing Practice) inspections in 2021, GCP (Good Clinical Practice) inspections in 2022 and was followed by the go-live of pharmacovigilance inspections in September 2022.

EMA launched IRIS in 2018. The system is gradually being rolled out to cover all EMA's regulatory and scientific business areas and is accessible by EMA, MAHs/applicants and EEA NCAs. It aims at improving efficiency, transparency and collaborative work as part of EMA's digital transformation programme.

The key benefits of the coordination of inspections using IRIS are efficiency gains for EMA, MAHs/applicants and the EU regulatory Network, increased security, reduced risk of unintentional disclosure of confidential information and better knowledge management. To ensure a smooth rollout, several training sessions have been organised for EMA staff, NCA inspectors and industry users.

Remote inspections

Due to travel restrictions during the pandemic, more than half of the pharmacovigilance inspections in 2020 were conducted remotely. This was made possible by guidance on remote pharmacovigilance inspections during a crisis situation that was previously issued by the pharmacovigilance Inspections Working Group, which outlines the steps to be followed during remote pharmacovigilance inspections of MAHs. Thanks to this process, EMA and NCAs could continue to check that MAHs met the requirements for monitoring the safety of medicines, even when the possibility of travelling was significantly restricted.

Based on this experience, remote inspections are considered a useful tool that will be used also outside of crisis scenarios and in specific cases (e.g. when it is not possible to inspect physically or for follow-up inspections to assess corrective and preventive actions plan) with a view to gain efficiency while maintaining high standards. However, remote inspections will not replace on-site inspections.

Supporting decision on PSUSA cycle

Another area of focus was the optimisation of the PSUR single assessment cycles. MAHs for active substances and combinations of active substances that are subject to assessment at EU level must submit the relevant PSURs according to the EU reference dates (EURD) list.

To support decision-making for determining PSUR frequencies of the EURD list, EMA developed a statistical tool called the EURD Tool. This tool considers readily available data from different electronic sources (e.g. number of cases in EudraVigilance, number of signals in EPITT, number of referrals and the age of the product) to determine a PSUR frequency.

In the past years, the EURD tool has been tested and validated in consultation with EU Member States. In 2021, PRAC agreed that the EURD Tool was able to assign relevant PSUR frequencies. The tool, which is expected to simplify and optimise this process, is planned to be used in the coming years on a subset of more than 1,000 entries for which a PSUR frequency of 13 years and a Data Lock Point (DLP) of 2025 was allocated at the time of the creation of the EURD list. Thereafter, use of the tool for reassigning PSUR cycles to entries with other DLPs/cycles may be considered.

Chapter 2

Overview of key activities by area

Overview of key activities by area

This section presents an overview of EU pharmacovigilance activities between 2019 and 2022 and includes quantitative and qualitative data. Further quantitative data summarising the work of the EU pharmacovigilance network are available in the Annexes at the end of the report.

This section covers in detail activities conducted by the PRAC during the reporting period, as well as other activities in support of safety evaluations that were led by other committees.

PRAC activities – overview

The PRAC is the EMA's committee responsible for assessing and monitoring the safety of human medicines. The Committee provides recommendations on questions on pharmacovigilance and risk management systems, including the monitoring of their effectiveness, to the CHMP and CMDh.

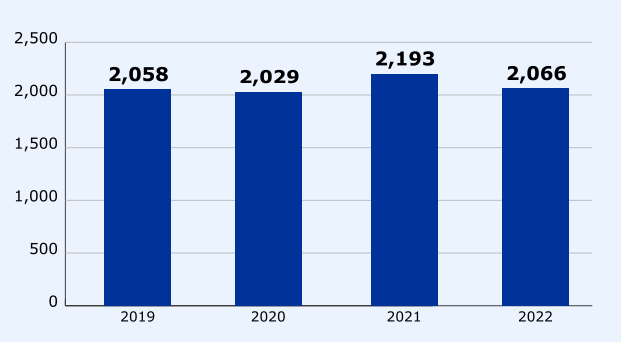
The work is organised within PRAC in such a way that the assessment is generally performed by an appointed NCA on behalf of the EU Network, with a final recommendation based on this assessment being issued by the Committee as a whole.

In 2021, the PRAC began its fourth term and the Committee voted to prolong the mandate of Dr. Sabine Straus and Dr. Martin Huber as Committee chair and vice-Chair, respectively, for another three years. The Committee celebrated its 10th anniversary in 2022.

At the same time, new representatives of patients' and healthcare professionals' organisations were appointed for a three-year mandate. Representatives of civil society play an important role in the Agency's work. Within PRAC, the role of representatives of patients' and healthcare professionals' organisations is to ensure that the needs and views of the groups they represent, as well as the real-life implications of any Committee recommendations, are taken into account during the discussions and decisions of the Committee. Civil society representatives have the same voting rights as the other PRAC members.

The number of items on the PRAC's agenda has stabilised over the past years, with over 2,000 items included in the PRAC agenda yearly.

Figure 1. Total PRAC agenda items



The bulk of the work relates to ongoing safety monitoring (PSURs and signals) and the assessment of RMPs and PASS. Details are provided in the following sections.

Adverse reaction reporting

Collecting reports of medical events and problems that occur following the use of a medicine is one of the pillars of the EU safety monitoring system. Healthcare professionals and patients are encouraged to report all suspected adverse reactions individuals may have experienced, even if it is unclear whether the medicine was the cause. Reports of suspected ADRs received by NCAs and MAHs are transmitted to EudraVigilance, the European database of suspected ADR reports. EudraVigilance is the tool that EMA and NCAs use for monitoring the safety of all authorised medicines in the EU, as well as medicines studied in clinical trials. It centralises all the ADR reports received within the EEA as well as serious reports collected outside the EEA for all medicines authorised in the EU.

The overall number of ICSRs received, both from within and outside the EEA, increased dramatically in 2021 reaching 3.5 million, almost twice as many as those received in 2020 (see figure 2). This increase was mainly driven by the reporting linked to the COVID-19 vaccines, as about 48% of these reports (1.7 million) were related to them.

A similar trend was observed in 2022, although to a minor extent. The number of reports received was 1.6-fold higher than the amount received in 2020, about 40% of which were again linked to COVID-19 vaccines (for more details about reports in EudraVigilance, see Annex 4A).

Looking at the EEA reports only, the number of reports increased by 115% in 2021 relative to 2020 and around 70 % of those concerned COVID-19 vaccines (about 1.2 out of 1.7 million). Again, similar trends were observed in 2022 (increase of around 80% in the number of reports received compared to 2020; about 62% of the EEA reports were related to COVID-19 vaccines).

In the EEA, the number of serious reports received in 2021 and 2022 also increased compared to 2020 but to a lesser extent (50 to 55% increase over 2020; see figure 3). About 55% of these related to COVID-19 vaccines (264,000 in 2021 and 256,000 in 2022).

Figure 2. ICSRs in EudraVigilance post-authorisation module[40]

	EEA	Non-EEA	Total
2019	968,689	1,034,123	2,002,814
2020	812,784	1,008,455	1,821,239
2021	1,745,290	1,780,565	3,525,976
2022	1,451,946	1,456,138	2,908,264

Figure 3. Serious ICSRs in EudraVigilance post-authorisation module (EEA)[40]

2019	2020	2021	2022
384,890	312,103	484,307	469,583

40 The data presented in this report were extracted on 10 January 2023 and may slightly differ from those included in other previously published annual reports, possibly due to deduplication and nullification of reports that have taken place following those publications. In addition, some discrepancies in ADR numbers may be caused by delayed ICSRs processing caused by the high volume of cases received during the COVID-19 pandemic.

As in previous years, in 2019 and 2020 the majority of reports received in the EEA were submitted by healthcare professionals. However, this trend reversed in 2021 with an over 3-fold increase in patient reporting (from about 201,000 in 2020 to 851,000 and 703,000 in 2021 and 2022, respectively). The majority of reports received from outside the EEA still came from healthcare professionals (see figure 4 and figure 5).

The inversion in the trend in the EEA likely results from communication campaigns carried out across the EU to encourage citizens to report to their national authorities suspected side effects experienced after vaccination; over 80% of patients reports received in 2021 and 2022 were related to COVID-19 vaccines.

Most reports received from patients were related to non-serious adverse events. Serious reports accounted for about 16% of the total number of patient reports submitted in the EEA in 2021 and 2022, compared with 23% in 2020.

Figure 4. Indvidual case safety reporting to EudraVigilance (EEA)

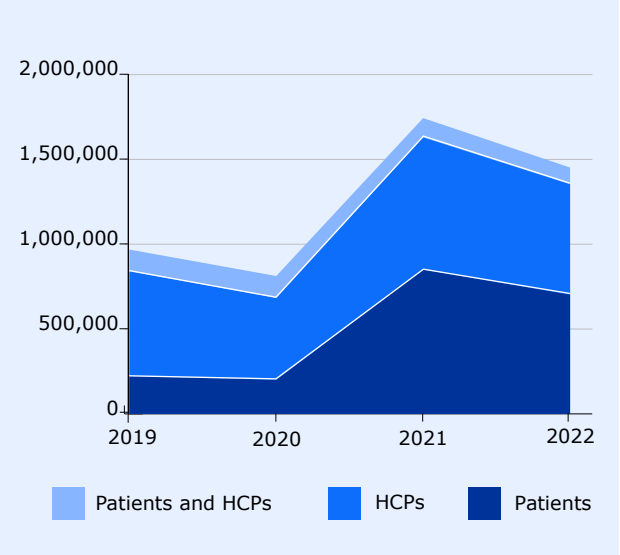
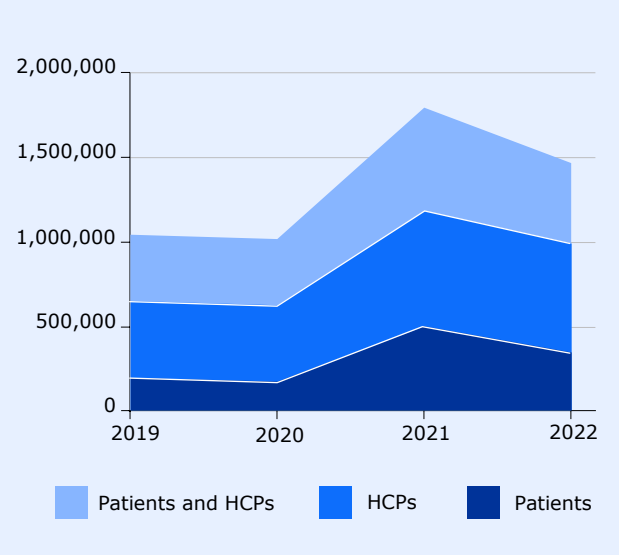


Figure 5. Indvidual case safety reporting to EudraVigilance (non-EEA)



New international standards to improve reporting of suspected side effects

Following a decision by the EMA's Management Board in 2019, a new data format for reporting suspected side effects of medicines to EudraVigilance became mandatory on 30 June 2022.

This format is based on the standards set by the International Organization for Standardization (ISO), namely the ISO ICSR Standard and the ISO terminology on pharmaceutical dose forms and routes of administration.

These standards improve the quality of data collected and the analytical capabilities in EudraVigilance. This further supports regulatory authorities and companies in detecting and addressing safety issues with medicines, and therefore allows better protection of patients. In addition, the ISO standards strengthen the protection of personal data in the records of ICSRs. EMA and the HMA jointly developed a guide in 2015 (which was revised in 2021) to help pharmaceutical companies, sponsors of clinical trials and medicines regulatory authorities in EU Member States prepare for the use of the new standards. Throughout 2022, EMA further supported stakeholders by providing various guidance to ensure their readiness in achieving this important milestone.

Medical literature monitoring
Medical literature is an important source of information for the identification of suspected ADRs.

MAHs are usually responsible for monitoring the medical literature on their medicines and reporting individual cases of suspected ADRs into EudraVigilance and national safety databases, in line with GVP Module VI.

However, for a number of substances with many marketing authorisations and multiple MAHs in the EEA, EMA provides a medical literature monitoring service in order to avoid duplication of effort, reduce the number of duplicate reports and enhance quality and consistency of the safety monitoring of medicines. This service was launched in June 2015 and was successfully audited by external auditors in 2021.

In June 2020, the medical literature monitoring service was expanded to cover 9 additional substance groups that were being used as possible treatments for COVID-19. These were in addition to 6 pre-existing substance groups that were also related to COVID-19 (see figure 6).

Additional monitoring
In 2013, the EU introduced a system to label medicines that are being monitored particularly closely by regulatory authorities.[41] These medicines are described as being under additional monitoring. Their product information is marked by a black triangle, and they are monitored more intensively than other medicines. This is generally because less information is available for these medicines, for example because they contain a new active substance or have been approved in circumstances where there are limited data. Therefore, reporting of suspected ADRs is particularly encouraged and the interval between PSURs may be shorter than for other medicines. As more is understood about the medicine, it will eventually be removed from the list of medicines subject to additional monitoring.

EMA maintains the list of medicines subject to additional monitoring, which is reviewed every month by PRAC and published by EMA and NCAs on their websites. At the end of 2022, there were 334 CAPs on this list and 31 NAPs. In addition, 1,227 NAPs were included in the Annexes to the list, which relate to individual active substances included mainly due to the imposition of a PASS as a result of a referral procedure.

Although the main objective of the additional monitoring scheme was to stimulate spontaneous reporting of suspected ADRs, recent research[42,43] has not been able to provide conclusive evidence of an impact on the reporting of ADRs or detection of safety signals for the medicines concerned. A survey of Member States highlighted that a large number of medicines were subject to additional monitoring because of an imposed PASS despite having been on the market for several years. Furthermore, the survey highlighted a certain degree of misunderstanding among patients and healthcare providers about the reason for the inclusion of the black triangle in the product information. The scope of the additional monitoring concept is being reconsidered, and in this context other approaches to improve spontaneous reporting will be explored.

Figure 6. Medical literature monitoring

Year	Literature articles reviewed	ADR reports added to EV	Unique cases identified
2019	355,634	9,676	6,495
2020	388,898	9,535	6,154
2021	487,635	9,190	6,665
2022	718,375	8,278	6,161

41 Defined by Article 23 of Regulation (EC) No 726/2004 and Article 11 of Directive 2001/83/EU, as amended; the implementing regulation for the black triangle is (EU) No 198/2013
42 Segec A, et al. Does additional monitoring status increase the reporting of adverse drug reactions? An interrupted time series analysis of EudraVigilance data.
- Januskiene J, et al. What are the patients' and health care professionals' understanding and behaviors towards adverse drug reaction reporting and additional monitoring?.
43 Report from the Commission to the European Parliament and the Council on the national and European Medicines Agency experience regarding the list of medicines for human use subject to additional monitoring.

Signals

Signal detection and assessment is at the core of pharmacovigilance. It allows new or emerging concerns to be picked up quickly and regulatory action to be taken to protect public health.

While thousands of potential signals are reviewed every year, only a small proportion is eventually validated, when the available evidence suggests that there might be a possible causal association between the ADR and a medicine. For those validated signals a thorough assessment is carried out to appraise all the available information, including data that may be requested to relevant MAHs. At the end of the assessment, if a causal association with the medicine is considered at least a reasonable possibility, the PRAC will recommend swift action, typically an update of the product information, in order to inform patients and healthcare professionals about the new safety information and provide recommendations to minimise the risk of harm when needed.

Both the EU Member States and EMA are involved in signal detection activities.

Between 2019 and 2022, EMA's signal management team reviewed over 7,000 potential signals, the great majority of which had their source in EudraVigilance reports. In the period 2021-2022, 17% of the potential signals reviewed by the EMA were related to COVID-19 vaccines. Thousands more potential signals were reviewed by the Member States.

Of all the signals reviewed during the reporting period, 273 were validated by EMA, the Member States or MAHs and then confirmed by the PRAC rapporteurs or lead Member States (see figure 7). Those went on to be prioritised and assessed by PRAC. Data from EudraVigilance contributed to triggering 85% of those 273 signals and 36 signals out of 273 were related to COVID-19 vaccines or therapeutics.

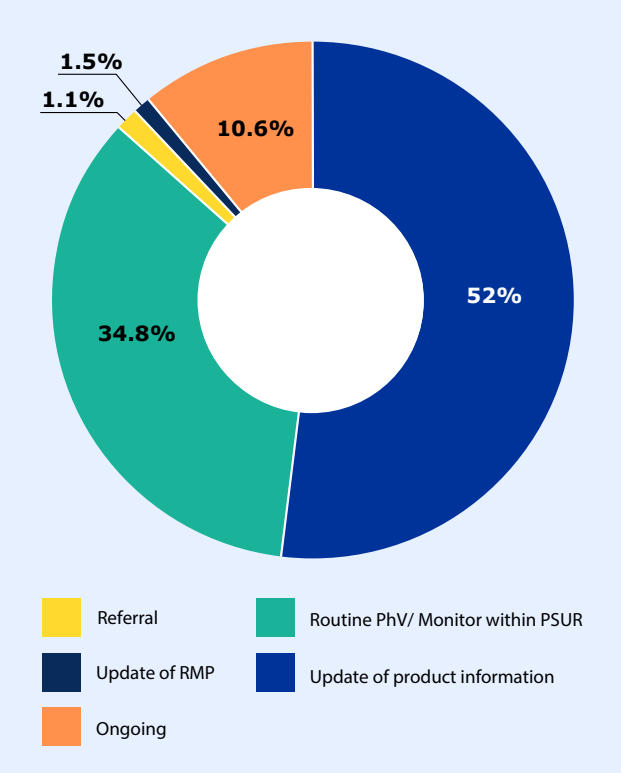
Figure 7. Signals assessed by PRAC 2019-2022

Validated by EMA	154
Validated by MSs	118
Validated by MAH	1
Total	**273**

Following assessment, around half of these signals (142) resulted directly in a PRAC recommendation to update the product information, the major source of guidance on the use of medicines for healthcare professionals and patients. In 16 cases, more targeted information in the form of a DHPC was considered necessary by the PRAC.

In three cases a referral procedure to examine the safety concern in more depth was deemed necessary (see figure 8).

Figure 8. Signal outcomes 2019-2022



Signal management has proven to be able to respond very rapidly to potential safety concerns. An example is the signal of thrombosis with thrombocytopenia syndrome (TTS) with the adenovirus-based COVID-19 vaccine Vaxzevria.

Thanks to the commitment, flexibility and engagement of the EU network, as well as the unprecedented level of cooperation with worldwide regulators and academic researchers, it was possible to use resources and expertise from across the globe and adopt innovative approaches while analysing the evidence. This allowed the EU Network to respond rapidly to a safety concern with major implications on public health and to communicate transparently throughout all the stages of the assessment process.

Vaxzevria COVID-19 vaccine and signal of thrombosis with thrombocytopenia syndrome (TTS)

Vaxzevria (formerly COVID-19 Vaccine AstraZeneca) received a conditional marketing authorisation in the EU on 29 January 2021 for active immunisation against COVID-19 in adults.

On 7 March 2021, Austria alerted the EU regulatory network to unusual cases of thromboembolic events following administration of Vaxzevria, including one fatal, and suspended the use of a specific batch of the vaccine. More than 3 million doses of Vaxzevria had been administered in the EEA at that time. Over the following days more Member States paused vaccination with certain batches of Vaxzevria or with the vaccine altogether.

On 9 March 2021, based on a preliminary assessment by PRAC and EMA's biologics working party, a batch-specific issue was considered unlikely, and a broader evaluation of thromboembolic events was initiated. Within three days, a signal procedure was started under an accelerated timetable and data from a wide range of sources were analysed, including EudraVigilance data, quality, clinical and pre-clinical data, literature data and data from the MAH. This led to the identification of a new risk possibly linked to the vaccine: a rare combination of thrombosis with thrombocytopenia, defined later on as TTS. An extraordinary PRAC meeting was held on 18 March 2021 to discuss the available evidence and warranted actions. By 24 March 2021, Vaxzevria's product information had been updated and healthcare professionals had been warned about the risk through a DHPC.

To help better understand what was then a new clinical entity, an independent expert meeting was convened on 29 March 2021, gathering experts in haematology, neurology, cardiology, infectiology, immunology, virology and epidemiology from all over Europe. Their insights were discussed at an extraordinary PRAC meeting on 31 March 2021. A causal association between Vaxzevria and TTS was then considered plausible and PRAC recommended on 7 April 2021 a further update of the vaccine's product information, which was implemented on 9 April 2021, in order to list TTS as a rare side effect and stress the importance of prompt specialist medical treatment to facilitate recovery and avoid complications. A second DHPC was sent to healthcare professionals on 13 April 2021 and the full assessment report was published on the EMA website.

To help address remaining gaps in knowledge on the exact pathophysiology of TTS and optimal risk minimisation measures, the MAH was requested to perform non-clinical studies, to further analyse clinical trial data and to amend planned clinical and observational studies. This was reflected in an updated RMP. EMA and the EU Member States maintained a close monitoring and analysis of cases of TTS.

After careful review, it was concluded that the overall benefit-risk of Vaxzevria remained positive, in view of the rarity of the side effect and the level of efficacy observed. However, in order to better support Member States in their decisions on who to vaccinate with which vaccine as part of their national vaccination campaigns, the European Commission requested on 9 April 2021 through Article 5(3) of Regulation (EC) No 726/2004 that EMA, with the leadership of CHMP, perform an analysis of available data to better characterise the risks and benefits of the vaccine in different age groups and genders, in the context of the disease epidemiology, as well as identify possible risk factors and provide a recommendation on the administration of a second dose of the vaccine. This contextualisation showed that the benefits of Vaxzevria increased

with increasing age and infection rates although there was not enough data to contextualise the risk according to sex, nor to identify other possible risk factors. In addition, there were no or limited data to change the existing recommendation regarding a second dose. The analysis and interim opinion of CHMP were published on the EMA website on 23 April 2021. The CHMP's final conclusion, which confirmed the interim advice, was published in September 2021 (further information on the risk contextualisation exercise can be found on page 63).

The concern

TTS, sometimes termed 'vaccine-induced prothrombotic immune thrombocytopenia' (VIPIT) or 'vaccine-induced immune thrombotic thrombocytopenia' (VITT), is a clinical entity first observed following the administration of Vaxzevria.

TTS has been likened to heparin-induced thrombocytopenia. The two syndromes present similar clinical and serological features, as observed in the laboratory data of affected patients. Both involve antibodies that recognise platelet factor 4 and activate platelets, leading to platelet consumption and thromboembolic complications. TTS can manifest as venous thrombosis, often in unusual locations such as cerebral or abdominal veins, as well as arterial thrombosis, concomitant with thrombocytopenia. Some cases have been fatal.

Cases of TTS have also been observed in people who received Jcovden (formerly COVID-19 Vaccine Janssen). Both vaccines contain an adenovirus vector that encodes the SARS-CoV-2 spike protein.

In June 2022, EMA organised a workshop to bring together international regulators, academic researchers as well as the companies marketing the 2 adenoviral vector vaccines to review the current understanding of the pathophysiology of TTS, and to discuss next steps in the research agenda.

Research and analytics

Rapid analyses of reports in EudraVigilance have been instrumental in the evaluation of the TTS concern, from adjudication of individual cases of potential TTS by clinical experts to O/E analyses using background rates generated by the ACCESS consortium by way of identification and monitoring of patterns and trends. For instance, O/E analyses showed at an early stage a higher than expected number of observed cases of cerebral venous sinus thrombosis in the EEA, especially in the younger age groups. EudraVigilance data were also used by independent research teams working on TTS, leading to several publications in the scientific literature.

Several studies using electronic health records have been funded by EMA to help assess the risk of thromboembolic events in patients vaccinated with Vaxzevria and other COVID-19 vaccines (see section on observational research starting on page 19).

Building on the benefit-risk contextualisation exercise on TTS, a study commissioned by EMA is now looking at developing a toolkit to support calculations and interpretation of similar exercises with other vaccines in the future.[44]

44 Benefit Risk contextualisation of COVID-19 vaccines in the EU. EUPAS44229

From the early detection of the signal of TTS, there was an unprecedented level of cooperation and coordination between EMA and other regulators across the globe as well as National Immunization Technical Advisory Groups (NITAGs) and other health organisations, but also with academic researchers and experts, to generate and share rapidly evolving knowledge, for instance case definitions.

Transparency and timely information for the public
Updating the public and healthcare professionals regularly and promptly, as knowledge on the signal evolved was at the forefront of the Agency's priorities. A dedicated press briefing took place after each key PRAC meeting and no less than 11 standalone communications on the issue were published on the EMA website, as were the assessment reports, both at preliminary and final stages. The timelines for adopting, implementing and publishing product information updates and DHPCs were also considerably reduced from standard timelines of several to just a few days.

Risk management plan

Every year the PRAC assesses hundreds of RMPs for medicines. The RMP, which is used to proactively identify possible safety risks with a new medicine or indication and propose proportionate measures to manage and monitor them, allows medicines to be made available in a timely manner without exposing patients to unacceptable levels of risk.

RMPs describe the medicine's safety profile, how risks will be identified, managed and monitored once the medicine is authorised and how further information will be gathered from follow-up studies. RMPs ensure that relevant knowledge gaps will be filled and uncertainties on potential safety issues reduced.

Between 2019 and 2022, almost 2,400 RMPs for CAPs were on the PRAC agenda. Many of the RMPs were updated RMPs of existing medicines, but about a fifth were for newly authorised medicines.

The majority of the updated RMPs evaluated were part of broader variation procedures which included updates other than those related to the RMP; these procedures were led by the CHMP (see figure 9).

Figure 9. RMPs on PRAC agenda

	2019	2020	2021	2022	Total
For medicines in pre-authorisation phase	95	125	126	113	**459**
For medicines in post-authorisation phase					
As part of PRAC-led variation	118	104	100	68	**390**
As part of CHMP-led variation	378	381	388	395	**1,542**
Total	**591**	**610**	**614**	**576**	**2,391**

About 42,000 RMPs were submitted to the NCAs of the Member States for products authorised nationally or through the decentralised and mutual recognition procedures (DCP and MRP respectively). RMPs for medicines authorised nationally need to be assessed by each NCA where they have been submitted. RMPs of products authorised through the DCP and MRP are submitted to all the NCAs of the Member States where the product is authorised, i.e. to the Concerned Member States, but are assessed only by a single Member State known as the Reference Member State (RMS). Assessments undertaken by the RMS are recognised simultaneously by the competent authorities of the Concerned Member States. As a result of this mechanism, about 8000 RMPs were assessed for products authorised through the DCP and MRP during the same period.

Below are examples of RMPs that enabled the timely authorisation of innovative advanced therapies that were crucial to address unmet medical needs but were associated with serious side effects or uncertainty about their long-term safety. The measures included in the RMPs aimed to allow patients' access to these new medicines while minimising the risks and filling the knowledge gaps, e.g. regarding long latency or extremely rare side effects.

Risk management – examples of advanced therapy medicines (ATMPs)

The Chimeric antigen receptor T cell (CAR-T cell) medicine **Abecma** was authorised in August 2021 for the treatment of multiple myeloma.

CAR-T cell therapies represent a new generation of personalised cancer immunotherapies that are based on collecting and modifying the patients' own immune cells to treat their cancer. Abecma was approved to treat multiple myeloma when the cancer has come back and has not responded to treatment. It is used in adults who have received at least three prior therapies and whose disease has worsened since the last treatment. These patients have a poor prognosis with few alternative options and therefore this medicine addresses a substantial unmet medical need.

Although CAR-T cell therapies offer hope to patients with very serious conditions, they can have serious side effects, both after administration and in the long-term. Therefore, only a stringent risk management system ensuring that appropriate risk mitigation and minimisation measures are in place has permitted such innovative medicines to be authorised in a timely manner.

At the time of authorisation, Abecma's RMP aimed at managing the risk of cytokine release syndrome, a potentially life-threatening side effect that can occur after injection. Specifically, it required that all designated hospitals where the medicine is given must have appropriate expertise, facilities and training systems and a supply of tocilizumab, a medicine used to treat cytokine release syndrome. Furthermore, an educational programme for healthcare professionals and patients was agreed and put in place in EU Member States where this medicine is marketed to warn about potential side effects and advise on prompt actions to take in the event that patients develop cytokine release syndrome.

The RMP also required the MAH to conduct a long-term study, based on data from a registry of patients receiving Abecma. Long-term side effects, such as the potential development of secondary malignancies as well as long-term real-life effectiveness will be monitored until 2042.

Roctavian is the first gene therapy medicine authorised to treat severe haemophilia A (congenital factor VIII deficiency) in adults who do not have antibodies against factor VIII and who have no antibodies against adeno-associated virus serotype 5 (AAV5). Roctavian is given as a single infusion and therefore has the potential to reduce the treatment burden for patients with severe haemophilia A who often need to receive infusions two to three times per week.

However, Roctavian can cause liver damage, a common side effect due to immune reaction induced by these AAV-based gene therapies. To mitigate this risk, as well as that of a potentially

reduced therapeutic effect, specific measures are outlined in the product information, including adequate monitoring of patients' hepatic enzymes, treatment with corticosteroids, and avoidance of concomitant hepatotoxic medications or alcohol. Furthermore, additional risk minimisation activities were considered essential for a positive benefit/risk balance. These include educational materials for healthcare professionals and patients, including information on how to manage side effects as well as uncertainties on the benefits, in particular in the long term. Adequate follow-up of patients included in the studies and of those treated in clinical practice have been imposed as part of the conditional marketing authorisation.

The timely authorisation of these medicines was also supported by their inclusion in the EMA's PRIME scheme. This is a voluntary scheme that provides early and enhanced scientific and regulatory support for medicines that have significant potential to address unmet medical needs. This allowed EMA's experts to provide guidance (scientific advice) on the sort of studies and evidence that the developer would need to provide in order to permit authorisation.

RMPs can include specific measures to prevent pregnancy in situations where a medicine can harm the unborn baby through exposure in-utero.

In March 2022, EMA released draft guidance for public consultation on the most appropriate measures to protect the health of women of childbearing potential, pregnant women and unborn babies in an Addendum of the GVP Module XVI on pregnancy prevention programmes (PPP) and other pregnancy-specific risk minimisation measures (addendum III).

The example in the box below illustrates how such measures can be put in practice.

Reducing harm to unborn babies

Gilenya (fingolimod) is used to treat adults and children over 10 years of age with highly active relapsing-remitting multiple sclerosis, a disease of the nerves where inflammation destroys the protective sheath surrounding the nerve cells.

The benefits of this medicine have been shown in clinical studies in adults and children; however, animal studies have shown that this medicine could cause reproductive toxicity, as the target of this medicine is also involved in the formation of blood vessels during the development of the embryo. Therefore, at the time of granting the initial marketing authorisation in 2011 "reproductive toxicity" was included as an important identified risk in the RMP for Gilenya, with measures to both characterise and minimise this risk, i.e. cumulative reviews requested in the PSURs and the establishment of a fingolimod Pregnancy Exposure Registry. This was set up to collect outcome data on babies born from women treated with Gilenya and compare them to reference information from general surveillance systems.

In 2019, a review showed that the risk of birth defects in infants who have been exposed to Gilenya during pregnancy is twice as high as the baseline risk of 2 to 3% observed in the general population. As a result, new measures to protect the health of babies exposed in utero to Gilenya were implemented and included in the medicine's RMP. In this context a meeting of the Scientific Advisory Group for Neurology was convened to gather the views of clinicians, experts from academia and patients' representatives on the current use of Gilenya, in particular in women planning a pregnancy, on the availability of alternative treatments for this patient population and on the impact that a restriction during pregnancy would have on patients and clinical practice.

Based on the data available on the risk and the advice received from experts on use of the medicine in clinical practice, it was decided that Gilenya should be contraindicated during pregnancy and in women of childbearing potential not using effective contraception. If a woman becomes pregnant while using Gilenya, the medicine must be stopped, and the pregnancy will have to be closely monitored. The product information and the educational materials (including physician's checklist, a guide for patients, parents and caregivers and a pregnancy-specific patient reminder card) were updated to appropriately reflect this risk and help counsel patients on the risk of reproductive toxicity. A DHPC was circulated to relevant healthcare professionals.

Post-authorisation safety studies (PASS)

A PASS can be carried out by the MAH after a medicine has been authorised to obtain further information on its safety or to determine the effectiveness of RMMs.

The PRAC assesses the protocols and results of such studies when they have been imposed on MAHs as part of their post-authorisation obligations and also reviews many non-imposed studies which have been requested within RMPs. Non-imposed studies are in fact studies requested by the PRAC that have to be listed in the RMP as an additional pharmacovigilance activity.

Between 2019 and 2022, the PRAC reviewed 806 protocols for non-imposed studies and 95 protocols for studies imposed as part of the marketing authorisation. It evaluated results for 16 imposed studies as well as many more results from non-imposed studies (see figure 10).

Member States imposed 6 PASS over the reporting period for NAPs or products authorised through MRP/DCP (see Annex 3).

Imposition of a PASS, for example as a result of a referral, is an important tool for evaluating the effectiveness of regulatory measures taken after a medicine has been authorised to minimise risks, as illustrated in the box below.

Figure 10. Post-authorisation safety studies

	2019	2020	2021	2022	Total
Imposed PASS protocol procedures finalised	43	13	23	16	**95**
Non-imposed PASS protocol procedures finalised	180	167	226	233	**806**
Imposed PASS result procedures finalised	3	2	6	5	**16**

Thiocolchicoside

Thiocolchicoside is a muscle relaxant that was authorised in the late 1950s through national procedures in several EU Member States for use orally or by injection into the muscles for the treatment of painful muscular disorders.

In 2013, as a result of a referral procedure, EMA recommended that the authorised uses of thiocolchicoside medicines should be restricted so that they are used as an add-on treatment for painful muscle contractures resulting from spinal conditions in adults and adolescents from 16 years of age. The maximum dose and number of days of treatment were also reduced.

This followed new data suggesting that thiocolchicoside was broken down in the body into a metabolite that could damage dividing cells, resulting in aneuploidy (an abnormal number or arrangement of chromosomes). Aneuploidy is a risk factor for harm to the developing fetus and reduced fertility in men and in theory could increase the risk of developing cancer.

Additionally, following the review thiocolchicoside was contra-indicated in pregnant and breastfeeding women, women of childbearing potential not using contraception and children and was not recommended for long-term treatment of chronic conditions.

Furthermore, EMA imposed several conditions on the MAHs to enhance its safe use by introducing additional RMMs and requiring them to conduct a drug utilisation study to assess theeffectiveness of these measures.[45] Educational materials were requested to inform prescribers and patients about the risk of genotoxicity.

Measuring the effectiveness of the risk minimisation measures
The study conducted by the MAHs aimed to evaluate the impact of the additional RMMs on prescribers' knowledge and prescribing practices. It was conducted in two European countries (France and Italy) over a period of 4 years (2015-2019). Data were collected by physicians in usual routine practice and anonymised.

The results showed that there was an improvement in compliance with restrictions concerning the daily dosage for the intramuscular forms, with compliance increasing from 75% in the pre-implementation phase to 83% after implementation of the risk minimisation measures. The compliance for oral forms remained at a high level (99%) throughout. As for the restrictions on treatment duration, the results also revealed an improvement in compliance pre- and post-implementation for the oral forms (from 46% to 54%) and intramuscular forms (from 25% to 35%). Furthermore, the majority of physicians were compliant with the restrictions concerning long-term treatment of chronic conditions.

The analysis of pregnancy and breast-feeding data did not demonstrate any effect of the intervention as the rates of off-label use were already significantly low (<5% for pregnancy and < 1% for lactation) prior to the implementation period.

As regards the restriction of use in women of childbearing potential not using contraception, the information on use of hormonal contraceptives or intrauterine devices was not recorded in the databases and therefore no conclusions on the prescribers' compliance with this contraindication could be made.

Overall, the results of the drug utilisation study satisfactorily demonstrate the effectiveness of the additional RMMs in improving prescribers' knowledge as well as in contributing to the safe use of thiocolchicoside.

Another example of how a PASS can facilitate evaluation of the effectiveness of regulatory measures taken post-marketing to address risks is provided below.

HES solutions for infusion

Hydroxyethyl-starch (HES) solutions for infusion were authorised at national level in several Member States for the management of hypovolaemia (low blood volume) caused by acute blood loss where treatment with alternative infusion solutions known as 'crystalloids' alone is not considered to be sufficient.

45 EUPAS11081 and EUPAS11765

The safety of these products was reviewed in two separate procedures in 2013, and a number of restrictions and measures to minimise the risk of kidney injury and death in certain patients (those critically ill, with burn injuries or with sepsis, a bacterial infection in the blood) were put in place at this time.

As a result of a third review conducted in 2018, the use of HES solutions for infusion was further restricted to accredited hospitals, and healthcare professionals prescribing or administering the medicines had to be trained in their appropriate use. Additionally, further warnings were introduced in the product information to remind healthcare professionals that these medicines must not be used in patients with sepsis or kidney impairment or in other vulnerable patients such as the critically ill. These measures were put in place to ensure that HES solutions for infusion were not used in patients who were at increased risk of harm. Companies marketing HES solutions for infusion were also requested to conduct a drug utilisation study to check whether these restrictions were adhered to in clinical practice, and to submit the results of this study to EMA.

The PRAC reviewed the results from this study, which showed that HES solutions for infusion were still being used outside the recommendations included in the product information. The Committee concluded in February 2022 that HES solutions continued to be used in certain groups of patients in whom serious harm had been demonstrated, and that the further restrictions introduced in 2018 had not sufficiently ensured that the medicines were used safely.

Since adherence to the set of measures agreed in 2018 was a condition for the safe use of HES solutions for infusion, and the study had shown this had not happened, the benefits of these medicines were no longer considered to outweigh their risks. The PRAC explored the possibility of introducing additional measures to ensure HES solutions are used according to the product information but concluded that there were no other measures, or combination of measures, that would be feasible and sufficient to protect patients.

In view of the serious risks that certain patient populations are still exposed to, PRAC recommended the suspension of the marketing authorisations for HES solutions for infusion in the EU.

In May 2022, the European Commission adopted a decision confirming the suspension of the marketing authorisations of HES solutions for infusion. The decision of the Commission provided the possibility that Member States, on an exceptional basis and for reasons related to public health considerations in their territory, could provisionally defer (for no longer than 18 months) the suspension of the marketing authorisations for HES solutions for infusion. In the event of such deferral, the previously agreed RMMs should be maintained and monitored within respective Member States.

Imposed PASS can also support the collection of data in sub-populations that were not represented in the clinical trials but will still be exposed to the medicine once authorised, thus informing subsequent updates of the label, as shown in the example below.

Adcetris

Adcetris (brentuximab vedotin) was approved in October 2012 and is currently indicated for rare lymphomas: Hodgkin's lymphoma, systemic anaplastic large cell lymphoma and cutaneous T-cell lymphoma (CTCL). Patients with Hodgkin's lymphoma and systemic anaplastic large cell lymphoma whose cancer have come back or have not responded to therapy generally have poor

outcomes and lack suitable treatments. As part of the conditional marketing authorisation, EMA imposed a PASS to further characterize the safety profile of Adcetris in a real-world population. This PASS[46] was a prospective, observational cohort study of patients who are prescribed Adcetris as part of routine clinical care and followed for up to 5 years to gather information on the occurrence of specific safety events.

The objectives of the study were to evaluate the occurrence of serious adverse events and specified AESIs, both serious and non-serious, and to identify and describe potential risk factors for peripheral neuropathy, an important risk identified with the medicine during the clinical trials of Adcetris.The study was carried out in the overall patient population, and to the extent possible in sub-populations under-represented in clinical trials, such as elderly patients (≥ 65 years) and patients with long-term exposure to the medicine (> 16 cycles).

The study results confirmed the known safety profile of the medicine, with the most commonly reported adverse events being nervous system disorders, infections and blood-related disorders. No further changes to the product information were deemed necessary as these events were already sufficiently addressed in the product information.

Furthermore, a subgroup analysis showed that the incidence of febrile neutropenia, neutropenia and pneumonia in the elderly was higher than in younger patients. As a consequence, the product information was updated to highlight these side effects in the elderly sub-population in order to keep healthcare professionals and patients well informed of the risks.

Periodic safety reporting (PSUR)

MAHs are required to submit reports on the evaluation of their medicine's benefit-risk balance to the regulatory authorities at regular, pre-defined intervals following the authorisation of the medicine. These reports, called PSURs, summarise data on the benefits and risks of the medicine and take into consideration all related studies carried out both in authorised and unauthorised indications.

For NAPs authorised in only one Member State, the assessment of PSURs is conducted by the competent authority in the Member State where the product is authorised. For medicines authorised in more than one Member State and for which the frequency and dates of submission of PSURs have been harmonised in the list of EU reference dates, an EU single assessment of all PSURs (called PSUSA) is carried out by an appointed NCA on behalf of the EU Network. After considering this assessment, the PRAC issues a recommendation to maintain, vary, suspend or revoke the marketing authorisation.

The PSUSA procedure may include CAPs only, CAPs and NAPs, or NAPs only, subject to the above conditions.

Between 2019 and 2022, the PRAC issued recommendations following the assessment of over 3,300 PSURs (see figure 11). Additionally, during the same period, over 2,800 PSURs for NAPs not subject to the EU single assessment were directly

Figure 11. PSURs and PSUSAs finalised

	2019	2020	2021	2022	Total
CAP-only	558	516	575	542	**2,191**
NAP-only	222	209	287	272	**990**
CAP/NAP	48	49	49	46	**192**
Total outcomes	**828**	**774**	**911**	**860**	**3,373**

46 EUPAS3583

submitted to the NCAs of the Member States where they were authorised (see table 3 of Annex 3).

The majority of PSUR/PSUSA procedures have confirmed the known benefit-risk of the medicine and no further updates of the product information was necessary. However, in almost 20% of cases, the PRAC recommended a variation of the marketing authorisation to optimise the safe and effective use of the medicine by patients and healthcare professionals (620 out of 3,373; see figure 12). No PSUR assessment led to a suspension or a revocation.

When a potentially serious safety issue is identified during a PSUR assessment but the available evidence is not sufficient to draw robust conclusions, PSURs may interface with other mechanisms of the EU pharmacovigilance system, such as referrals, that allow an in-depth review of the safety issue at stake, as illustrated by the example below.

Figure 12. PRAC outcomes of PSURs and PSUSAs

	2019	2020	2021	2022	Total
Maintenance	655	630	748	720	**2,753**
Variation	173	144	163	140	**620**
Total outcomes	**828**	**774**	**911**	**860**	**3,373**

Alemtuzumab

Alemtuzumab (Lemtrada) was indicated in 2019 for the treatment of patients with relapsing forms of multiple sclerosis to slow the worsening of physical disability and to reduce the frequency of clinical exacerbations.

During the assessment of the PSUR for Lemtrada rare but serious side effects, including deaths, were highlighted. These included: cardiovascular adverse events, such as cardiac ischaemia and myocardial infarction, in close temporal association with Lemtrada infusions, and immune-mediated diseases such as auto-immune hepatitis, hepatic injury, auto-immune-mediated central nervous system disease and Guillain-Barre Syndrome.

Limited information about these concerns, including information about the individual cases, was available during the PSUSA, precluding a thorough evaluation.

Therefore, in April 2019 an Article 20 referral procedure was triggered by the European Commission to assess the safety concerns and their impact on the benefit-risk balance of Lemtrada and to issue a recommendation on whether the relevant marketing authorisation should be maintained, varied, suspended or revoked.

Updated guidance for doctors and patients
Temporary measures were introduced at the start of the referral procedure to protect patients while the detailed evaluation was ongoing and a DHPC was sent to healthcare professionals.

As a temporary measure, it was recommended that treatment with Lemtrada should only be initiated in adult patients with highly active relapsing remitti ng multiple sclerosis despite a full and adequate course of treatment with at least two other disease modifying treatments, or in

adult patients with highly active relapsing remitting multiple sclerosis where all other disease modifying treatments are contraindicated or otherwise unsuitable. In addition, the PRAC made additional recommendations to healthcare professionals for monitoring patients before, during and after administration of Lemtrada.

The referral procedure concluded with PRAC issuing recommendations that were endorsed by the CHMP and replaced the temporary measures. Restrictions concerning the use of Lemtrada, put in place as interim measures at the start of the referral, were maintained. In addition, the PRAC recommended that the indication of the medicine should be further restricted so that Lemtrada is no longer used in patients with certain heart, circulation or bleeding disorders or in patients who have autoimmune disorders other than multiple sclerosis or patients with severe active infections until complete resolution.

The medicine should also only be given in a hospital with access to intensive care facilities and specialists who can manage serious adverse reactions.

The MAH was required to carry out a drug utilisation study to assess compliance with the therapeutic indication and effectiveness of RMMs, as well as a PASS to investigate the incidence of mortality in patients treated with Lemtrada compared to an adequate control.

Finally, the medicine's educational materials (physician's guide and the patient information pack) were updated to reflect the advice on minimising the risk of serious cardiovascular disorders, which may occur shortly after a Lemtrada infusion, and immune-related conditions, which may occur many months and possibly years after the last treatment.

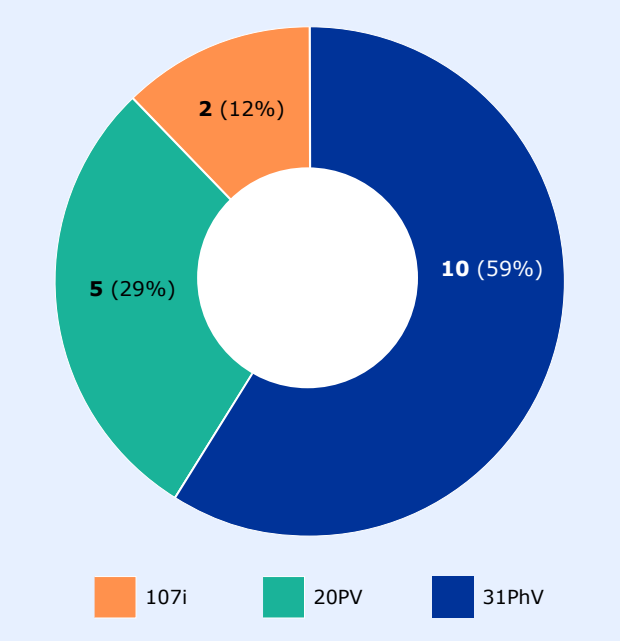
Safety referrals and Art 5.3 reviews including safety aspects

Safety referrals

Safety referral procedures are initiated to address substantial concerns over the safety or the benefit-risk balance of a medicine. In a referral, EMA is requested, on behalf of the EU, to conduct a scientific assessment of a particular medicine or class of medicines and issue a recommendation.

There are different types of referral procedures foreseen in the legislation; the article 107i procedures are triggered for safety reasons when an urgent action is necessary, while the article 20 and article 31 procedures may look at quality, safety and/or efficacy issues. Between 2019 and 2022, 17 pharmacovigilance referrals started and 17 concluded (see figure 13). This compares with 22 referrals initiated over the previous reporting period (2015-2018).

Figure 13. Procedures finalised at PRAC 2019-2022



Pharmacovigilance referrals may be triggered as a further regulatory tool to assess in more depth potential safety issues identified in the context of routine pharmacovigilance activities, such as PSUSA or signal assessment, to determine whether the introduction of RMMs is necessary and

establish whether the balance between benefits and risks for a given product remains positive. Seven of the 17 pharmacovigilance referrals originated from such routine pharmacovigilance activities (4 from PSUSAs and 3 from signals).

Outcome of referrals

Of the 17 pharmacovigilance referral procedures that were finalised during the reporting period:

- 13 led to variations to the MAs (such as restrictions of the indication, changes to the conditions of the marketing authorisations, new warnings), with the implementation of additional RMMs in 8 cases and imposed additional pharmacovigilance activities in one case;
- 4 medicines or class of medicines reviewed were considered to have a negative benefit-risk balance and are now withdrawn from the market:
    - fenspiride medicines: these medicines for non-serious cough could cause potentially serious and sudden heart rhythm problems;
    - pholcodine medicines: these medicines used to treat dry cough and symptoms of cold and flu, in combination with other substances, could cause life-threatening anaphylaxis in patients subsequently undergoing general anaesthesia with neuromuscular blocking agents;
    - amfepramone medicines: these medicines were used for obesity as adjuvant to diet and have been associated with increased risk of serious side effects, including cardiovascular disease, pulmonary arterial hypertension, dependency and psychiatric disorders, as well as harmful effects during pregnancy. The PRAC review concluded that those risks could not be adequately mitigated by effective RMMs;
    - ingenol mebutate (Picato): this medicine used to treat actinic keratosis had its marketing authorisation precautionarily suspended by the PRAC, while the referral was ongoing, due to its possible association with an increased risk of skin cancer. The MAH then decided to voluntarily withdraw its marketing authorisation and the PRAC's review later confirmed that the benefit-risk balance of Picato was negative.

For some medicines, PRAC introduced temporary measures early in the procedure to protect public health while the review was ongoing: this was the case with Lemtrada, Xeljanz, Picato, and medicines containing ulipristal acetate 5 mg.

As the outcome of referral procedures can have an important impact on clinical practice, engaging with relevant stakeholders (healthcare professionals and patients) during the safety reviews is essential to ensure appropriateness of the RMMs proposed and also to increase awareness of the regulatory framework, enhance awareness of the recommended measures and facilitate the implementation of recommendations at national level. Additionally, involving healthcare professionals and patients can help regulators better understand the root cause of certain safety issues, as illustrated in the case study below.

Methotrexate referral: the importance of stakeholders' engagement in PRAC reviews

In March 2018, PRAC was requested by the Spanish national competent authority to assess in an Article 31 referral the root cause of medication errors and their impact on the benefit-risk balance of oral formulations of methotrexate. This request followed reports of serious cases of overdose, sometimes fatal, in patients inadvertently receiving the product daily instead of weekly for indications that require weekly dosing. Despite the previous introduction of RMMs to address this issue, reports of medication errors continued to be received.

To further understand the root cause of these medication errors and the status of the implementation of the previously recommended RMMs, PRAC first consulted healthcare professionals' organisations though a survey. The feedback received confirmed that the

medication errors were occurring at all levels, from prescribing to administration, in hospitals or in an outpatient setting, and for reasons as varied as poor communication between healthcare professionals and patients, lack of knowledge, and inappropriate package sizes for the concerned indication.

To allow further reflection on any further RMMs, their feasibility and usefulness, a stakeholder meeting was convened. This meeting was attended by representatives of a number of patients' and healthcare professionals' organisations as well as physicians, pharmacists and nurses experienced with the use of methotrexate in non-oncology settings, representing all levels at which errors could be made.

These discussions led PRAC to recommend a set of new measures to prevent serious and potentially fatal errors with the dosing of methotrexate, including restricting who can prescribe these medicines, making warnings on the packaging more prominent and providing educational materials for patients and healthcare professionals. In addition, it was agreed that to help patients follow the once-weekly dosing, methotrexate tablets would be provided in blister packs and no longer in bottles (or tubes).

Once this referral was completed, a study was commissioned to examine the impact of these measures in clinical practice. The results of this study were being analysed at the end of 2022.

Safety referrals are assessed by the PRAC, and the conclusions are endorsed by the CHMP or the CMDh (when the medicines involved are NAPs only). When advanced therapy products are affected the expertise of the Committee for Advanced Therapies (CAT) is used to strengthen the decision-making process, as shown in the example below.

Zynteglo review: an example of collaboration with other EMA committees

In 2021, EMA received information about a case of acute myeloid leukaemia (AML) reported in a patient with sickle cell disorder. The patient had been treated 5.5 years earlier in a clinical study with an investigational gene therapy (bb1111) for the treatment of sickle cell disease. The medicine used the same lentiviral vector (or modified virus) as Zynteglo, an authorised gene therapy for the treatment of beta thalassaemia. Consequently, PRAC was requested by the European Commission to assess a possible causal association between the lentiviral vector and the case of cancer and the impact of these findings on the benefit-risk balance of Zynteglo in an Article 20 procedure.

The experts of the CAT and the PRAC collaborated closely to assess the available evidence.

The review, which considered two cases of AML in patients treated with bb1111, found that the viral vector was unlikely to be the cause of the cancer. After examining all the evidence, it was clear that there were more plausible explanations for the AML cases, including the conditioning treatment the patients received to clear out bone marrow cells and the higher risk of blood cancer in people with sickle cell disease.

Patients having Zynteglo treatment for beta thalassaemia also need conditioning treatment to clear out their bone marrow cells before receiving Zynteglo. Healthcare professionals were therefore recommended to explicitly inform patients receiving Zynteglo of the increased risk of blood cancers from medicines used in conditioning treatments. The monitoring recommendations were updated, advising healthcare professionals to check their patients for signs of blood cancers at least once a year for 15 years. Since this review, the medicine has however been withdrawn from the market at the request of the MAH, for commercial reasons.

In some cases, product specific data may emerge with a potential relevance for other products of the class, e.g. due to mechanistic considerations or data from further products suggesting a class effect, see example below.

Janus Kinase (JAK) inhibitors: an example of a class review

This review initiated in February 2022 was prompted by the final results from a clinical trial (study A3921133) of the JAK inhibitor Xeljanz (tofacitinib). This study showed that patients aged 50 years and older and at risk of heart disease who were taking Xeljanz for the treatment of rheumatoid arthritis were more likely to experience a major cardiovascular event and had a higher risk of developing cancer than those treated with medicines belonging to the class of TNF-alpha inhibitors, especially at high doses. The study also showed that compared with TNF-alpha inhibitors, Xeljanz was associated with a higher risk of death due to any cause, serious infections, and venous thromboembolism (VTE).

In addition, preliminary findings from an observational study involving another JAK inhibitor, Olumiant (baricitinib), suggested an increased risk of major cardiovascular problems and VTE in patients with rheumatoid arthritis treated with Olumiant compared with those treated with TNF-alpha inhibitors.

In view of the emerging safety data observed for these products and the shared mechanism of action, a class effect was suggested and thus a safety review of the class of products through an article 20 procedure was triggered.

Some measures to minimise these risks were already implemented for Xeljanz as result of a previous review finalised in 2020, which analysed the interim results of study A3921133. After release of the final results of this study, the product information for Xeljanz was further updated to reflect the increased risk of major cardiovascular problems, cancer and serious infections compared with medicines belonging to the class of TNF-alpha inhibitors.

As part of the class review carried out through an article 20 procedure, it was further concluded that the safety findings observed with Xeljanz (major cardiovascular problems, cancer, serious infections and death due to any cause) apply to all approved uses of JAK inhibitors in chronic inflammatory disorders. A group of clinical experts in rheumatology, dermatology and gastroenterology was consulted on the restrictions of use that were being considered to minimise these risks, including restrictions of indications, warnings and dose lowering.

Based on these findings and consultation with clinical experts, the PRAC decided that all JAK inhibitors should be used in the following patients only if no suitable treatment alternatives are available: those aged 65 years or above, those at increased risk of major cardiovascular problems (such as heart attack or stroke), those who smoke or have done so for a long time in the past and those at increased risk of cancer.

PRAC further concluded that JAK inhibitors should be used with caution in patients with risk factors for VTE other than those listed above. Further, the doses should be reduced in patient groups who are at risk of VTE, cancer or major cardiovascular problems, where possible.[47]

47 The initial PRAC recommendation and CHMP opinion were adopted in 2022. These were revised in January 2023 to further align dosing recommendations for the medicines concerned.

Article 5(3) opinions including safety aspects

EMA's CHMP may issue scientific opinions on any scientific matter related to medicines at the request of the Executive Director of EMA or of the European Commission. Requests for this type of scientific opinion fall under Article 5(3) of Regulation (EC) No 726/2004.

This regulatory tool was used to issue recommendations on the presence of nitrosamine impurities, a probable human carcinogen, in human medicines. In this context, PRAC provided input to CHMP on epidemiological approaches to study a potential link between the presence of nitrosamines in medicines and the development of cancer. Companies have been requested to have appropriate control strategies in place and, where necessary, to improve their manufacturing processes, in order to limit the presence of nitrosamines as much as possible and to ensure levels of these impurities do not exceed set limits.

In the context of the COVID-19 pandemic, this procedure was used to support the emergency use of certain therapeutics (e.g. Paxlovid, sotrovimab and Lagevrio) while a more comprehensive assessment was ongoing, as well as to contextualise the benefit-risk balance of Vaxzevria in different age groups and epidemiological contexts (see further information below).

Vaxzevria Art 5(3) review: benefits and risks in context

Following the identification of thrombosis with thrombocytopenia syndrome (TTS) as a rare but serious side effect with the COVID-19 vaccine Vaxzevria, in April 2021 EMA was requested by the European Commission to further analyse the risk of these rare blood clots in the context of the vaccine's benefits for different age groups and different rates of infection. The analysis aimed at informing national decision makers on the roll out of the vaccine, taking into account the pandemic situation and other factors such as vaccine availability.

PRAC supported EMA's CHMP in their assessment. The committees compiled a variety of data to perform their analysis. These included EudraVigilance data on cases of TTS, RWE and clinical data on the vaccine's effectiveness, and EEA vaccine coverage data submitted by the Member States to the ECDC and EMA. The review also considered the interim results of an EMA-funded study on the natural history of coagulopathy and use of anti-thrombotic agents in patients and persons vaccinated against SARS-COV-2 (EUPAS40414).

The analysis showed that the benefits of vaccination increase with increasing age and infection rates. The results were presented in graphs to help health authorities in the Member States visualise the benefit-risk balance in various contexts and support decisions on potential age cut-offs for the use of Vaxzevria in national vaccination campaigns.

Pharmacovigilance inspections

Pharmacovigilance inspections are conducted to ensure that requirements for monitoring the safety of medicines are met. The responsibility for carrying out these inspections rests with the national competent authorities. For CAPs, the competent authority of the Member State where the pharmacovigilance system master file (PSMF) is located acts as the supervisory authority and therefore has the responsibility to verify, on behalf of the EU, that the MAH and the pharmacovigilance system in place satisfy the pharmacovigilance requirements.

EMA, in cooperation with competent authorities in the Member States and with the input of the CHMP and PRAC as concerns priorities and triggers, prepares and maintains a risk-based programme of routine pharmacovigilance inspections for CAPs for human use and ensures its implementation. EMA also plays a key role in the coordination of pharmacovigilance inspections when a question or an issue arises ("for cause" inspections).

The role of the PRAC in the context of those pharmacovigilance inspections is to discuss triggers for pharmacovigilance inspections, and to assess the impact of inspection findings and the appropriateness and priorities of MAH corrective and preventive actions (CAPAs). The CHMP considers PRAC advice/recommendations and is involved in the implementation of any changes in the benefit-risk evaluation of products.

During the reporting period, the most common triggers of pharmacovigilance inspections were inaccuracies, inconsistencies and poor quality of data submitted by MAHs as part of PSUSA procedures. Other triggers of "for cause" inspections and PRAC plenary discussions were lack of compliance with agreed timelines of imposed PASS and concerns about the implementation of RMMs such as registries and educational material in each of the affected Member States.

In the context of risk-based programmes of routine pharmacovigilance inspections for CAPs, around 40 inspections were conducted every year. These inspections are just a subset of the total number of pharmacovigilance inspections conducted in the EU/EEA. Most EU/EEA pharmacovigilance inspections are conducted under the national pharmacovigilance inspection programmes which apply to MAHs of products authorised via all types of procedures. In addition to the supervisory authority inspections, there are also inspections that Member States may need to conduct locally (e.g., for affiliate sites or contractors) to complement the supervisory authority inspections (e.g., to verify compliance with local requirements, check local implementation of RMMs and compliance of local sites involved in key pharmacovigilance activities, etc.). Member States may also need to inspect pharmacovigilance systems of MAHs of NAPs. Around 200 inspections were conducted every year. Over the reporting period, Member States issued penalties to MAHs for non-compliance with pharmacovigilance obligations on 44 occasions. These include financial penalties of varying nature (e.g., injunction/warning letters). Some of the examples of non-compliance with pharmacovigilance obligations that have been highlighted by Member States during the reporting period were the failure to submit the contact details of the EU Qualified Person responsible for Pharmacovigilance (QPPV), despite several reminders, or to distribute DHPCs.

Findings of CHMP requested pharmacovigilance inspections

The main inspection findings observed in 2019, 2020 and 2021 are detailed in Annex 4 (section F). The most common issues the inspectors found concerned the following areas:

- Quality of ICSR reporting in EudraVigilance, including errors in coding, lack of minimum information to have a valid case (e.g., on the ADR or an identifiable patient) and insufficient follow-up on cases to collect more information (see example in the box on next page);

- Content and maintenance of the PSMF, including incomplete documentation. The PSMF is a detailed description of the pharmacovigilance system used by the MAH with respect to one or more authorised

medicinal products. These deficiencies jeopardise the QPPV oversight of the pharmacovigilance system and hinder the preparation and conduct of inspections. Inspections identified the root cause as being a lack of experience, knowledge and understanding by the QPPV and their staff of the importance of the PSMF and of its timely maintenance. To remedy the situation, pharmacovigilance activities were transferred to a pharmacovigilance service provider who revised the PSMF and carried out training activities;

- Lack of involvement of the QPPV in the establishment of the licence agreements with the partners carrying out pharmacovigilance tasks. The involvement of the QPPV in the contractual arrangements is important to ensure that they cover all necessary provisions relevant to the pharmacovigilance system;

- Control of access to computerised pharmacovigilance systems and the implementation and documentation of procedures to review authorised users. Following an inspection where these problems occurred, the MAH revised and implemented the relevant procedures;

- Incorrect implementation of planned CAPAs to address critical and major deficiencies. When these problems occurred, the implementation of the agreed CAPAs was subsequently closely monitored and the MAH requested to give regular updates on progress made;

- Lack of sufficient resources on the part of the MAH to adequately perform pharmacovigilance obligations. This required escalation within the MAH organisation to ensure increase of resources in the areas of concern;

- Inadequate quality management system for the performance of pharmacovigilance activities, including issues with written procedures, training, compliance monitoring/ deviation management, and MAH oversight/ audits;

- Incorrect implementation of RMMs.

MAHs were required to implement CAPAs to address the inspection findings. In most cases, the impact of these actions was assessed in the context of routine pharmacovigilance activities, e.g., PSUR assessment or signal detection. However, in a few cases, escalation to PRAC and additional actions were required. Examples of three pharmacovigilance inspection outcomes that were escalated to PRAC during the reporting period are presented below.

Escalation to PRAC

Issues with ICSR processing and reporting

In 2019, an inspection of an MAH's pharmacovigilance system found inappropriate handling of data related to ICSR content as well as inconsistencies in MedDRA coding. This kind of deficiency can affect the quality of the safety data reported and may therefore impact signal management activities as well as the assessment of safety issues for the concerned products.

The escalation was needed to alert the PRAC assessors and to agree on and prioritise the MAH's CAPAs. To rectify the problems, MAH was requested to correct the concerned cases in EudraVigilance, provide evidence of having done so, assess whether PSURs with the correct information needed to be resubmitted for further assessment and proactively take actions (Standard Operating Procedure revision and training) to prevent reoccurrence. The implementation of all CAPAs agreed with the inspectors was closely monitored through regular CAPA updates with an earlier re-inspection agreed (within 2 years instead of the 4 years routine cycle).

In the same area, in 2020, an inspection found that an MAH was not sufficiently following-up on ADR cases reported to retrieve the missing information on cases. It is common that the

information on suspected ADRs may be incomplete when reports are first received. These reports should be followed-up as necessary to obtain supplementary information to support the scientific evaluation of the cases. As part of the inspection, it was found that follow up of cases was not clearly described in the MAH's procedures and hence not implemented. The finding was also attributed to the personnel's poor understanding of the requirements. The MAH had to review cases and follow up on information missing, revise their internal procedures and put in place training.

Issue with implementation of RMMs

An inspection found that RMMs, specifically in relation to PPPs, failed to be implemented in a timely manner by an MAH. The MAH was required to submit information on the PPPs and product-specific safety information so that the PRAC could assess the impact of this delay on the benefit-risk balance of each affected product and decide on the CAPAs required.

In addition, as the PPPs were implemented in a variety of ways at Member State level, the escalation to PRAC facilitated coordination of NCA follow up activities (i.e., further inspection or liaison with local affiliate) to verify the MAH compliance at national level and consider any further actions required to control distribution/importation where adherence to the PPP may be compromised.

Failure in routine pharmacovigilance activities

In 2020, inspection of an MAH pharmacovigilance system pointed out deficiencies in post-marketing data collection and review, in signal management (e.g., in relation to incomplete processes and lack of personnel training and expertise) and in the implementation of RMMs. The deficiencies identified affected the data available for assessment in PSURs and signal detection. These findings were escalated to the PRAC and the MAH was requested to submit the missing data for assessment. The PRAC and inspectors agreed on prioritisation of CAPAs by the MAH, close monitoring of the CAPAs' implementation with two-monthly progress update report submissions and an earlier "for cause" re-inspection (within 2 years instead of the 4-year routine cycle) to verify the implementation of the agreed CAPAs by the MAH.

COVID-19 pandemic and impact on pharmacovigilance inspections

As described on page 42, in 2020 the pharmacovigilance Inspections Working Group issued guidance on remote pharmacovigilance inspections of MAHs during a crisis situation, and more than half of the pharmacovigilance inspections were conducted remotely in 2020. Based on this experience, remote inspections will continue to be used in specific cases (e.g., when it is not possible to inspect physically; follow-up inspections to assess CAPA plans).

The unprecedented increase in suspected ADR reporting following the marketing authorisation of COVID-19 vaccines required a review of processes and adjustments to the existing regulatory measures to intensify the monitoring of MAHs' compliance with pharmacovigilance requirements. For all COVID-19 vaccines, a proactive approach was endorsed by PRAC, which included:

- early communication with pharmaceutical companies to request information on the pharmacovigilance system in place and business continuity plans;
- early post-authorisation inspections of the pharmacovigilance systems of the MAHs for COVID-19 vaccines to assess:

- their readiness to process a large amount of safety data and produce complete and accurate monthly SSRs;
- their ability to promptly detect signals and evaluate new information that may impact the benefit-risk balance of those vaccines;
- the existence and appropriateness of business continuity plans and mechanisms to actively manage evolving situations.

- pre-authorisation inspections for MAHs new to the EU and/or to the centralised procedure.

EMA collaborated with several international partners during the COVID-19 pandemic and, on the basis of applicable confidentiality arrangements, specifically with the US FDA, Swissmedic, Health Canada and the MHRA to share information on inspections.

All these measures aimed to ensure that the MAHs had the resources and systems in place to support intensive monitoring, which was a key consideration of regulators in the decision to allow a more rapid EU approval process for COVID-19 vaccines

Coordination and collaboration

At EU level

Coordination and collaboration within the EU Network are at the core of the EU pharmacovigilance system. EMA and the EU Member States are responsible for coordinating the EU's safety monitoring of medicines. Detailed planning and coordination for the varied pharmacovigilance activities are therefore required and built into the Network's systems on a day-to-day, month-to-month level. One example of such coordination is the EU Incident Management plan (EU-IMP) which enables the EU Network to rapidly and effectively manage incidents over the lifecycle of medicines. The EU-IMP may be triggered by any member of the EU Network after new information on a public health concern is received from any source. In 2019, the EU-IMP had been in place for 10 years and an overview of its achievements was published.[48] This overview shows that this system helped the EU Network manage a wide scope of incidents with important public health impact through routine measures, without the need for escalation to a crisis.

At the level of the EMA committees, a high level of coordination and collaboration is also required and illustrated through a number of examples in the previous sections, e.g., in the context of pharmacovigilance inspections and article 5.3 scientific opinions.

EMA also works closely with other decentralised agencies of the EU, particularly those with similar areas of work. As described on page 40, EMA and ECDC launched an important initiative in 2022, the EU Vaccine Monitoring Platform, to jointly strengthen the continuous monitoring of the safety and effectiveness of vaccines in the EU.

Beyond the EU

A central pillar in the EU Network strategy to protect public health is the strengthening of collaboration at international level to promote harmonisation, convergence and reliance of regulatory requirements and decisions, sharing of information and addressing common challenges.

EMA has bilateral confidentiality arrangements with 8 third-country regulators (Australia, Brazil, Canada, Japan, Switzerland, US, WHO and the European Directorate for the Quality of Medicines & HealthCare [EDQM]). These arrangements enable the parties to exchange confidential information and provide a framework for regulatory cooperation. To allow rapid exchanges of information during crises (nitrosamines issue and the COVID-19 pandemic), ad-hoc confidentiality arrangements were signed during the reporting period between EMA and other authorities (e.g., Singapore, Korea, Taiwan, United Kingdom, New Zealand); these were limited in scope and time.

In this context, the exemption granted by the European Data Protection Supervisor for sharing information with international regulators without

48 Santoro et al. Navigating stormy waters: 10 years of operation of the European Union Regulatory Network Incident Management Plan for Medicines for Human Use

the need to redact personal data greatly facilitated exchange of safety and pharmacovigilance information. No instances of attempts to re-identify individuals have been reported.

Coordination and collaboration within the EU Network and between the Network and other international regulators and public health bodies were considerably reinforced during the reporting period, mainly in the context of the pandemic. Most of these activities, including the new OPEN programme, are described in the first part of this report on the response to the COVID-19 pandemic (see section on international collaboration during the pandemic starting on page 28).

Another key forum where EMA collaborates and exchanges information with international partners is the pharmacovigilance cluster, which takes the form of regular teleconferences between EMA (including relevant members of the EU Network) and the FDA, with Health Canada and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) as observers. Their main objective is to share information on safety issues and to provide advance notice of anticipated regulatory action and of plans to communicate safety informationto the public. The teleconferences are also an opportunity for EMA and FDA to share experiences, lessons learned, best practices and insights on the safety of medicines, especially in instances where one regulator may have more experience than another, for example due to earlier approval. Between 2019 and 2022, 33 teleconferences took place to discuss various safety topics. An example is the discussion in 2019 on rare cases of neoplasms, including malignancies, in children treated with Increlex (mecasermin), a recombinant human insulin-growth factor-1 indicated for the long-term treatment of growth failure in children with certain conditions. The medicine had been available in the US as an orphan drug since 1986 and was approved for marketing in 2005 in the US and in 2007 in the EU. When the above safety concern initially emerged, EMA benefited from information from the US, where the medicine had been available for longer. The evaluation of this safety issue was initially triggered by a signal procedure, after which the MAH submitted the available evidence and proposed labelling changes. The discussion at the cluster teleconference aimed at sharing views at an early stage on the evidence and the quality of data submitted in the EU and US. Following a review of the data, "benign and malignant neoplasms" was listed as a side effect in the product information and the use of the medicine was contraindicated in children and adolescents with active or suspected neoplasia, or with any condition or medical history which increases the risk of benign or malignant neoplasia.

Another important example related to the implementation of RMMs with the COVID-19 vaccine Jcovden (see box below).

Preparation for the roll out of the COVID-19 vaccine Jcovden

While the assessment of the signal of rare cases of unusual blood clots with the adenovirus-based COVID-19 vaccine Vaxzevria was still ongoing in the EU, three reports of thrombosis with thrombocytopenia (TTS) were reported for Jcovden, another adenovirus-based COVID-19 vaccine recently authorised in the EU. Of these 3 cases, one originated from the pivotal phase III trial and two originated from the US regulatory authorities and were discussed in forums such as the EMA-FDA cluster. At the time of the signal confirmation in the EU, Jcovden had not yet been rolled out in the EU and spontaneous reports originating from the EU/EEA were not available. Consequently, the sharing of data from the US was crucial to the further evaluation of this particular safety issue with Jcovden. After further rounds of assessment of the signal, additional data were confirmed by the US authorities. Those were critical to the implementation in April 2021 of RMMs aimed at mitigating the risk of TTS with Jcovden prior to the rollout of the vaccine within national campaigns throughout the EU.

Capacity building

As the EU pharmacovigilance system and its wide range of activities keep evolving, it is essential that knowledge and expertise be continuously maintained across the EU Network to ensure that pharmacovigilance tasks continue to be carried out to the highest EU standards, in a consistent and efficient way. For this reason, EMA maintains and expands an offering of training courses and platforms for discussion for all the EU assessors. Capacity building also extends towards non-EU regulators, and in particular to countries that are candidates for EU membership.

Training

The EU Network Training Centre (EU NTC) was launched in 2015 to promote good scientific and regulatory practices across the EU network along with harmonised training standards, through the provision of high quality and relevant training shared through a European central platform.

Between 2019 and 2022, the total number of training courses (face-to-face, webinars and online courses) made available to the EU Network in the catalogue of the EU NTC increased from 306 to 545. The number of online training courses, including recordings of webinars, narrated presentations and e-learning courses, increased from 108 to 282.

During the reporting period, 20 new online pharmacovigilance courses were made available, including recordings of PRAC assessor trainings, the Webinar on European Network of Centres in Pharmacoepidemiology and Pharmacovigilance (ENCePP), and webinars on the Incident Review Network and on RWE. The total number of Pharmacovigilance courses (face-to-face, webinars and online courses) available during the reporting period was 26.

To ensure that pharmacovigilance activities related to the COVID-19 medicines were conducted in an efficient and consistent way, trainings were provided in 2020 on the safety of vaccine in general, and of COVID-19 vaccines in particular. In 2021, trainings on the objectives, methods and analytical approach in relation to RMM effectiveness and impact research were also provided. In 2022, training was provided on the assessment and regulatory follow-up of impact research commissioned by EMA and on industry-sponsored RMM effectiveness studies.

One of the key training objectives for pharmacovigilance is ensuring that regulators and other key players, such as the pharmaceutical industry, can use the EudraVigilance system appropriately. In 2019, 22 on-site EudraVigilance training sessions on ICSR reporting were organised in 12 different cities in the EU and between 2020 and 2022 35 virtual trainings on EudraVigilance were offered; these were attended by 900 people in total. Additionally, 4 virtual EudraVigilance training sessions for clinical trials sponsors on ICSRs submissions were organised in 2022 and attended by 58 users.

Over the reporting period, around 30 training sessions were organised on the Extended EudraVigilance Medicinal Product Dictionary (XEVMPD), with 500 people trained, and one EVDAS training session was organised for NCAs in 2020 with 40 pharmacovigilance assessors trained. Additionally, in 2022, over 120 users registered for an XEVMPD online training via the e-learning platform and a virtual training on the screening of suspected unexpected serious adverse reactions (SUSARs) from interventional clinical trials in EVDAS was organised with an attendance of almost 90 users.

In 2019, some activities, such as info days or webinars, could not take place due to BCP linked to Brexit. However, in 2020 and 2021, two info days on EudraVigilance and signal management were organised, with 320 people attending in total.

Strategic learning meetings

Eight strategic review and learning meetings (SRLM) were organised among PRAC members during the reporting period, in some cases jointly with the CHMP, CAT or CMDh.

These meetings allow committee members to review current practices in Member States and discuss specific topics, strategic or process-related issues, in order to continuously improve safety monitoring.

During the reporting period, various topics were discussed, with a view to make proposals to

promote the efficiency of pharmacovigilance processes. These topics included patients' access to innovative products, abuse of and dependence on opioids in Europe, rational use of medicines, ways to enhance the collaboration with WHO in the areas of pharmacovigilance, medicine safety in pregnant and breastfeeding women and the need to develop guidance and training to support assessors and Committee members.

Pre-accession assistance and international capacity building

In 2019, EMA started a project in the context of the Instrument of Pre-accession Assistance (IPA) with candidate and potential candidate (formerly "accession") countries.

The main aim of the project is to provide training on the application of the "EU acquis", necessary for joining the EU in the future, as it relates to medicines. The training courses, initially planned to be delivered face-to-face, were conducted on-line due to the COVID-19 pandemic, with speakers from EMA, Member States and the European Commission.

Twenty online courses, ranging from basic to advanced, were delivered at various levels, including 5 related to the following pharmacovigilance topics:

- The EU system for pharmacovigilance;
- COVID-19 vaccines: authorisation, use and vigilance;
- Carrying out a pharmacovigilance inspection;
- RMPs: theory and practice;
- RMPs: case studies.

A platform for dialogue and exchange of information between EMA and candidate and potential candidate countries was also created through the project, and regular (3-monthly) virtual meetings have been carried out between EMA and contact points in those countries. Due to the pandemic situation, the exchange of information focused on COVID-19 related topics, with special attention given to the safety of vaccines and therapeutics.

EMA also supported international capacity-building in the area of pharmacovigilance, in particular in academic frameworks of Asia-Pacific Economic Cooperation countries, with meetings held in person (2019) and online (2020 and 2021), as well as in the context of training sessions organised by the WHO South-East Asia Region and the Saudi FDA.

Conclusions and further steps

The EU pharmacovigilance system has matured significantly since the revised pharmacovigilance legislation came into effect 10 years ago. One of the areas that evolved considerably, particularly during the current reporting period, is how the EU Network measures and takes action to improve the effectiveness of its pharmacovigilance activities and regulatory actions. The framework for this, introduced in 2016 as part of the PRAC Impact Strategy, was strengthened through several initiatives.

As more studies have been commissioned to measure the impact of RMMs, the EU Network established a process to follow up and act on the study results in a systematic way. As some limitations have been observed in several of these studies, making it difficult to reach firm conclusions, steps will be taken to enhance the study designs to mitigate the impact of these limitations on the outcome. In terms of RMM implementation, the PRISMA pilot, which brings together patients, healthcare professionals and regulators, will soon become fully operational and further support the implementation of RMMs in healthcare practice. A further initiative is the development of a reflection paper on digital support tools for implementing and evaluating the effectiveness of RMMs which will be the basis for future guidance for stakeholders.

Another key area that has evolved is the use of RWE to support decision making. In line with the European Medicines Agencies network strategy to 2025 and the EMA Regulatory Science to 2025, EMA and the NCAs took steps to build a more sustainable platform to access, analyse and incorporate into the decision-making process a wide range of healthcare data from across the EU.

The launch of DARWIN EU® in 2022 was a key milestone towards achieving this goal. After the initial onboarding of 10 databases in 2022, more databases will be added to DARWIN EU® in the next reporting period to increase its capacity to generate RWE and support regulatory decision-making. DARWIN EU® will also support research on the impact of regulatory actions by providing broader access to electronic healthcare data; the experience gained so far from commissioned impact research will support the transition of certain impact studies to DARWIN EU® in the near future.

During the reporting period, certain processes were simplified or automated to improve efficiency. For instance, the decision to publish the full body of certain RMPs based on set criteria, instead of only the summaries, will remove the need for developers of generic medicines to request those documents. Another example is the integration of pharmacovigilance inspections into IRIS, a secure online platform for handling product-related scientific and regulatory procedures, which will increase security, improve the management of information and facilitate collaborative work.

The COVID-19 pandemic also prompted the adoption of innovative and more flexible approaches. For example, a significant proportion of pharmacovigilance inspections were conducted remotely in 2020. The new hybrid (in person/ remote) inspections model used during the pandemic will now be considered in other contexts, with a view to improving efficiency while maintaining high standards. The pandemic also prompted other changes such as the development of tools for analysing ADRs and public engagement which are described below.

During the reporting period, the Network developed further guidance for the good conduct of pharmacovigilance activities (GVP modules), for example, in relation to pregnant and breastfeeding women, pregnancy prevention and methods for evaluating the effectiveness of RMMs. While the development of some GVP guidance had to be put on hold because of the consecutive business continuity plans, further guidance is expected in the forthcoming period, for example on digital tools as mentioned above.

Response to the COVID-19 pandemic

The EU Network introduced numerous measures as part of its response to the COVID-19 crisis and enhanced the development and refinement of methods to harness the unprecedented volume of safety data generated for the vaccines. Enhanced monitoring and preparedness allowed the rapid identification, evaluation and contextualisation of TTS. As a result, the risk of this new clinical entity was minimised. This case, as well as the example of myocarditis, illustrate how spontaneous and real-world data complement each other, the former enabling rapid risk identification, the latter enabling further characterisation of the risk. In addition, enhanced international collaboration

enabled the sharing of information in real time, alignment of research questions and methods, and provision of consistent information to healthcare professionals and the public.

A lessons-learned exercise on the EU response to this public health crisis was initiated in 2021, and although it was still ongoing by the time this report concluded, several learnings have already emerged as important elements, and are described below.

Intensive and real-life monitoring

The intensified safety monitoring of vaccines and treatments for COVID-19 required an exceptional level of commitment and dedication of EU experts and other stakeholders.

The enhanced monitoring of COVID-19 vaccines through monthly safety reports submitted by the MAHs and assessed by the EU Network, intensified screening of EudraVigilance and the collection of data from observational studies proved to be instrumental in identifying new safety issues early and taking prompt regulatory actions. In particular, the SSRs allowed for the streamlining of the assessment of multiple ongoing safety topics in one single procedure, accelerating decision making. Monthly SSRs were a useful tool to support safety monitoring at the early post-approval stages when limited information on the safety of COVID-19 vaccines was available. However, their frequency was re-considered beyond the first 6 months, based on the rapid accumulation of data and considering the Network's workload. Similarly, after an initial period of weekly monitoring, the frequency of ADRs screening in EudraVigilance was revisited to maintain an intensified monitoring of those products while ensuring a sustainable use of the Network's resources.

Readiness and preparedness were crucial for near real-time surveillance during the pandemic. The ability of EMA to leverage its framework contracts with academic consortia early on ensured that the needs for RWD to generate RWE were met. For instance, background rates for AESIs were made available before the authorisation of the first COVID-19 vaccines or could be rapidly generated or updated as needed, enabling faster and better assessment of safety issues.

Public funded studies can provide invaluable information in a crisis situation, however, while several observational studies were commissioned to support safety monitoring, results were not always available in time to inform ongoing assessments. Very recent data from large populations are needed to address emerging safety concerns in a timely manner, especially when those relate to rare safety outcomes. However, the frequency of healthcare database updates may at times not be adequate to provide such data. In addition, data at different levels of healthcare services, such as hospitals, are often not available. Nevertheless, these studies have contributed to the collective body of evidence supporting the favourable benefit-risk profile of COVID-19 vaccines, including for important safety concerns still under monitoring by EMA and MAHs, such as myocarditis.

Looking ahead, there is a need to continue establishing networks, study protocols and processes proactively so that evidence on safety and effectiveness can be generated rapidly, particularly in a crisis. In addition, widening the range of RWD sources available, improving harmonised data collection across Member States, as well as increasing expertise on RWD and RWE within the EU Network were identified as areas for improvement. The initiatives started during the reporting period in this area, including the establishment of DARWIN EU® and the EU Vaccine Monitoring Platform, are expected to address some of these limitations by maintaining a network of RWD sources and facilitating a rapid access to a wider EU range of healthcare data and stakeholders from across the EU. These are reflected in EMA's extended mandate.

Improving tools to monitor ADRs

ADR data collected in EudraVigilance were an invaluable source of information supporting safety monitoring; evidence from EudraVigilance contributed to triggering about 85% of the signals assessed by PRAC during the reporting period. The intensified collection, processing and screening of suspected ADRs in EudraVigilance or other spontaneous reporting databases greatly supported safety assessments but proved to be highly resource-intensive and reliant on the performance of information technology systems.

Public interest in the safety of COVID-19 vaccines led to a significant increase in the number of EU citizens accessing EudraVigilance information through the public European database of

suspected ADR reports (adrreports.eu). Since this database shared the same platform with EudraVigilance, there was a knock-on effect on the performance of the latter, with a negative impact on the capability of the EU Network to perform safety queries. To overcome this problem, the platforms used for EudraVigilance and the public database were separated using a modernised and improved underlying infrastructure, which improved performance significantly.

Despite these improvements, there is still a need to upgrade these systems to achieve a higher level of automation, increase flexibility, enhance data extraction and querying functionalities. Plans to achieve these objectives were under way at the end of the reporting period and are expected to materialise in the coming years.

Another learning from the pandemic was the knock-on effect of the increased reporting of ADRs with COVID-19 vaccines on the overall data analysis. As the vaccination campaigns in the EU progressed, it appeared that the large proportion of ADRs related to COVID-19 vaccines in EudraVigilance (about 14% of the total ADRs as of May 2022) may affect signal detection for other medicines. EMA and the Members States therefore started testing methodologies to counteract this potential masking effect. The outcome of these activities will inform future methodologies for signal detection.

In the face of the challenges posed by the largest global public health crisis in a century, it clearly emerged that pharmacovigilance systems capable of mobilizing and channelling resources as dictated by the dynamic course of events are needed to provide effective responses.

Further consideration will be given in the forthcoming period on how to best rationalise further the pool of resources within the EU Network and release capacity promptly for redeployment towards critical activities, should the need arise. In the spirit of rationalising the use of resources, the concept of additional monitoring of new substances may be revisited and other initiatives to improve spontaneous reporting will be explored.

Enhancing engagement

On the communication side, new information on the safety of COVID-19 vaccines was communicated to the public in a timely manner, acknowledging the unknowns and uncertainties while explaining how knowledge gaps were going to be filled. The increased transparency applied to COVID-19 products, in particular with regards to the pre-authorisation phase and safety aspects after approval, was crucial to address public demand for more information. These exceptional transparency measures devised for the COVID-19 pandemic were formally adopted at the end of 2022 for future public health emergencies.

Engagement with the public took on a new dimension with the organisation of fortnightly press briefings at the peak of the pandemic and regular public meetings, allowing journalists and members of the public to ask questions to EU experts directly. Amongst the learnings, the need for more research to define optimal tools for risk communication and data visualisation and to ensure that recommendations are well understood and acted upon by citizens, was identified.

Although the pandemic has already offered the opportunity to strengthen the Network's collaboration and communication with the ECDC, there is certainly scope to enhance these further, including by creating new links with national public authorities, the NITAGs, and the national experts' bodies advising on vaccination programmes coordinated by ECDC. This would help alleviate differences in public health recommendations across EU Member States, which have proved to be challenging in the context of the COVID-19 pandemic and would likely reinforce public trust. Some of these learnings are being addressed as part of EMA's extended mandate which became applicable in March 2022 and reinforces EMA's role in crisis preparedness and management of medicines and medical devices.

The period covered by this report has been exceptional due to the COVID-19 pandemic and the necessity to put in place a strong response to the public health emergency. Still, the EU Network was able to continue delivering for public health due to a strong EU pharmacovigilance system and the endless dedication of all its actors. The Network emerges from the pandemic with a strengthened system, simplified processes and new tools, capabilities, and collaborations, e.g. through the VMP and DARWIN EU. All of those create the premises to make the Network able to face any future crises, in line with the EMA's extended mandate.

Annexes

Annex 1. Legal basis

The legal framework of pharmacovigilance for medicines marketed within the EU is provided for in Regulation (EC) No 726/2004[49] and in Directive 2001/83/EC[50], as amended by Regulation (EU) No 1235/2010[51] and Directive 2010/84/EU[52], respectively, which entered into force from July 2012.

The performance of pharmacovigilance activities was further refined in 2012 by Commission Implementing Regulation (EU) No 520/2012[53] which stipulates roles and responsibilities regarding certain aspects of pharmacovigilance for marketing authorisation holders, national competent authorities and EMA.

The EU Member States and EMA, in consultation with relevant stakeholders, have also produced, and regularly update, good pharmacovigilance practice guidelines which explain in detail how pharmacovigilance activities should be carried out.

This report is produced in response to the Commission obligation under Article 29 of Regulation (EC) No 726/2004 as amended by Regulation (EU) No 1235/2010, regarding reporting on the activities of EMA as well as a similar obligation under Article 108b of Directive 2001/83/EC as amended by Directive 2010/84/EU regarding the performance of pharmacovigilance tasks by the Member States.

[49] https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0001:0033:en:PDF
[50] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32001L0083
[51] https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0001:0016:EN:PDF
[52] https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0074:0099:EN:PDF
[53] https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:159:0005:0025:EN:PDF

Annex 2 – EMA-funded studies related to COVID-19

Subject	Contract signature	Date of final report[54]	EU PAS Register number* and publications as of Dec. 2022
EU infrastructure for COVID-19 vaccine monitoring ('ACCESS') • Background incidence rates of AESIs • Template protocols for vaccine safety and effectiveness studies • Feasibility of monitoring vaccine coverage, safety and effectiveness in EU healthcare databases	19/05/2020	Q4 2020	EUPAS37273 EUPAS39370 EUPAS39361 EUPAS39289 Williame et all. 2021 Willame et al. 2022
Multicentre collaboration for COVID-19 patient medication cohort studies ('E-CORE')	08/06/2020	Q3 2021	EUPAS38759
Impact of COVID-19 infection and medicines in pregnancy ('CONSIGN')	17/07/2020	Expected in Q3 2023	• WP1 (EHRs): 39438 • WP2 (COVI-PREG): 39226 Favre et al. 2022 • WP3 (INOSS): 40489 Meta-analysis: 40317
Natural history of coagulopathy and use of anti-thrombotic agents in COVID-19 patients	17/11/2020	Q3 2021	EUPAS40414 Burn et al. 2022 (1) Burn et al. 2022 (2)
Early safety monitoring of SARS-CoV-2 vaccines in EU Member States (*Early-Covid-Vaccine-Monitor*/'ECVM') • Prospective in vaccinees (WP1): BE, SK, FR, DE, IT, NL, UK • Healthcare databases (WP2): in ES, IT, NL, UK	11/12/2020	WP1: Expected in Q2 2023 (study extended into WP2 of CVM) WP2: Q1 2022	WP1: EUPAS39798 WP2: EUPAS40404 Sturkenboom et al. 2022 (medRxiv)

Safety monitoring of COVID-19 vaccines in the EU (*Covid-Vaccine-Monitor*/'CVM')
 	
• Prospective in vaccinees:
  ○ WP1 (special populations): NL, IT, PT, RO, SK, ES, CH, HR
  ○ WP2 (general population): NL, DE, BE, FR, IT, HR, RO, SK, IE, CH, ES
• Healthcare databases (WP3/WP4): framework for signal strengthening (incidence rates to support EMA O/E analyses, methodology), 9 data sources in 5 countries (IT (3), ES (3), NL (1), UK (1) and NO (1))
	06/04/2021	Expected in Q2 2023	EUPAS42504 (WP1)
			EUPAS39798 (WP2)
			EUPAS42467 (WP3/WP4)
			Bots et al. 2022

[54] This column reflects the dates when final reports are provided to EMA, ahead of publication on the EU PAS Register.

Subject	Contract signature	Date of final report[54]	EU PAS Register number* and publications as of Dec. 2022
Association between thromboembolic events and COVID-19 vaccines	29/06/2021	Q1 2022	EUPAS44469 Li et al. 2022 Xie et al. 2022
Benefit-risk contextualisation of COVID-19 vaccines in the EU	28/07/2021	Q2 2022	EUPAS44229
Vaccine-induced immune thrombotic thrombocytopenia and thrombosis syndrome (VITT/TTS) after vaccination against SARS-CoV-2 (COVID-19)	19/10/2021	Expected in Q1 2023	EUPAS45098
Impact of EU label changes and regulatory communication on SARS-CoV-2 adenovirus vector vaccines in context of thrombosis with thrombocytopenia syndrome (TTS): risk awareness and adherence	04/11/2021	Expected in Q1 2023	EUPAS44970
Comparative effectiveness of heterologous and homologous primary- and booster SARS-CoV-2 vaccination schedules in the Nordic countries	17/02/2022	Q3 2022	EUPAS46537 Andersson et al. 2022 (medRxiv)
Effectiveness of COVID-19 vaccination in 5 EU countries	20/04/2022	Expected in Q1 2023	EUPAS47725
Association between COVID-19 vaccines and paediatric safety outcomes in children and adolescents aged 5-19 in the Nordic countries	03/08/2022	Expected in Q1 2023	EUPAS48979

* Search Studies (encepp.eu)

WP: work package

Annex 3. Pharmacovigilance activities at Member State level

The following tables provide detailed quantitative information regarding pharmacovigilance activities undertaken at national level as reported by the NCAs of the EU Member States, Iceland and Norway.

Table 1. Total number of RMPs submitted to each NCA concerning products authorised nationally or via MRP/DCP (total including both RMPs associated with new MAAs and RMPs related to post-authorisation activities)

	AT	BE	BG	CY	CZ	DE-Bfarm	DE-PEI	DK	EE	ES
2019	N/A	169	337	71	/	1,659	139	574	/	695
2020	N/A	157	495	110	/	1,904	83	533	/	737
2021	N/A	171	380	93	/	1,495	85	658	35	735
2022	111	320	394	240	/	642	24	379	440	1,149

	FI	FR	GR	HR	HU	IE	IS	IT	LT	LU
2019	349	N/A	294	269	967	127	68	280	5	/
2020	343	N/A	287	227	1,084	128	44	310	10	182
2021	406	N/A	215	270	904	140	40	247	30	137
2022	348	532	238	349	800	155	48	269	16	132

	LV	MT	NL	NO	PL	PT	RO	SE	SI	SK
2019	437	36	485	380	1,185	370	378	258	205	353
2020	417	27	407	359	1,136	396	468	303	207	384
2021	442	32	456	451	1,384	525	249	307	103	438
2022	330	54	442	335	757	948	347	273	186	467

	EU Total
2019	10,090
2020	10,738
2021	10,428
2022	10,725

NB: the numbers are not directly comparable across different Member States and the heterogeneity may reflect different systems to record and count RMP submissions. For instance, in some Members States the information on the number of RMPs submitted with variations was not available and has not been included or the numbers of RMP statements submitted at the time of renewal (when a country is the concerned Member State) may have been included in some countries and not in others.

Table 2. Total number of RMPs assessed by NCAs as Reference Member State for an MRP/DCP

	AT	BE	BG	CY	CZ	DE-Bfarm	DE-PEI	DK	EE	ES
2019	72	11	0	0	160	50	30	136	12	105
2020	71	6	0	8	226	193	11	101	20	89
2021	61	7	2	1	147	200	21	104	25	103
2022	89	5	2	4	177	285	13	81	59	38

	FI	FR	GR	HR	HU	IE	IS	IT	LT	LU
2019	28	N/A	2	22	125	24	42	12	5	0
2020	39	N/A	5	15	204	40	30	9	9	0
2021	41	N/A	0	28	209	42	34	18	28	0
2022	43	9	1	24	186	47	26	12	12	0

	LV	MT	NL	NO	PL	PT	RO	SE	SI	SK
2019	46	32	243	21	73	321	2	81	12	2
2020	43	22	209	26	50	221	2	109	15	8
2021	42	24	233	14	128	454	3	105	38	11
2022	20	50	186	5	397	510	2	211	19	17

	EU Total
2019	1,669
2020	1,781
2021	2,123
2022	2,510

Table 3. Total number of PSURs submitted to each NCA for NAPs containing substances or combination of active substances not included in the EURD list and not included in the PSUR Work Sharing list

	AT	BE	BG	CY	CZ	DE-Bfarm	DE-PEI	DK	EE	ES
2019	N/A	6	1	0	15	43	14	3	2	37
2020	N/A	4	0	0	15	57	5	0	4	55
2021	N/A	8	0	0	10	28	8	1	3	41
2022	6	5	0	0	7	26	6	1	2	33

	FI	FR	GR	HR	HU	IE	IS	IT	LT	LU
2019	4	119	4	0	22	8	N/A	43	0	0
2020	2	299	5	0	20	13	N/A	301	0	0
2021	2	356	4	0	16	6	N/A	64	0	0
2022	0	458	2	0	9	2	0	33	0	0

	LV	MT	NL	NO	PL	PT	RO	SE	SI	SK
2019	3	9	11	5	92	27	15	10	1	22
2020	5	3	8	3	72	22	19	9	0	21
2021	2	3	12	2	60	11	7	4	0	14
2022	1	2	3	2	84	26	10	3	0	23

	EU Total
2019	516
2020	942
2021	662
2022	744

Table 4. Total number of PASS imposed by each NCA on NAPs or products authorised through MRP/DCP (imposed at authorisation or post authorisation and conducted only in one NCA), excluding those that have been imposed as an outcome of a referral or other EU-level regulatory action

	AT	BE	BG	CY	CZ	DE-Bfarm	DE-PEI	DK	EE	ES
2019	N/A	0	0	0	0	0	0	0	0	0
2020	N/A	0	0	0	0	0	0	0	0	0
2021	N/A	0	0	0	0	0	0	0	0	0
2022	N/A	0	0	0	0	1	1	0	0	0

	FI	FR	GR	HR	HU	IE	IS	IT	LT	LU
2019	0	N/A	0	0	1	0	N/A	1	0	0
2020	0	N/A	0	0	1	0	N/A	0	0	0
2021	0	N/A	0	0	1	0	N/A	0	0	0
2022	0	N/A	0	0	0	0	0	0	0	0

	LV	MT	NL	NO	PL	PT	RO	SE	SI	SK
2019	0	0	0	0	0	0	0	0	0	0
2020	0	0	0	0	0	0	0	0	0	0
2021	0	0	0	0	0	0	0	0	0	0
2022	0	0	0	0	0	0	0	0	0	0

	EU Total
2019	2
2020	1
2021	1
2022	2

Table 5. Total number of penalties to MAHs regarding noncompliance with their pharmacovigilance obligations

	AT	BE	BG	CY	CZ	DE-Bfarm	DE-PEI	DK	EE	ES
2019	0	0	0	0	2	8	0	0	0	0
2020	0	0	0	0	0	9	0	0	0	0
2021	0	0	0	0	1	2	0	0	0	0
2022	N/A	0	0	0	1	0	0	0	0	0

	FI	FR	GR	HR	HU	IE	IS	IT	LT	LU
2019	0	3	N/A	0	0	0	N/A	0	0	0
2020	0	1	N/A	0	0	0	N/A	0	0	0
2021	0	2	N/A	0	0	0	N/A	1	0	0
2022	0	0	0	0	0	0	0	0	0	0

	LV	MT	NL	NO	PL	PT	RO	SE	SI	SK
2019	0	0	0	0	0	0	0	1	0	0
2020	0	0	0	0	0	0	0	0	0	0
2021	0	0	0	0	0	12	0	0	1	0
2022	0	0	0	0	0	0	0	0	0	0

	EU Total
2019	14
2020	10
2021	19
2022	1

NB: the penalties counted are financial or of a different nature (e.g., injunction/warning letter). Some of the examples of non-compliance with pharmacovigilance obligations that have been highlighted by Member States in the reporting period were the lack of submission of the contact details of the EU QPPV (despite several reminders) or of the local distribution of DHPC.

Additional pharmacovigilance activities conducted by EU Member States

In addition to their standard activities and ongoing communication work, 27 Member States (Austria, Belgium, Bulgaria, Croatia, Czech Republic, Cyprus, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Spain, Sweden, Slovenia, Slovakia), as well as Iceland and Norway, reported on whether additional pharmacovigilance activities had been conducted during the reporting period, including training and educational activities aimed at healthcare professionals or patients and on the funding of studies and academic projects. Below is a high-level summary of some of the activities that have been highlighted by several NCAs. More extensive details may be provided on the website of the NCAs.

Activities aimed at stimulating ADR reporting and improving their quality and interpretation
• Training (e-learning, webinars, lectures at graduate/post-graduate courses, workshops) of healthcare professionals and medicine/pharmacy/nurse students aimed at raising awareness on pharmacovigilance systems and additionally monitored substances • Participation in events aimed at promoting ADR reporting, e.g. annual #medsafetyweek campaign and the International adverse event week • Participation in healthcare professional seminars/conferences to advise healthcare professionals on how to report ADRs and incorporation of ADR reporting forms into healthcare practitioners' software such as e-prescription or healthcare databases • Enhancement of layout of website of NCAs to facilitate electronic reporting of ADRs (via electronic forms, mobile application, etc.) and public access to information on those • Development of brochures/leaflets to support interpretation of ADR reports • Participation in patient safety days to raise awareness on risk related to medication errors • Media outreach (television, radio, Facebook, Twitter) • Contribution to the release of translations of MedDRA in additional EU languages

Activities aimed at supporting enhanced safety monitoring of COVID-19 vaccines/therapeutics
• Development of brochures, infographics • Media outreach and participation in television and radio programmes in the context of vaccination campaigns to stimulate and support reporting of ADRs with COVID-19 vaccines/therapeutics • Setting up a pilot infrastructure for extracting information from hospitals and/or general practitioners systems, when needed, to support validation of potential signals for COVID-19 vaccines • Daily communication with reporters to promote quality of data reported • Simplification of online reporting tools, including development of COVID-19 specific forms (and their update to align them with newly authorised vaccines) and of reporting platforms

Activities aimed at supporting enhanced safety monitoring of COVID-19 vaccines/therapeutics
to make it easier for vaccinees to select vaccine/dose, or capture additional information of interest • More systematic use of sensitivity analyses, stratification by gender, age groups, different risk periods to ease validation/assessment/communication of nationally reported cases • Rearrangement of internal resources to speed up ICSRs processing (case prioritisation, duplicate detection, follow-up for cases of interest) • Exploration of possible use of artificial intelligence and other automation tools (for report processing and retrieval of information) • Enhancement of collaboration with regional pharmacovigilance centres and scientific clinical associations (provision of expert opinion) and establishment of multidisciplinary committees with experts from specific therapeutic areas • Setting up a COVID-19 crisis management team

Activities aimed at enhancing safety communication and stakeholders' engagement
• Publication of pharmacovigilance newsletters/bulletins/targeted communications/DHPC • Incorporation of electronic educational materials and DHPCs in healthcare practitioners' (physicians and pharmacists) software such as e-prescription database, dispensing systems and other hospital or General Practitioners medical records databases. This allowed prescribers to learn about new safety information at the time of prescribing, reducing the need for DHPC or distribution of educational material on paper • Distribution of DHPCs and other safety information via digital tools and use of social media to raise awareness about new risks, new/updated educational materials, new important safety communications • Development of questionnaire for DHPC recipients to get insights on how the information provided will be used and how their content and format could be improved • Consultation of patients' associations prior to disseminating new educational material and dissemination through those and learned societies • Establishment of patient fora where information on how to report ADRs could be shared and feedback obtained • Setting up patient fora to widen engagement with patients/patients' organisations • Contribution to national prescribing guides for general practitioners <u>Specifically, for COVID-19 vaccines and therapeutics</u>: • Training (even prior to roll-out of vaccines) of healthcare professionals to inform them about the vaccine authorisation process, which vaccines would become available, explain role of NCAs in the safety monitoring, and to encourage reporting of suspected ADRs • Publication of periodic reports (up to weekly frequency) with new information related to COVID-19 vaccines

Activities aimed at enhancing safety communication and stakeholders' engagement
• Information sheets for healthcare professionals to prevent medication errors with the different pharmaceutical forms and with bivalent vaccines • Provision of answers to journalists and citizens (through requests for access to information) on vaccines safety

Topics of research projects
• COVID-19 vaccines, e.g. to calculate and monitor the incidence rate of AESIs after COVID-19 vaccination; to assess association between specific AESIs and COVID-19 vaccine administration; to assess the effectiveness of COVID-19 vaccines in preventing COVID-19; participation in the Cohort Event Monitoring of Safety of COVID-19 vaccines conducted at EU level; observational research to gain insights into tolerability of COVID-19 vaccines via feedback gathered through a smartphone app • Other pharmacovigilance topics, e.g. ADRs leading to emergency department visits, optimisation of signal detection algorithm for serious ADRs, enhancing medicinal product safety in children/adolescents, safety of biological medicines, compliance with recommendations and effectiveness of RMMs, impact of EU labelling changes on medicine use and prescribing trends.

Annex 4. Pharmacovigilance activities at EU level

A. Adverse drug reactions

ICSRs from EudraVigilance post-authorisation module (EVPM) [55]			
Year	**EEA**	**Non-EEA**	**Total[56]**
2019	968,689 Serious: 384,890	1,034,123 Serious: 1,021,860	2,002,814 Serious: 1,406,751
2020	812,784 Serious: 312,103	1,008,455 Serious: 996,070	1,821,239 Serious: 1,308,173
2021	1,745,290 Including 1,170,253 COVID-19 related (67%) Serious: 484,307 including 264,230 COVID-19 related (55%)	1,780,565 Serious: 1,728,622	3,525,976 including 1,697,688 COVID-related (48%) Serious: 2,213,024 including 757,423 COVID-related (34%)
2022	1,451,946 including 885,216 COVID-19 related (61%) Serious: 469,583 including 255,996 COVID-19 related (55%)	1,456,138 Serious:1,422,128	2,908,264 including 1,140,583 COVID-19 related (39%) Serious:1,891,867 including 500,618 COVID-19 related (26%)

Number of EVPM ICSRs reported from EEA countries [55,57]										
	Patients			**HCPs**			**Patients and HCPs**			**Total ICSRs**
Year	**Serious**	**Non-serious**	**All**	**Serious**	**Non-serious**	**All**	**Serious**	**Non-serious**	**All**	
2019	52,013	171,240	223,253	294,371	322,637	617,008	38,506	89,922	128,428	968,689
2020	45,880	154,853	200,733	228,321	254,122	482,443	37,902	91,706	129,608	812,784
2021	138,668	712,255	850,923*	305,249	473,166	778,415	39,182	74,748	113,930	1,743,268
2022	118,832	583,811	702,643*	317,642	333,037	650,679	33,109	65,515	98,624	1,451,946

* Over 80% of the total number of ICSRs reported by patients in the EEA related to COVID-19 vaccines (n=723,083 in 2021, and n=578,476 in 2022).

Number of EVPM ICSRs reported from non-EEA countries [55,57]										
	Patients			**HCPs**			**Patients and HCPs**			**Total ICSRs**
Year	**Serious**	**Non-serious**	**All**	**Serious**	**Non-serious**	**All**	**Serious**	**Non-serious**	**All**	
2019	188,070	2,021	190,091	448,477	5,320	453,797	385,314	4,923	390,237	1,034,125
2020	167,380	1,855	169,235	443,927	5,437	449,364	384,763	5,093	389,856	1,008,455
2021	464,798	29,468	494,266	663,976	16,067	680,043	601,042	7,210	608,252	1,782,561
2022	326,997	13,443	340,440	628,201	13,310	641,511	466,922	7,249	474,171	1,456,122

55 Those data were extracted on 10 January 2023 and may slightly differ from those included in other previously published reports, possibly due to deduplication and nullification of reports that have taken place following those publications, as well as to delayed ICSRs processing caused by the high volume of cases received during the COVID-19 pandemic.
56 The total number of EVPM ICSRs may slightly differ from the sum of EEA and non-EEA cases because it also includes the number of cases with primary source country "not specified"
57 The number of ICSRs reported by patients includes the following report types: "Spontaneous", "Other", "Not available to sender (unknown)" and "Studies". The latter report type may be used for reports submitted in the context of patient support programmes.

B. Signals

Potential signals reviewed by EMA	2019	2020	2021	2022
Total	1,806	1,888	1,829*	1,605**
Originating from EudraVigilance screening	78%	81%	88%	83%

* Of which 344 signals related to COVID-19 vaccines

** Of which 230 signals related to COVID-19 vaccines

Outcomes of signal procedures over 4Y period - 2019-2022	N.	%
Update of product information	142	52.0%
Routine pharmacovigilance/monitor within PSUR	95	34.8%
Referral	3	1.1%
Update of RMP	4	1.5%
Ongoing	29	10.6%
Total number of signals analysed by PRAC	273	100.0%

Breakdown of signals with COVID-19 vaccines and therapeutics	2019	2020	2021	2022
Number of signal procedures for COVID-19 vaccines	0	0	21	16 **
Number of signal procedures for COVID-19 therapeutics	0	1	2*	0

**One signal related to a therapeutic is counted twice, in 2020 when the assessment started and in 2021 when it concluded*

***Three signals related to vaccines were counted twice, in 2021 when the assessment started and in 2022 when it concluded.*

List of signal procedures with COVID-19 vaccines and therapeutics

INN	Product name	V/T	Issue	Outcome as of end of 2022
Remdesivir	Veklury	T	Acute kidney injury	routine pharmacovigilance / monitor within PSURs
Remdesivir	Veklury	T	Sinus bradycardia	update of product information
COVID-19 Vaccine	Vaxzevria	V	Anaphylactic reaction	update of product information and DHPC

INN	Product name	V/T	Issue	Outcome as of end of 2022
(ChAdOx1-S [recombinant])				
COVID-19 Vaccine (ChAdOx1-S [recombinant])	Vaxzevria	V	Capillary leak syndrome	update of product information and DHPC
Tozinameran, COVID-19 mRNA vaccine (nucleoside modified)	Comirnaty	V	Signal of localised swelling in persons with history of dermal filler injections	update of product information
Tozinameran, COVID-19 mRNA vaccine (nucleoside modified)	Comirnaty	V	Erythema multiforme	update of product information
Elasomeran, COVID-19 mRNA vaccine (nucleoside modified)	Spikevax	V	Immune thrombocytopenia	routine pharmacovigilance / monitor within PSURs
Tozinameran, COVID-19 mRNA vaccine (nucleoside modified)	Comirnaty	V	Immune thrombocytopenia	routine pharmacovigilance / monitor within PSURs
COVID-19 Vaccine (ChAdOx1-S [recombinant])	Vaxzevria	V	Embolic and thrombotic events (SMQ)	update of product information and RMP; DHPC
COVID-19 Vaccine (Ad26.COV2-S [recombinant])	Jcovden	V	Embolic and Thrombotic events (SMQ)	update of product information and RMP; DHPC
COVID-19 Vaccine (ChAdOx1-S [recombinant])	Vaxzevria	V	Acute macular outer retinopathy	update of RMP
Tozinameran, COVID-19 mRNA vaccine (nucleoside modified)	Comirnaty	V	Myocarditis and pericarditis	update of product information and RMP; DHPC
Tozinameran, COVID-19 mRNA vaccine	Comirnaty	V	Glomerulonephritis and nephrotic syndrome	routine pharmacovigilance / monitor within PSURs

INN	Product name	V/T	Issue	Outcome as of end of 2022
(nucleoside modified)				
Elasomeran, COVID-19 mRNA vaccine (nucleoside modified)	Spikevax	V	Erythema multiforme	update of product information
Elasomeran, COVID-19 mRNA vaccine (nucleoside modified)	Spikevax	V	Glomerulonephritis and nephrotic syndrome	routine pharmacovigilance / monitor within PSURs
COVID-19 Vaccine (ChAdOx1-S [recombinant])	Vaxzevria	V	Immune thrombocytopenia	update of product information and RMP; DHPC
Elasomeran, COVID-19 mRNA vaccine (nucleoside modified)	Spikevax	V	Myocarditis and pericarditis	update of product information and RMP; DHPC
Tozinameran, COVID-19 mRNA vaccine (nucleoside-modified); Elasomeran, COVID-19 mRNA vaccine (nucleoside-modified); COVID-19 Vaccine (Ad26.COV2-S [recombinant]); COVID-19 Vaccine (ChAdOx1-S [recombinant])	Comirnaty, Spikevax, Jcovden, Vaxzevria	V	Multisystem inflammatory syndrome	routine pharmacovigilance / monitor within PSURs
Tozinameran, COVID-19 mRNA vaccine (nucleoside modified)	Comirnaty	V	Myocarditis and pericarditis	update of product information
Elasomeran, COVID-19 mRNA vaccine	Spikevax	V	Myocarditis and pericarditis	update of product information

INN	Product name	V/T	Issue	Outcome as of end of 2022
(nucleoside modified)				
Elasomeran, COVID-19 mRNA vaccine (nucleoside modified)	Spikevax	V	Amenorrhoea	ongoing (within PSUR/PSUSA)
Elasomeran, COVID-19 mRNA vaccine (nucleoside modified)	Spikevax	V	Heavy menstrual bleeding	update of product information
Tozinameran, COVID-19 mRNA vaccine (nucleoside modified)	Comirnaty	V	Amenorrhoea	ongoing (within PSUR/PSUSA)
Tozinameran, COVID-19 mRNA vaccine (nucleoside modified)	Comirnaty	V	Heavy menstrual bleeding	update of product information
Elasomeran, COVID-19 mRNA vaccine (nucleoside modified)	Spikevax	V	Capillary Leak Syndrome	update of product information
Tozinameran, COVID-19 mRNA vaccine (nucleoside modified)	Comirnaty	V	Capillary leak syndrome	routine pharmacovigilance / monitor within PSURs
Tozinameran, COVID-19 mRNA vaccine (nucleoside modified)	Comirnaty	V	Autoimmune hepatitis	ongoing (within PSUR/PSUSA)
Elasomeran, COVID-19 mRNA vaccine (nucleoside modified)	Spikevax	V	Autoimmune hepatitis	ongoing (within PSUR/PSUSA)
COVID-19 Vaccine (ChAdOx1-S [recombinant])	Vaxzevria	V	Corneal graft rejection	routine pharmacovigilance / monitor within PSURs

INN	Product name	V/T	Issue	Outcome as of end of 2022
Tozinameran, COVID-19 mRNA vaccine (nucleoside modified)	Comirnaty	V	Corneal graft rejection	routine pharmacovigilance / monitor within PSURs
Elasomeran, COVID-19 mRNA vaccine (nucleoside modified)	Spikevax	V	Corneal graft rejection	routine pharmacovigilance/ monitor within PSURs
Tozinameran, COVID-19 mRNA vaccine (nucleoside modified)	Comirnaty	V	Histiocytic necrotizing lymphadenitis	ongoing (within PSUR/PSUSA)
Tozinameran, COVID-19 mRNA vaccine (nucleoside modified)	Comirnaty	V	Vulval ulceration	ongoing (Signal)
COVID-19 Vaccine (ChAdOx1-S [recombinant]	Vaxzevria	V	Pemphigus and pemphigoid	ongoing (Signal)
Tozinameran, COVID-19 mRNA vaccine (nucleoside modified)	Comirnaty	V	Pemphigus and pemphigoid	ongoing (Signal)
Elasomeran, COVID-19 mRNA vaccine (nucleoside modified)	Spikevax	V	Pemphigus and pemphigoid	ongoing (Signal)

V= Vaccine; T= Therapeutic; PV= Pharmacovigilance

C. Post-authorisation safety studies

	2019	2020	2021	2022	Total
Imposed PASS protocol procedures started*	46	17	22	17	102
Imposed PASS protocol procedures finalised*	43	13	23	16	95
Non-imposed PASS protocol procedures started	144	158	143	217	662
Non-imposed PASS protocol procedures finalised	180	167	226	233	806
PASS amendment	11 (started), 9 (finalised) + 6 follow up amendments (started) and 6 (finalised)	19 (started), 14 (finalised) + 9 follow up amendments (started) and 7 (finalised)	17 (started), 18 (finalised) + 15 follow up amendments (started) and 11 (finalised)	20 (started), 18 (finalised) + 12 follow up amendments (started) and 14 (finalised)	67 (started), 59 (finalised) + 42 follow up amendments (started) and 38 (finalised)
Imposed PASS result procedures started	3	4	11	2	20
Imposed PASS result procedures finalised	3	2	6	5	16
PASS scientific advice through SAWP	3	1	1	1	6

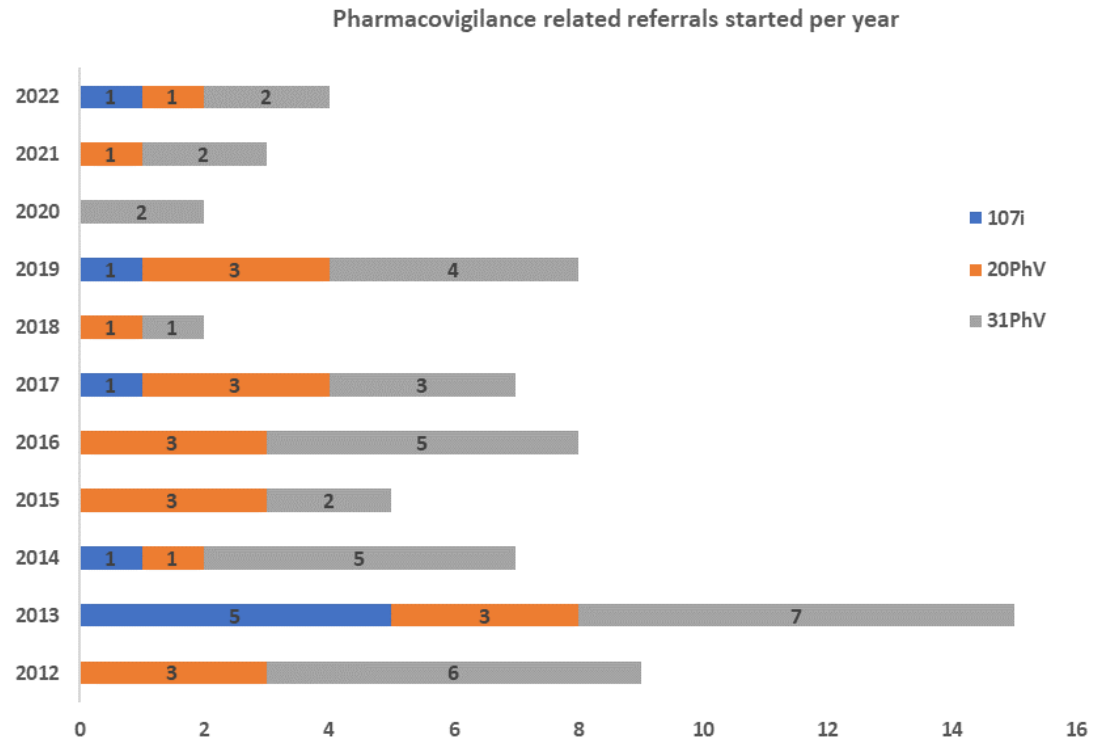
* The numbers presented include both new PASS protocols and PASS protocol follow up

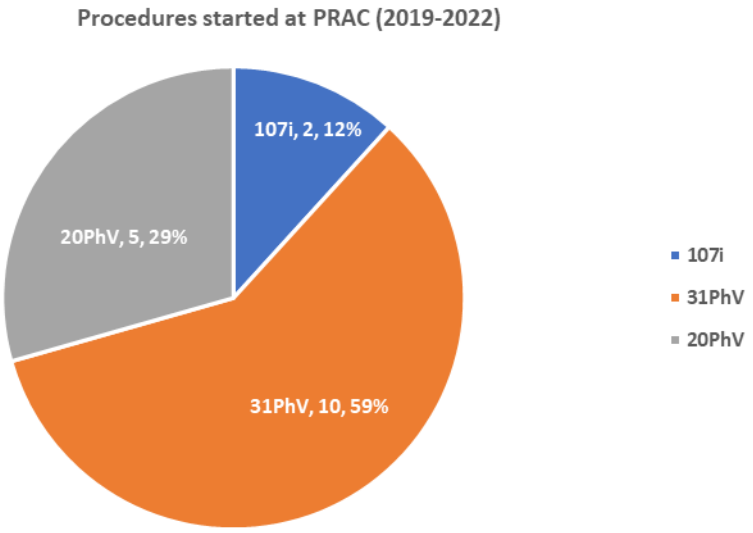
D. Periodic safety reporting

PSURs and PSUSAs finalised	2019	2020	2021	2022	Total
CAP-only	558	516	575	542	2,191
NAP-only	222	209	287	272	990
CAP/NAP	48	49	49	46	192
Total outcomes	828	774	911	860	3,373

PRAC outcomes of PSURs and PSUSAs	2019	2020	2021	2022	Total
Maintenance	655	630	748	720	2,753
NAP-only	166	161	226	216	769
CAPs/NAPs and CAPs only	489	469	522	504	1,984
Variation	173	144	163	140	620
NAP-only	56	48	61	56	221
CAPs/NAPs and CAPs only	117	96	102	84	399
Total outcomes	828	774	911	860	3,373

E. Referral procedures





List of safety-related referrals 2019-2022

Procedure name	INN	Legal basis (article)	Started	Finalised
Methotrexate-containing medicinal products	methotrexate	31PhV	Apr-18	Aug-19
Fenspiride-containing medicinal products	fenspiride hydrochloride	107i	Feb-19	May-19
Fluorouracil and fluorouracil-related substances	capecitabine, fluorouracil, tegafur, flucytosine	31PhV	Mar-19	Apr-20
Estradiol-containing (0.01% w/w) medicinal products for topical use	oestradiol	31PhV	Apr-19	Jan-20
Lemtrada	alemtuzumab	20PhV	Apr-19	Nov-19
Xeljanz	tofacitinib	20PhV	May-19	Nov-19
Leuprorelin-containing depot medicinal products	leuprorelin	31PhV	Jun-19	Jun-20
Cyproterone-containing medicinal products	cyproterone	31PhV	Jul-19	Mar-20
Picato	ingenol mebutate	20PhV	Sep-19	Apr-20
Ifosfamide-containing solutions	ifosfamide	31PhV	Mar-20	Apr-21
Ulipristal acetate 5mg	ulipristal acetate	31PhV	Mar-20	Nov-20
Amfepramone-containing medicinal products	amfepramone	31PhV	Feb-21	Nov-22

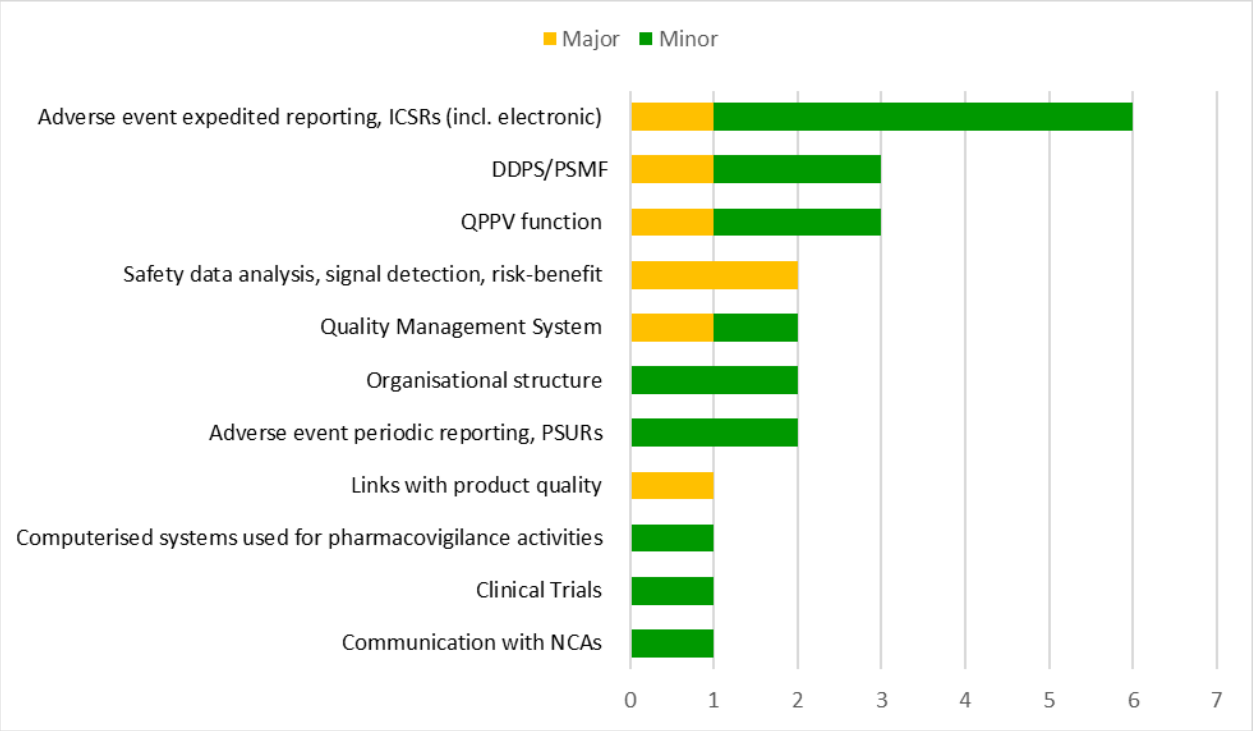
Procedure name	INN	Legal basis (article)	Started	Finalised
Zynteglo	betibeglogene autotemcel	20PhV	Mar-21	Jul-21
Nomegestrol and Chlormadinone	nomegestrol and chlomardinone	31PhV	Oct-21	Sep-22
Terlipressin	terlipressin	31PhV	Jan-22	Nov-22
Janus Kinase inhibitors (JAKi) inhibitors	baricitinib, tofacitinib, upadicitinib, filgotinib, abrocitinib	20PhV	Feb-22	Nov 22
Topiramate	topiramate	31PhV	Sep-22	Ongoing
Pholcodine	pholcodine	107i	Sep-22	Dec-22

Note: PhV means pharmacovigilance

F. Inspections

At the time of finalisation of this report, data on pharmacovigilance inspections carried out in 2022 were not yet available.

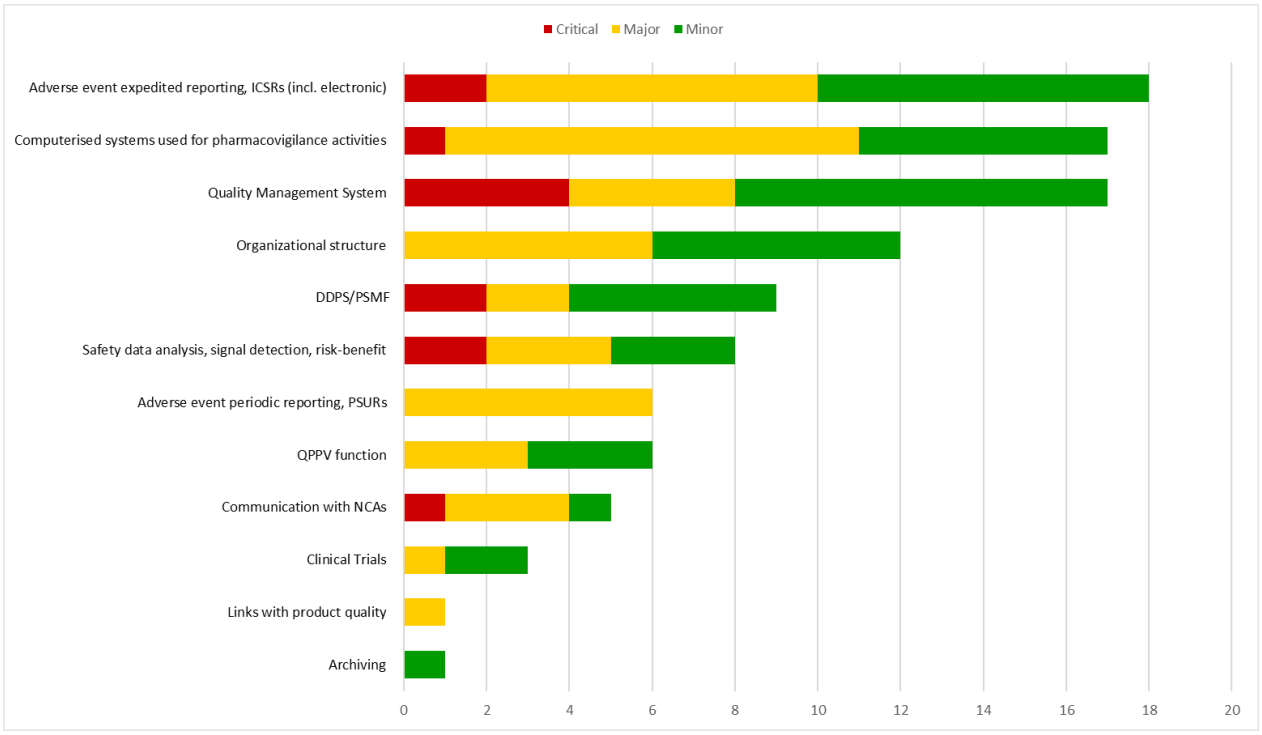
CHMP inspections conducted in 2019: number of findings per category classified as critical, major or minor



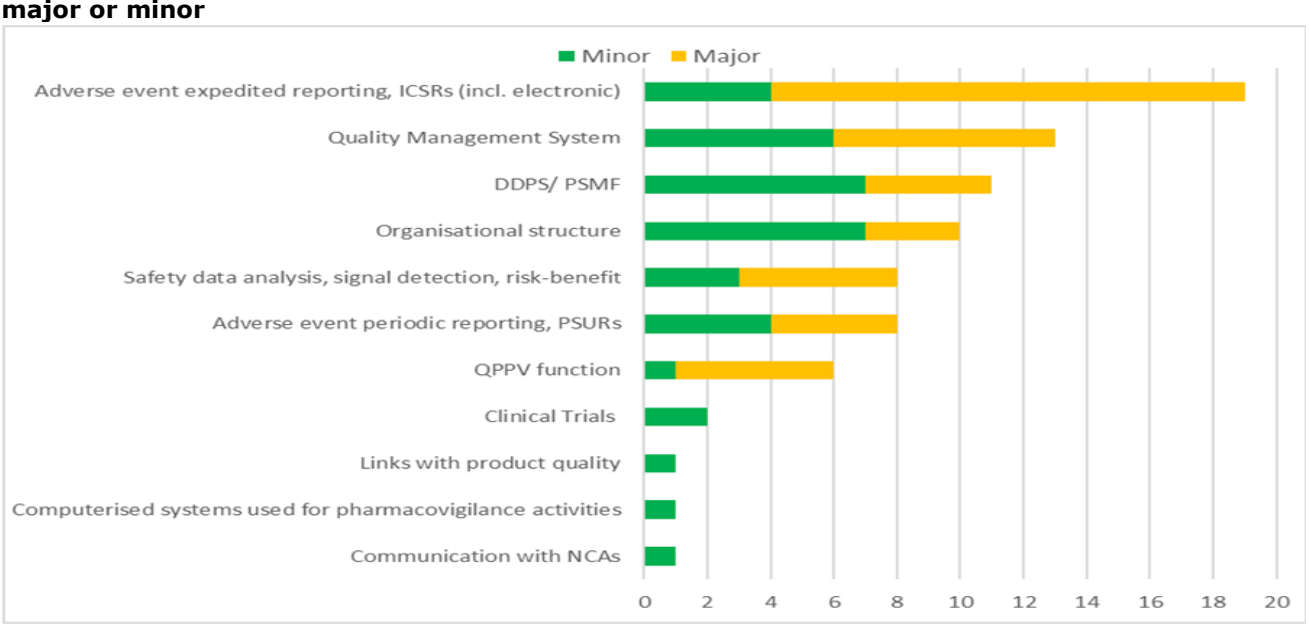
Notes: DDPS: Detailed description of the pharmacovigilance system

No finding was classified as critical in 2019.

CHMP inspections conducted in 2020: number of findings per category classified as critical, major or minor



CHMP inspections conducted in 2021: number of findings per category classified as critical, major or minor



Note: no finding was classified as critical in 2021.

G. Good pharmacovigilance practice

GVP modules released for public consultation in the reporting period:

1. Guideline on good pharmacovigilance practices (GVP): Module XVI - Risk minimisation measures: selection of tools and effectiveness indicators (Rev 3) - Consultation closed in 2021

2. Guideline on good pharmacovigilance practices (GVP): Module XVI Addendum II - Methods for effectiveness evaluation - Consultation closed in 2021

3. Draft guideline on good pharmacovigilance practices (GVP): Product- or population-specific considerations III: Pregnant and breastfeeding women - Consultation closed in 2020

4. Draft guidelines on good pharmacovigilance practices (GVP): Addendum III of Module XVI on pregnancy prevention programmes and other pregnancy-specific risk minimisation measures - Consultation closed in May 2022.

List of abbreviations

Abbreviation	Definition
AAV5	Adeno-associated virus serotype 5
ACCESS Consortium	vACcine Covid-19 monitoring readinESS
ACE inhibitors	Angiotensin converting enzyme inhibitors
ACSoMP	WHO Advisory Committee on Safety of Medicinal Products
ADR	Adverse drug reaction (side effect)
AESI	Adverse event of special interest
AML	Acute myeloid leukaemia
ARB	Angiotensin receptor blocker
ATE	Arterial thromboembolism
ATMP	Advanced therapy medicinal product
BCP	Business continuity plan
BfARM	Bundesamt für Arzneimittel und Medizinprodukte, the Federal Institute for Medicines and Medical Devices, one of the two German federal medicines regulators
CAP	Centrally authorised product, a medicine authorised by the European Commission based on an evaluation by EMA
CAPA	Corrective and preventive action
CAR-T	Chimeric antigen receptor T-cell, a type of white blood cell that has been modified outside the body to enable it to attack cancer cells
CAT	Committee for Advanced Therapies
CDC, US	Centre for Disease Control and Prevention, US
CHMP	Committee for Medicinal Products for Human Use, EMA's scientific committee responsible for the overall evaluation and opinion on marketing authorisation applications for centrally authorised products
CMDh	Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human, a medicines regulatory body representing the European Union (EU) Member States, Iceland, Liechtenstein and Norway.
CONSIGN study	COVID-19 infectiOn aNd medicineS In pregnancy study
cRAO	Central retinal artery occlusion
CTCL	Cutaneous T-cell lymphoma
DARWIN EU®	Data Analysis and Real-World Integration Network
DCP	Decentralised procedure
DDPS	Detailed description of the pharmacovigilance system
DHPC	Direct healthcare professional communication, a letter sent to inform doctors about an issue relating to a medicine
DLP	Data lock point
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
E-CORE project	Evidence for COVID-19 Observational Research Europe project
EDQM	European Directorate for the Quality of Medicines & HealthCare

Abbreviation	Definition
EEA	European Economic Area
HER	Electronic health record data
EMA	European Medicines Agency
ENCePP	European Network of Centres in Pharmacoepidemiology and Pharmacovigilance, a partnership involving 147 centres across Europe
EPITT	European pharmacovigilance issues tracking tool
ETF	Emergency Task force
EU	European Union
EU-IMP	EU incident management plan
EUL	WHO emergency use listing
EU NTC	EU Network training centre
EU PAS Register	European Union electronic register of post-authorisation studies
EURD	List of European Union reference dates and frequency of submission of periodic safety update reports (a list of active substances for which PSURs must be submitted and the dates and frequencies at which this should occur).
EVDAS	EudraVigilance data analysis system
FDA	Food and Drug Administration, the medicines regulator for the United States of America
GACVS	WHO Global Advisory Committee on Vaccine Safety
GCP	Good clinical practice
GMP	Good manufacturing practice
GVP	Good pharmacovigilance practice, guidelines on how pharmacovigilance activities should be carried out
HES	Hydroxyethyl-starch solutions
ICSR	Individual case safety report, a standardised format for reports of suspected side effects
ICMRA	International Coalition of Medicines Regulatory Authorities
INN	International non-proprietary name
IPA	Instrument of pre-accession assistance
LMS	Lead Member State, a Member State that acts on behalf of the Network in assessing pharmacovigilance data for a particular active substance *or* Learning Management System
MAA	Marketing authorisation application
MAH	Marketing authorisation holder, the company marketing a medicine
MedDRA	Medical dictionary for regulatory activities. It is a standardised medical terminology to facilitate sharing of regulatory information internationally for medical products for human use
MHRA	Medicines & Healthcare products Regulatory Agency, the UK regulatory agency
MHLW, Japan	Ministry of Health, Labour and Welfare, Japan
mRNA	Messenger ribonucleic acid
MRP	Mutual recognition procedure
MS	Member State, one of the constituent nations of the European Union
nAMD	Neovascular (wet) age-related macular degeneration

Abbreviation	Definition
NAP	Nationally authorised product, a medicine evaluated and authorised by national regulators
NCA	National competent authority, a national medicines regulator
NITAGs	National immunisation technical advisory groups
O/E analyses	Observed versus expected analyses
PAS	Post-authorisation study, a study carried out after a medicine has been authorised and marketed; may be imposed or requested by regulators during the authorisation process
PASS	Post-authorisation safety study, a post-marketing study focusing on the safety of a medicine
PEI	Peter Ehrlich Institut, one of the two German federal medicines regulators
PI	Product information (in the EU it consists of the summary of product characteristics for healthcare professionals and the package leaflet for patients)
PIP	Paediatric investigation plans
PMDA, Japan	Pharmaceuticals and Medical Devices Agency, Japan
PPP	Pregnancy prevention programme
PRAC	Pharmacovigilance Risk Assessment Committee, EMA's main committee for assessing issues about medicines safety
PRIME scheme	Priority Medicines scheme which provides early and enhanced scientific and regulatory support for medicines that have a significant potential to address unmet medical needs
PRISMA	PRAC Risk Minimisation Alliance
PROTECT	Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium, a public-private partnership to examine ways to strengthen safety surveillance and the monitoring of the benefit-risk of medicines in Europe. Completed in 2015
PSMF	Pharmacovigilance system master file
PSUR	Periodic safety update report, a report that each marketing authorisation holder must submit at defined intervals, providing an updated evaluation of the benefit-risk-balance of a medicine. They include the results of studies carried out with the medicine, as well as any other new information on safety or benefits, and cover both authorised and unauthorised uses.
PSUSA	Periodic safety update – single assessment, a PSUR carried out for a group of medicines that contain the same active substance or combination of active substances and whose assessment period has been synchronised. This allows for more efficient use of resources and also ensures that these related medicines are evaluated in a consistent way.
QPPV	Qualified person responsible for pharmacovigilance
RMM	Risk minimisation measure
RMP	Risk management plan. Part of the dossier of information legally required from each company wishing to market a medicine in the EU. The plan identifies known and potential safety issues with the medicine, and includes binding commitments on how the medicine will be monitored for safety during its lifetime. It also identifies the actions that will be taken to minimise the risks and provide evidence where it is lacking, so as to ensure the most favourable balance of risks against the medicine's benefits.

Abbreviation	Definition
RWD	Real-world data. These are data derived from a variety of sources relating to the use of medicines in patients in real-world settings, as opposed to the controlled conditions of a randomised controlled trial. They may include data from electronic health records, patient registries and health insurance claims
RWE	Real word evidence. This is clinical evidence regarding the use and potential benefits or risks of a medicine derived from analysis of real world data
SARS-CoV2	Severe acute respiratory syndrome coronavirus 2
SMQ	Standardised MedDRA query
SOP	Standard operating procedure
SPEAC	Safety Platform for Emergency Vaccines Collaboration
SRLM	Strategic review and learning meetings
SSR	Summary safety reports
SUSAR	Suspected unexpected serious adverse reaction
TNF	Tumor necrosis factor
TTS	Thrombosis with thrombocytopenia syndrome
UK	United Kingdom
UMC	Uppsala monitoring centre
US	United States of America
VAC4EU	Vaccine monitoring collaboration for Europe
VIPIT	Vaccine-induced prothrombotic immune thrombocytopenia
VITT	Vaccine-induced immune thrombotic thrombocytopenia
VTE	Venous thromboembolism
vTME	Vaccine targeted medical events
WHO	World Health Organization
xEVMPD	eXtended EudraVigilance Medicinal Product Dictionary, also known as the Article 57 database, containing information on all authorised medicines in the EU

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