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2022 Annual Report on EudraVigilance for the European Parliament, the Council and the Commission

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Abbreviations used in the document

ADR	Adverse Drug Reaction
CAP	Centrally Authorised Product
E2B(R3)	ICH Guideline 'Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports', revision 3
EC	European Commission
EDQM	European Directorate for the Quality of Medicines and HealthCare
EEA	European Economic Area
EMA	European Medicines Agency
ESTRI	Electronic Standards for the Transfer of Regulatory Information
EV-EWG	EudraVigilance Expert Working group
eRMR	electronic Reaction Monitoring Report
eVPR	excel Validation Perpetual Report
EU	European Union
EVCTM	EudraVigilance Clinical Trials Module
EVDAS	EudraVigilance Data Analysis System
EVPM	EudraVigilance Post-authorisation Module
FDA	Food and Drug Administration (United States)
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICSR	Individual Case Safety Report
ISO	International Standards Organisation
LMS	Lead Member State
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labor and Welfare (Japan)
MLM	EMA's Medical Literature Review service
MS	Member State
NAP	Nationally Authorised Product
NCA	National Competent Authority
PASS	Post-Authorisation Safety Study
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
PRAC	Pharmacovigilance Risk Assessment Committee
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Review
PSUSA	Periodic Safety Update Single Assessment
QPPV	Qualified Person responsible for Pharmacovigilance
RMP	Risk Management Plan
SUSAR	Suspected Unexpected Serious Adverse Reaction
vTME	vaccine Targeted Medical Events
WHO	World Health Organization
WHO-UMC	World Health Organisation - Uppsala Monitoring Centre
XEVMPD	eXtended EudraVigilance Medicinal Product Dictionary

1. Executive summary

Collecting reports of medical events and problems that occur following the use of a medicinal product is one of the pillars of the European Union (EU) safety monitoring system. Healthcare professionals and patients are encouraged to report all suspected adverse reactions individuals may have experienced after administration of a medicinal product, even if it is unclear whether the medicine or vaccine was the cause.

EudraVigilance, the European database of suspected adverse drug reaction (ADR) reports, is the tool that the European Medicines Agency (EMA) and national competent authorities (NCAs) use to monitor the safety of all authorised medicines in the EU as well as medicines studied in clinical trials. Timely detection and assessment of safety signals from sources such as EudraVigilance complements the benefit-risk evaluation of medicinal products via assessment of periodic safety update reports (PSURs) and risk management plans (RMPs) by the Pharmacovigilance Risk Assessment Committee (PRAC). EudraVigilance is therefore one of the cornerstones of EU pharmacovigilance (See Figure 1).

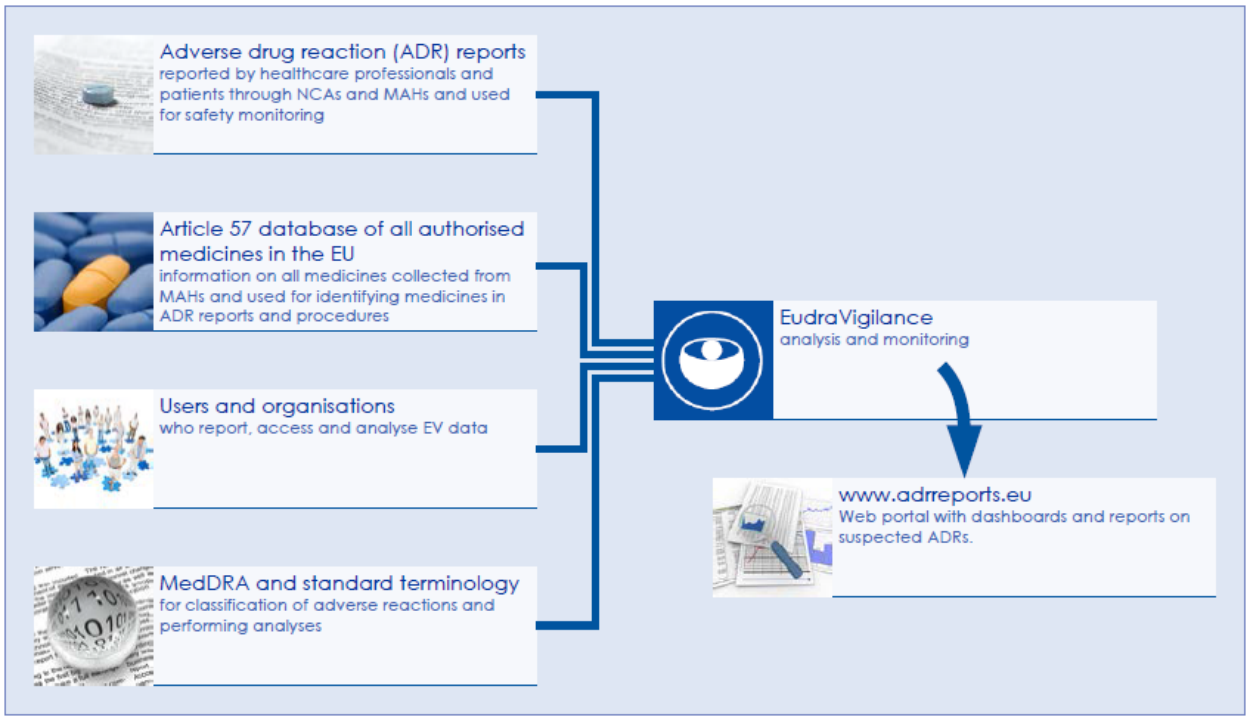


Figure 1. EudraVigilance users, data sources and data use.

The EudraVigilance database currently holds over 25.3 million individual case safety reports (ICSRs) relating to 14.8 million unique suspected ADR case reports[1] and is one of the largest pharmacovigilance databases in the world. It is continuously improved to enhance functionalities that allow for a better support of pharmacovigilance activities and the protection of public health.

This annual report is produced in accordance with Regulation (EC) No. 726/2004, Article 24(2), paragraph 2 and summarises the EudraVigilance-related activities performed in 2022, notably:

[1] One case may contain several ICSRs (initial and follow-up).

- ***EMA's pharmacovigilance system.*** In 2022, the system remained efficient in detecting and processing suspected safety issues. For example, the EU was at the forefront in dealing with several COVID-19 vaccine-related signals and analysis of EudraVigilance data was central to their assessment (e.g. signal of menstrual disorders with COVID-19 vaccines).
- ***Collecting and processing suspected adverse drug reaction reports***. In 2022, 2.9 million ICSRs related to suspected ADRs occurring after authorisation were collected and managed in EudraVigilance (an 18% decrease compared to the previous year). Number of ICSRs originating from the European Economic Area (EEA) decreased by 17% and non-serious reports by 23%, but still are higher than in pre-pandemic years. A large proportion of the reports were related to COVID-19 vaccines, which account for 1,14 million (39%) of all ICSRs. Of all COVIID-19 vaccines related ICSRs collected, 885,216 (61%) originated from the EEA.
- ***Screening for, and review of, potential signals***. In 2022, EMA's signal management team reviewed in detail 1,605 potential signals[2], including 230 from enhanced COVID-19 vaccine monitoring, for 1,333 centrally authorised products (CAPs) from screening the EudraVigilance database and other sources (a 12% overall decrease versus 2021). In addition 405 vaccine Targeted Medical Events (vTMEs), a list of adverse reactions of special interest that are continuously monitored for COVID-19 vaccines, were reviewed in 2022. For active substances of nationally authorised products (NAPs), the monitoring of ADR reports is shared between the NCAs. A Lead Member State (LMS) is currently appointed for monitoring safety data of 1,873 active substances. NCAs also monitor all medicines authorised nationally in their country for which no LMS has been appointed.
- ***Supporting the central role of the PRAC in assessing and monitoring the safety of human vaccines and medicines in the EU***. All detected and validated signals which are confirmed by a Rapporteur or LMS are brought to the attention of the PRAC for initial analysis, prioritisation and assessment. In 2022, the PRAC prioritised and assessed 64 confirmed signals (a 26% decrease versus 2021), with 86% of them based on review of EudraVigilance data. Of the 64 confirmed signals, 39 were validated by the Agency and 25 were validated by the Member States (MSs); 49 were for CAPs, 8 for NAPs and 7 for both CAPs and NAPs. Of the signals assessed by the PRAC, 25% were related to COVID-19 vaccines (same as in 2021).
- ***Transparency and public access to aggregated EudraVigilance data***. By the end of 2022, the *European database of suspect adverse drug reactions reports* included information on 4,310 active substances, of which 900 were contained in CAPs and 3,410 in NAPs. This included timely and transparent provision of data on the authorised COVID-19 vaccines.
- ***Enhanced communications.*** Safety updates for the COVID-19 vaccines were published on a monthly basis until the end of 2022. Full assessment reports for signals of public health interest continued to be published. Regular stakeholder meetings for the public and press briefings were convened to keep the public informed on the latest COVID-19 developments and how the European regulatory system is working to protect public health.
- ***Training and support activities***. Extensive training offerings are available online as e-learning for all stakeholders and training for the EU network is available through the EU Network Training Centre[3].

[2] A signal refers to information on one or more observed adverse reactions potentially caused by a medicine and that warrant further investigation

[3] https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance/eudravigilance-training-support

2. Operation of EudraVigilance including its further development

EudraVigilance is a central pillar for pharmacovigilance activities in the EEA. The system enables the effective monitoring of suspected adverse reactions and detection of risks related to medicines and it is therefore a major contributor to the protection and promotion of public health. EudraVigilance also facilitates the reporting of suspected unexpected serious adverse reactions (SUSARs) that occur during clinical trials with investigational medicinal products.

EudraVigilance is maintained by EMA on behalf of the EU medicines regulatory network. Previous annual reports have highlighted the major enhancements of the system that was launched on 22 November 2017 and the benefits in terms of simplified reporting, data access, analysis tools, quality and scalability of the system.

The key activities undertaken in 2022 are summarised here:

EMA launched in the EudraVigilance Data Analysis System (EVDAS) a new Clinical Trials Monitoring dashboard in order to enable the assessing Member States to perform the tasks related to the SUSAR screening and assessment in EudraVigilance. This allowed implementation of the requirements established by the Commission Implementing Regulation (EU) 2022/20 of 7 January 2022 laying down rules for the application of Regulation (EU) No 536/2014 of the European Parliament and of the Council in relation to the cooperation between Member States in the safety assessment of clinical trial. Together with the launch of the EVDAS dashboard, EMA created a step-by-step training manual where the tools and the data outputs are fully described.

To support the implementation of the new Clinical Trials legislation, and more specifically the SUSAR screening and assessment, EMA organised a training webinar on the use of the Clinical Trials Monitoring EVDAS dashboard in January 2022. The webinar was attended by 89 people from the Member States and it was recorded. The online course is available in the EU Network Training Centre for future training needs.

With the application of the new Clinical Trial regulation (Reg (EU) No 536/2014), and to facilitate the forwarding of SUSARs from the EudraVigilance Clinical Trials Module (EVCTM) to the Member States concerned, SUSAR re-routing functionality in EudraVigilance was implemented on 31 January 2022.

Following a PRAC recommendation in October 2019 and the confirmation and announcement by EMA's Management Board in December 2019, the following International Standards Organisation (ISO) Standards have been mandatory from 30 June 2022:

- the ISO ICSR Standard, as referred to in Article 26(2)(a) of the Commission Implementing Regulation (EU) No 520/2012, and the modalities on how to use this ISO ICSR Standard defined in the ICH Guideline 'Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports', revision 3 (E2B(R3)) documentation;
- the ISO terminology on pharmaceutical dose forms and routes of administration referred to in Article 25(1)(f) of Commission Implementing Regulation (EU) No 520/2012.

The revision of the EU ICSR Implementation guide supporting the implementation of the above ISO Standards had taken place in March 2021. Moreover, EMA published in February 2022, with an update in May 2022, a change management plan and a guideline to import European Directorate for the Quality of Medicines and HealthCare (EDQM) terms from EMA SPOR RMS. In 2022, EMA has supported stakeholders to ensure their readiness in achieving this important milestone.

Using the internationally agreed ICSR Standards in format and terminology is a major step towards strengthening data quality and analytical capabilities in EudraVigilance.

With regards to data protection, EMA, in collaboration with the European Commission and the Member States, developed and published the Joint Controllership Arrangement With regard to EudraVigilance Human. This Arrangement sets out the allocation of respective roles, responsibilities and practical arrangements between the Parties for compliance with their data protection obligations under Regulation (EU) 2018/1725 and Regulation (EU) 2016/679, respectively, when carrying out processing operations of personal data of data subjects collected as part of the use of EV.

As defined in the Pharmacovigilance Plan of the EU Regulatory Network for COVID-19 Vaccines issued in 2020, EudraVigilance has continued to play a crucial role during 2022 in facilitating the early detection of emerging risks with the COVID-19 vaccines and therapeutics.

The Detailed guidance on ICSRs in the context of COVID-19 was updated in 2022 to incorporate detailed guidance clarifying the recording in ICSRs of vaccine dose-schedule received by patients and facilitating the distinction of reactions linked to mixed vaccines administration. Recommendations are also provided for the coding of lack-of-therapeutic-efficacy notification referring to COVID-19 vaccines and for the management of cases when no information is available on the specific COVID-19 vaccine received by patients.

With the authorisation of the adapted bi-valent mRNA COVID-19 vaccines in 2022, EMA engaged with the Member States and the concerned Marketing Authorisation Holders (MAHs) to agree on a naming convention for the active substances to be used within the submission of ICSRs. This allows allocation of the ICSRs to the correct vaccines and will therefore differentiate the submission of cases for the adapted vaccines versus the original ones, enhancing the safety surveillance for the different vaccines available on the EU market.

A dedicated COVID-19 EVDAS dashboard, available to NCAs and EMA to support the monitoring of ADR reports related to COVID-19 vaccines, was updated to include the new vaccines and safety topics to be closely monitored. This dashboard was updated several times in 2022 to accommodate business needs, including the monitoring of signals together with the transparency and communication activities.

EMA, via a contractor's agreement, during 2022 undertook the task to enter and submit to EudraVigilance cases related to the COVID-19 vaccines reported to the NCAs by patients and healthcare professionals. In this way EMA supported Member States with the unprecedented number of cases reported in the context of the COVID-19 pandemic.

Following the May 2022 outbreak of mpox virus (formerly known as monkeypox) in several non-endemic countries, including throughout Europe and in North America, without known epidemiological links to endemic areas, EMA issued a Note for guidance to the NCAs regarding the management of adverse reactions associated with the vaccines used in EU MSs to prevent mpox disease. Moreover, EMA engaged with the concerned MAH to remind them of their reporting obligation for suspected ADRs from within and outside the EU and the EudraVigilance downloading options available to record EU cases from NCAs in their pharmacovigilance system to fulfil their pharmacovigilance obligations.

Similar to the COVID-19 vaccines, EMA created a dedicated EVDAS dashboard available to NCAs and EMA to support monitoring of the ADR reports related to the mpox vaccines.

The departure of the United Kingdom (UK) from the EU had consequences on the operation of EudraVigilance. The implementation of Brexit in the database took place from 1 January 2021,

including the implementation of the Northern Ireland protocol as determined in the Notice to Stakeholders on the Withdrawal of the United Kingdom and EU rules for medicinal products for human use and veterinary medicinal products published on 13 March 2020. The relevant changes include, amongst others, the categorisation of UK cases as non-EEA cases from 1 January 2021 and the possibility to use the country code 'XI' to identify the cases from Northern Ireland within the UK, thus facilitating the ICSR reporting requirements. Cases with country code 'XI' are considered EEA cases in the database.
During 2022, it has been observed that some MAHs have obtained old (pre-2021) master cases with Great Britain as country of origin from the from the EudraVigilance web interface (EVWEB) Level 2A downloads. Those cases have then been transmitted by the MAHs to the UK regulatory authority, who have made them available to other MAHs, who have then retransmitted the cases back to EudraVigilance. This created a series of duplicates and therefore it was decided to remove all Great Britain cases from the EVWEB Level 2A downloads to prevent MAHs accessing old Great Britain master cases. Discussions with the UK regulatory authority on this have taken place and the strategy has been discussed at the EudraVigilance Expert Working Group.

The EudraVigilance gateway software (Gateway for the Electronic Standards for the Transfer of Regulatory Information (ESTRI) was upgraded in 2022. The update was done first in the EudraVigilance test system (XCOMP) in order to enable organisations to test the connection and then followed by the upgrade in the production environment.

Within the Medical Literature Monitoring (MLM) service, a new contract was signed with the service provider in May 2022, following the call for service launched in 2021. Moreover, EMA has continued reviewing the results and the corrective and preventive actions of the audit performed in 2021, and relevant measures have been put in place. EMA, together with the service provider, has also reviewed the results of the satisfaction surveys conducted every six months. These surveys provide MAHs with an opportunity to express their views, opinions and perceptions about EMA's MLM Service.

Data management activities have been carried out as described in the guide on EudraVigilance data management activities by the European Medicines Agency.

EMA has continued providing the monthly publication of spreadsheets with information on nullified ICSRs to facilitate case reconciliation by NCAs and MAHs.

In May 2022, EMA permitted the possibility for MAHs to increase the number of EVDAS users from five to ten. This was made possible following technical improvements, system performances and stress tests to guarantee the functioning of EVDAS for all the users. An announcement on this measure was issued to all the EU Qualified Persons responsible for Pharmacovigilance (QPPVs).

EMA and the European Commission (EC) extended until the end of 2023 the pilot for the obligation and transitional arrangements regarding monitoring of EudraVigilance by MAHs. The EC had launched a targeted stakeholder consultation on the Commission Implementing Regulation 52/2012 on pharmacovigilance activities, seeking feedback on the proposed amendments, including MAH requirements for EudraVigilance monitoring. The deadline for the consultation was 15 October 2021. Further announcements by the EC on this topic are awaited.

The EudraVigilance Expert Working group (EV-EWG) met twice in 2022, on 23 March and 11 October. Moreover, a new work programme for the EV-EWG, covering the period 2023-2024, is expected to be published at the beginning of 2023. EMA-MSs Pharmacovigilance Business team met regularly to discuss, agree on and issue guidance for the different EudraVigilance operations.

During 2022, EMA has been working on the technical and testing aspects for the monthly provision of compliance reports, for the purpose of monitoring of ICSR submission time frames to all EudraVigilance-registered organisations. These reports are expected to go live in 2023.

EMA has continued working on the Signal and Safety Analytics project, with the objective of reviewing the EudraVigilance data analytics platform and tools in order to enable the Agency and the Network to more effectively and efficiently deliver evidence from data-driven interrogation of ADR reports.

The EudraVigilance training page has been updated to launch the training on the enhanced EudraVigilance system and the training course for clinical trial sponsors, which will be available in 2023.

3. Data collection and data quality

Medicinal product information

In the database of all medicinal products authorised in the EU (the "Article 57 database"), the total number of medicinal product entries by MAHs in the eXtended EudraVigilance Medicinal Product Dictionary (XEVMPD) was 998,060 as of 31 December 2022, regardless of authorisation status (e.g. valid, withdrawn). These entries relate to both medicines authorised through the centralised procedure and those authorised via national procedures. These data are a very important public health resource, as they allow for better identification of medicines in reports of suspected ADRs, better coordination of safety monitoring, faster implementation of new safety warnings and improved communication with stakeholders. The dataset also includes information on the location of the Pharmacovigilance System Master File (PSMF). Full details on these items are presented in Annex III.

Reporting of ADRs and patient involvement

Every report of a suspected ADR by a patient or healthcare professional contributes to safety monitoring and thus to the safe and effective use of medicines. Additionally, robust research[4] has demonstrated that collating reports into big datasets and using statistical analyses of the data allows safety issues to be detected, and therefore dealt with, more rapidly. In this context, the reporting of suspected ADRs into EudraVigilance underpins the operation of the EU pharmacovigilance system.

In 2022, 2,908,262 ICSRs were collected and managed in EudraVigilance. This figure represents a 18% decrease compared to the numbers recorded in 2021, and is characterised by a marked decrease in EEA reports (-17%) and in non-serious reporting (-23%). A large proportion of the reports were related to COVID-19 vaccines, which accounted for 39% (1,140,583) of all the ICSRs, and 61% (885,216) of the ICSRs originating in the EEA.

The number of reports submitted directly by patients and consumers through the NCAs and MAHs (647,393) saw a 17% decrease compared to the previous year. However, the number submitted in 2022 was still substantially above the yearly average in terms of patient reporting, as 2021 showed an unprecedented increase in reporting due to the authorisation and roll-out of the first COVID-19 vaccines (See Figure 2). In 2022, reports associated with COVID-19 vaccines accounted for 85% (551,716) of the reports submitted directly by patients and consumers through the NCAs and MAHs in 2022.

[4] Alvarez Y et al. Validation of statistical signal detection procedures in EudraVigilance post-authorization data: a retrospective evaluation of the potential for earlier signalling. Drug Saf. 2010; 33(6):475-487.

Detailed information relating to these figures is provided in Annex II.

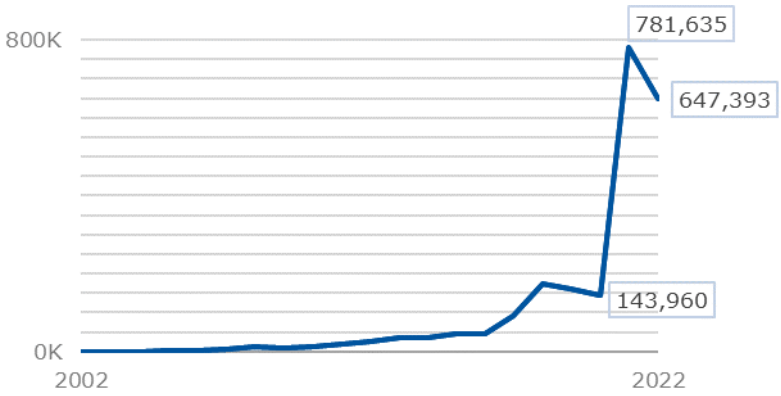


Figure 2. Trend of ADR reports from patients and consumers received in the EEA by NCAs and MAHs and reported to EudraVigilance.

EudraVigilance also continued to support the reporting of SUSARs that occurred during clinical trials, in accordance with EU clinical trial legislation[5] (see Annex II).

Data Quality

Data quality assurance is vital to support pharmacovigilance and provides the basis for successful data analysis, scientific assessment and decision making to protect public health. This is a shared responsibility between EMA, NCAs and MAHs. In accordance with the pharmacovigilance legislation, EMA operates procedures that ensure the quality and integrity of data collected in EudraVigilance. These include providing guidance and training, providing business rules for data entry, ensuring the correct identification of medicinal products associated with reported adverse reactions, removing duplicate reports, ensuring timely submission of serious and non-serious adverse reactions, adhering to coding practices and standards, and adequately documenting cases.

In addition to the above-mentioned provisions, the Agency's efforts to improve data quality include providing feedback to individual reporting organisations concerning ICSRs, performing data quality reviews of XEVMPD submissions and conducting a classification of adverse reaction reports utilising the medicinal product data of the XEVMPD. These activities are summarised in Annex IV.

4. Data analysis

EMA's pharmacovigilance system has been efficient in detecting issues and dealing with them. For example, the EU was at the forefront in dealing with the signal of menstrual disorders associated with COVID-19 mRNA vaccines and EudraVigilance analysis was central to the assessment. The PRAC has recommended that heavy menstrual bleeding should be added to the Spikevax and Comirnaty product information as a side effect of unknown frequency. The network also identified and mitigated the risk for renal tubular acidosis and hypokalaemia with codeine/ibuprofen, issuing key messages that national competent authorities can use when drafting their communication to relevant healthcare professionals and informing patients of signs of abuse and dependence and risks of serious harm. The PRAC also

[5] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

considered that prescription-only medicine status would be the most effective risk minimisation measure to mitigate the harm associated with abuse and dependence of these products.

EudraVigilance data monitoring is a collaborative effort between NCAs and EMA and, since February 2018, MAHs (as part of the signal management pilot). The safety information contained in EudraVigilance is continuously screened through statistical reports called electronic Reaction Monitoring Reports (eRMRs). In 2022, over 23,000 individual eRMRs were generated for NCAs and EMA's signal management team. These were produced every two weeks for medicinal products subject to additional monitoring and monthly, three-monthly or six-monthly for other products. The frequency of eRMR generation was changed in the third quarter of 2022, moving to less frequent monitoring: monthly (instead of every two weeks) for medicinal products subject to additional monitoring and 3-monthly (instead of every month) for routinely monitored products.

In 2021, eRMRs were produced weekly for the authorised COVID-19 vaccines to support the enhanced monitoring pandemic plan. With more experience gained with COVID-19 vaccine safety, monitoring frequency was changed from weekly monitoring to bi-weekly and finally, in the third quarter of 2022, to monthly. Additional analyses continued to be performed in EVDAS, including screening of line listings and disproportionality and subgroup analyses.

Screening of these outputs is one of the principal sources of validated signals, i.e. information on observed ADRs potentially caused by a medicine that warrant further investigation. For CAPs, EMA leads this monitoring: 1,605 potential signals were reviewed by the Agency in 2022, including 230 relating to COVID-19 vaccines and 1,375 relating to other products (see Annex V for further breakdown). In 2022, the number of vTMEs reviewed for COVID-19 vaccines on an ongoing basis was 405.

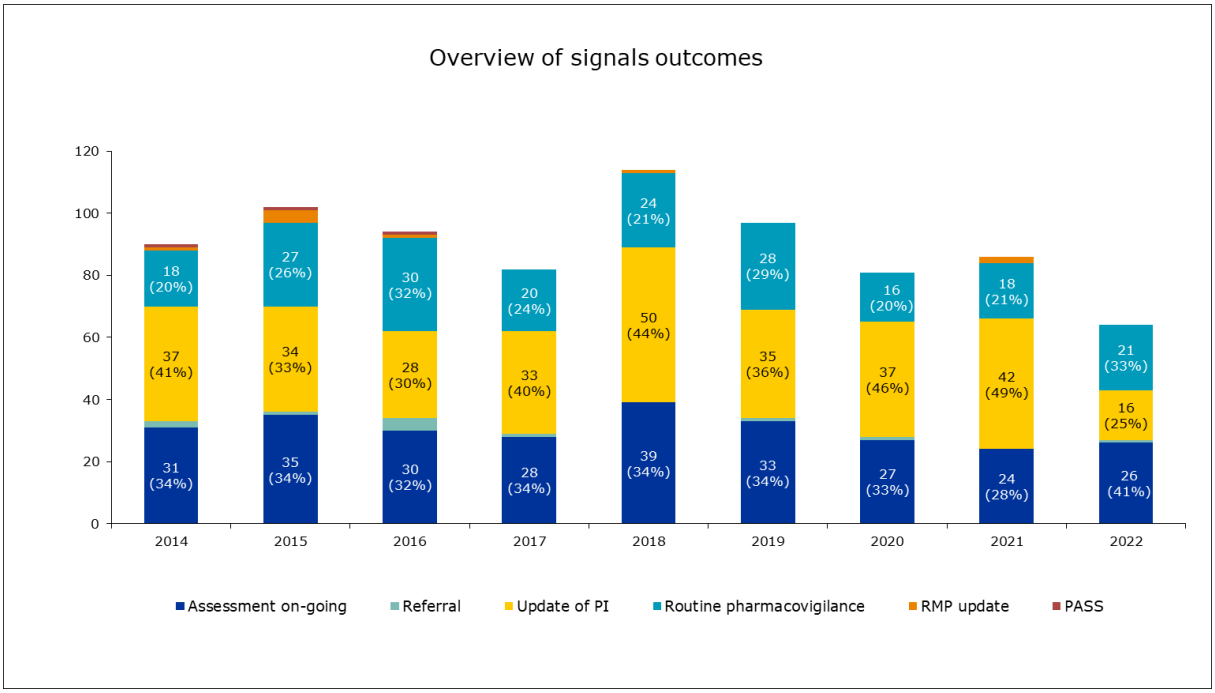
For active substances contained in NAPs, the monitoring of ADR reports in EudraVigilance and in national databases is shared between the NCAs, in line with the 'List of substances and products subject to worksharing for signal management'[6] which defines a LMS for each active substance included. The list was updated in 2022, following changes in Periodic Safety Update Single Assessment (PSUSA) leadership and in marketing authorisation status. It currently includes 1,873 active substances. NCAs also monitor all medicines authorised nationally in their country for which no LMS has been appointed.

All detected and validated signals which are confirmed by the Rapporteur or LMS are brought to the attention of the PRAC for initial analysis, prioritisation and assessment. In 2022, the PRAC prioritised and assessed 64 confirmed signals (a 26% decrease compared to 2021, see Figure 3).

Of the 64 signals assessed by the PRAC, 55 (86%) included data from EudraVigilance. Sixteen signals (25%) resulted in a recommendation to update the product information for patients and healthcare professionals, thus providing updated guidance on the safe and effective use of the medicines. For 21 signals (33%) continuing with routine safety monitoring of the medicine was considered sufficient. The evaluation of 26 signals (41%) is ongoing in 2022, including 16 via a follow-up signal procedure and 10 in upcoming PSURs/PSUSAs. One signal resulted in a referral procedure; no signals resulted in Post-Authorisation Safety Studies (PASS).

[6] http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500226389

Figure 3. Overview of signals assessed by the PRAC



Of the 64 signals assessed by the PRAC in 2022, 16 (25%) were related to COVID-19 vaccines. Eight of these signals were raised by EMA and eight by MSs. This included signals of high public interest, such heavy menstrual bleeding reported following use of mRNA vaccines[7] (November 2022). EudraVigilance monitoring thus facilitated early detection and timely assessment of new ADRs or new aspects of already known ADRs (such as changes in their frequency or severity). This, in turn, resulted in prompt warnings and advice to prescribers and patients. Further details on all signals assessed by the PRAC in 2022 can be found in Annex V. The progress of process improvements and simplifications in signal management is detailed in Annex VI.

A pilot is on-going whereby MAHs of selected active substances[8] must monitor them in EudraVigilance and inform EMA and NCAs of validated signals with their medicines[9]. As of December 2022, the Network had received 52 standalone signal notifications from MAHs. Of these, 11 signals were considered valid and processed accordingly, ultimately leading to 1 signal being confirmed for evaluation by the PRAC (no new signals were confirmed in 2022). All other MAHs also have access to cases for their medicinal products and therefore can integrate EudraVigilance data into their own signal management processes. In July 2022, the European Commission decided to further extend the pilot until the end of 2023, pending the update of the Commission Implementing Regulation[10] based on the experience gained with the pilot.

[7] https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/covid-19-vaccines-safety-update-10-november-2022_en.pdf
[8]Based on all active substances and combinations that were included in the list of medicinal products subject to additional monitoring as of 25 October 2017 (Rev. 49). https://www.ema.europa.eu/documents/other/list-active-substances-involved-pilot-signal-detection-eudravigilance-marketing-authorisation_en.xls
[9] https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:159:0005:0025:EN:PDF
[10] Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council Text with EEA relevance

5. Transparency, communication and training.

Safety updates for the COVID-19 vaccines, as well as full assessment reports for signals of public health interest, were published on a monthly basis. EMA has now ceased the publication of monthly safety updates for COVID-19 vaccines with the last safety update being for December 2022. The wide uptake of COVID-19 vaccines in immunisation programmes during the pandemic led to a rapid accumulation of extensive safety data from spontaneous reports of suspected ADRs. Since the first vaccines were authorised in December 2020, EMA's monthly safety updates have provided information on the assessment of these reports and data from other sources. The majority of the EU population has now received at least one COVID-19 vaccine[11] and data from clinical trials, other studies and spontaneous reporting have established the safety profiles of these vaccines.

As for all medicines authorised in the EU, monitoring and timely assessment of emerging safety data will continue for the COVID-19 vaccines. If there are any major safety-related changes to the existing product information for any COVID-19 vaccine, these will be communicated in the PRAC highlights, together with dedicated public health communications as needed. For each vaccine, all identified side effects are listed in the relevant product information in all the languages of the EU/EEA (see section 1). High-level information on suspected ADR reports will continue to be updated monthly on EMA's webpage on COVID-19 vaccines. The European database of suspected drug reaction reports (https://www.adrreports.eu/) will continue to be updated weekly.

Stakeholder meetings for the public and regular press briefings were convened to keep the public informed on the latest COVID-19 developments and how the European regulatory system is working to protect public health. PRAC agendas, minutes and signal recommendations, including translations into all official EU languages of PRAC recommendations for changes to the product information following signal assessments, continued to be published every month on the EMA website. These efforts have supported transparency and public trust in the work of the Agency and have allowed for better and faster updates to product information.

Public access to aggregated EudraVigilance data has been available since 2012 via aggregated reports available in the European database of suspect adverse drug reactions reports (www.adrreports.eu) and was further improved in November 2017 by providing additional outputs, such as line listings and ICRS forms. By the end of 2022, the website provided information on a total of 4,310 active substances, of which 900 were contained in CAPs and 3,410 in NAPs. ADR data was also available to the general public on ten COVID-19 vaccines.

The Agency has also continued responding to requests for information from EudraVigilance or access to EudraVigilance documents, in line with the current EudraVigilance Access Policy. In total, 29 requests were answered (11 fewer than in 2021) within a median of 16 working days for external requests. Of these 29 requests, 13 (45%) were received from the EU regulatory network, supporting the scientific assessment of pharmacovigilance procedures, and the remaining 16 (55%) were from external requesters. There were no requests from journalists in 2022, whilst EMA had received 11 such requests in 2021. More details are provided in Annex VII.

In addition to the requests linked to the EudraVigilance Access Policy, EMA received a high number of queries from the public in relation to ADR data on COVID-19 vaccines available in the public database. In response to the high demand for information from the public, EMA regularly publishes aggregated data from EudraVigilance on the EMA website in order to provide key data on COVID-19 vaccines in a public friendly manner and combat misinformation circulating online.

[11] The European Centre for Disease Prevention and Control (ECDC) collects these exposure data from EU Member States as well as from the additional countries of the European Economic Area (EEA) Norway, Iceland and Liechtenstein.

The Agency organised several trainings, operational and technical support activities, many of which were open to all stakeholders.

- 11 training sessions on EudraVigilance ICSR submissions (all virtual), with 235 users trained in total (https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance/eudravigilance-training-support#virtual-live-hands-on-training-course-on-enhanced-eudravigilance-system-section)
- 4 training sessions on EudraVigilance ICSR submissions for clinical trial sponsors (all virtual), with 58 users trained in total (https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance/eudravigilance-training-support#virtual-live-hands-on-training-course-for-clinical-trial-sponsors-section)
- 1 virtual webinar on EVDAS clinical trials monitoring dashboard (Screening and assessment of SUSARs from interventional clinical trials) with 89 people attending.
- PRAC assessors training took place in November 2022 and was focussed on pharmacovigilance assessments. Over 300 assessors registered for the event.
- 9 XEVMPD-related training sessions have taken place virtually in 2022 and 155 users were trained.
- 127 participants followed the XEVMPD training via the dedicated e-learning platform in 2022.
- No EudraVigilance or Signal Management Information Days took place in 2022.

6. Conclusion

EudraVigilance has continued to play a crucial role during 2022 and it remains a central pillar for pharmacovigilance activities in the EEA. It played a critical role in facilitating the early detection, management and mitigation of emerging risks related to authorised COVID-19 vaccines (including signals of high public health importance such as heavy menstrual bleeding).

In 2022, 2.9 million ICSRs were collected and managed in EudraVigilance, a 18% decrease compared to the previous year. However, reporting to EudraVigilance in 2021 was the highest annual total ever recorded, mainly driven by COVID-19 vaccine reports. The number of ICSR reports received in 2022 was still substantially above the yearly average. As in 2021, a large proportion of the reports were related to COVID-19 vaccines, which accounted for 39% (1,14 million) of all the ICSRs, and more than half of them originated in the EEA. Based on these reports, over 23,000 statistical outputs were produced and screened for the identification of signals which were subsequently assessed by the PRAC. Almost 25% of signals discussed at PRAC related to COVID-19 vaccines (the same as in 2021).

EudraVigilance currently contains over 25.3 million ICSRs, corresponding to 14.8 million unique suspected ADR case reports. It is being used by EMA, EU NCAs and MAHs, and plays a key role in global surveillance, with over 1.7 million individual cases (or 1,479,328 ADR reports) forwarded to the World Health Organization (WHO) database in 2022.

Significant enhancements implemented in the database in previous years are now in routine operation and several new improvements were implemented in 2022. To support the implementation of the new clinical trials legislation, EMA launched a new Clinical Trials Monitoring EVDAS dashboard in order to enable the assessing MSs to perform tasks related to the SUSAR screening and assessment in EudraVigilance. Functionality in EudraVigilance for SUSAR re-routing to MSs was available from 31 January 2022.

Following a PRAC recommendation and the confirmation by EMA Management Board in 2019, several ISO Standards have been mandatory from 30 June 2022. During 2022, EMA has supported stakeholders in this important milestone to ensure their readiness.

Many developments that were initiated in 2021 in relation to the COVID-19 pandemic were further updated in 2022. This included several updates to include the new vaccines and safety topics to a dedicated COVID-19 EVDAS dashboard available to NCAs and EMA. Similar to the COVID-19 vaccines, EMA created a dedicated EVDAS dashboard available to NCAs and EMA to support monitoring of the ADR reports related to the mpox vaccines following the outbreak of the mpox virus.

EMA undertook the task during 2022 to enter and submit to EudraVigilance cases reported by patients and healthcare professionals to the NCAs related to the COVID-19 vaccines. In this way EMA could support MSs with the unprecedented number of cases reported in the context of the COVID-19 pandemic.

The operation of EudraVigilance thus continues to contribute significantly to the protection of public health and the reduction of risks associated with the use of medicines and vaccines.

Annex I – Summary of EudraVigilance related activities

Implementation activities	Status
Operation and maintenance of EudraVigilance by EMA in collaboration with Member States. [*Legal basis:* Regulation (EC) 726/2004, Article 24]	New system operational since 22 November 2017. Maintenance continued.
Initiation of pilot for signals validated and notified by MAH based on EudraVigilance monitoring. [*Legal basis:* Commission Implementing Regulation (EU) 520/212, Article 18 and 21]	Started 22 February 2018. Continued during 2022.
Data quality review and duplicate management of adverse reaction reports in EudraVigilance. [*Legal basis:* Regulation (EC) 726/2004, Article 24(3)]	Continued during 2022.
Collection of core data set for all medicinal products authorised in the EU in EudraVigilance. [*Legal basis:* Regulation (EC) 726/2004 Article 57(2), second subparagraph]	Continued during 2022.
Providing all suspected adverse reaction reports occurring in the Union to the World Health Organization Uppsala Monitoring Centre (WHO-UMC) directly from EudraVigilance. [*Legal basis:* Regulation (EC) 726/2004 Article 28c(1), second subparagraph]	Continued during 2022.
Operation of the signal management processes based on EudraVigilance data, including the monthly provision of eRMRs to lead Member States for non-CAPs and provision of eRMRs to MAHs, as well as the production and review of eRMRs for CAPs by EMA. [*Legal basis:* Regulation (EC) 726/2004, Article 28a Directive 2001/83/EC, Article 107h Commission Implementing Regulation (EU) 520/212, Article 18(2), 18(3), 21 and 23]	Continued during 2022.
Access to adverse reaction data held in EudraVigilance for CAPs and certain substances included in NAPs http://www.adrreports.eu/ [*Legal basis:* Regulation (EC) 726/2004, Article 24]	Continued during 2022.
Operation of the Medical Literature Monitoring service [*Legal basis:* Regulation (EC) 726/2004, Article 27]	Continued during 2022.

Annex II – EudraVigilance data-processing network and number of suspected adverse reaction reports processed by the EudraVigilance database

EudraVigilance data-processing network (EudraVigilance Gateway)

The EudraVigilance data-processing network, as referred to in Article 24 of Regulation (EC) No. 726/2004, facilitates the electronic exchange of adverse drug reaction (ADR) reports between the Agency, national competent authorities (NCAs) and marketing authorisation holders (MAHs) for all medicines authorised in the European Economic Area (EEA). This network, known as the EudraVigilance gateway, has been in continuous operation since December 2001. On average the system was available 99.8% of the time throughout the year[12], exceeding the required 98% availability (see Figure 4).

Figure 4. EudraVigilance gateway availability per month. The requirement is 98%. Please note that the scale starts at 80%.

EudraVigilance database

For medicinal products authorised in the EEA, ADR reports are collected from both within and outside the EEA. Each individual case in EudraVigilance refers to a single patient; an individual case is composed of at least one ICSR (or ADR report), called the initial report, which might be complemented by follow-up reports with updated additional information on the case. These reports, both initial and follow-up, are known as individual case safety reports (ICSRs) or ADR reports.

By 31 December 2022, the EudraVigilance database held a total of 25,343,950 ICSRs, referring to 14,839,772 individual cases (Figure 5). The EudraVigilance post-authorisation module (EVPM) contained 23,666,070 ICSRs (14,380,894 individual cases) and the clinical trial module (EVCTM) contained 1,677,880 ICSRs (458,878 individual cases).

[12] Only unplanned downtime is taken into consideration

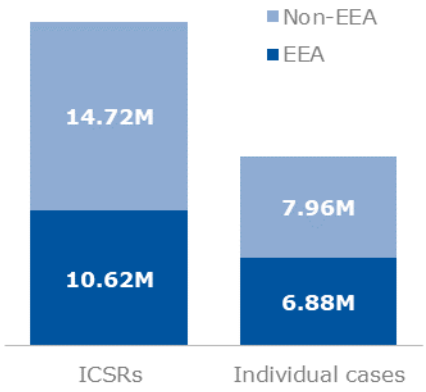


Figure 5. Number of ICSRs versus individual cases received in the EudraVigilance database from its inception in December 2001 until 31 December 2022, split by origin of the report (in- or outside the EEA).

Figure 6 presents the number of ICSRs processed per year in EVPM split by cases occurred inside and outside the EEA. Figure 7 presents the total number of ICSRs received in EVPM for 2022, compared to the number of individual cases they are referring to.

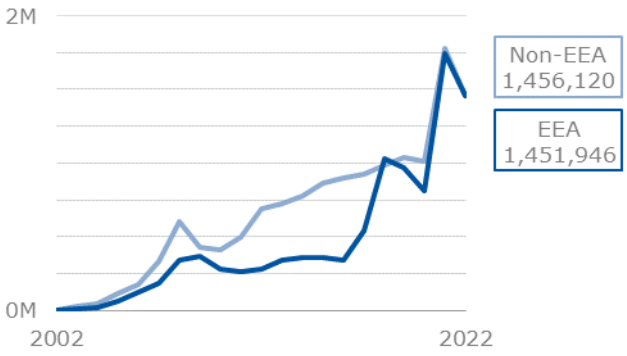


Figure 6. Number of ICSRs processed per year in EVPM split by cases occurred inside and outside the EEA.[13]

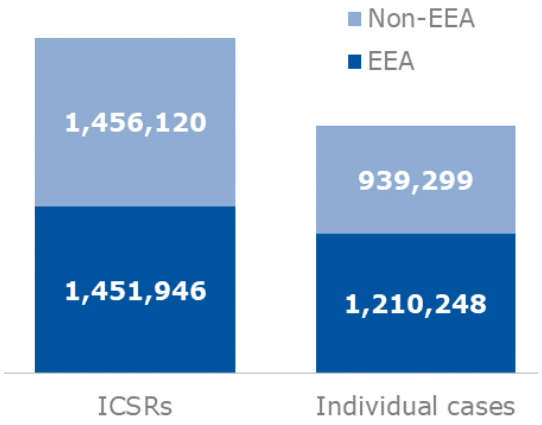


Figure 7. Number of ICSRs versus the number of individual cases in 2022 in EVPM.

The numbers presented in Figures 8 and 9 refer to the ICSRs received in EVPM. A total of 23,666,070 EVPM ICSRs have been processed over the years up to the end of 2022, of which 2,908,262 EVPM ICSRs were processed in 2022. This represents a 18% decrease compared to the numbers recorded in 2021, and it is characterised by a decrease in EEA (-17%, Figure 6) and non-serious (-23%) reporting. ICSRs are subsequently made available for signal detection and data analysis by the Agency and NCAs in the Member States.

[13] Non-serious EEA ADR reports need to be submitted only since November 2017.

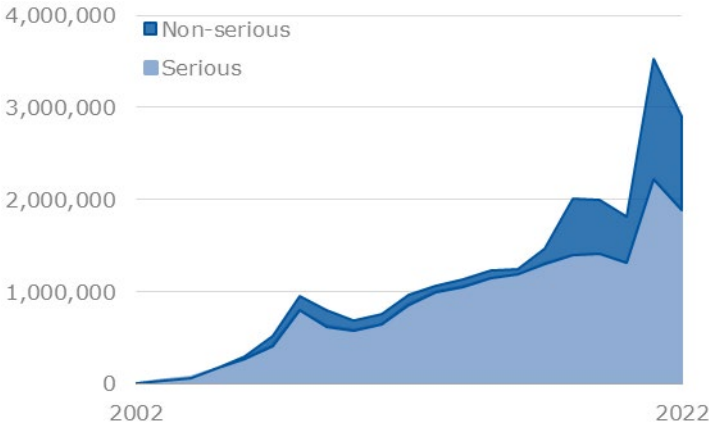


Figure 8. Number of ICSRs processed per year in EVPM.

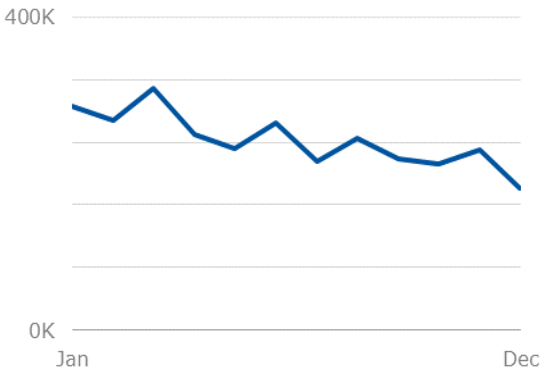


Figure 9. Number of ICSRs processed per month in EVPM in 2022.

In 2022, 647,393 ICSRs were submitted by European patients and consumers through the NCAs and MAHs, referring to 580,669 individual cases. This is a decrease of 17% in the number of such reports compared to the previous year (Figure 10), but still more than in pre-pandemic years. A significant proportion of these reports continues to be related to COVID-19 vaccines, which account for 87% of the individual cases (Table 1). The mandatory reporting of non-serious EEA cases to EudraVigilance since November 2017 has been a key driver of the overall increased patient reporting observed in the past 5 years.

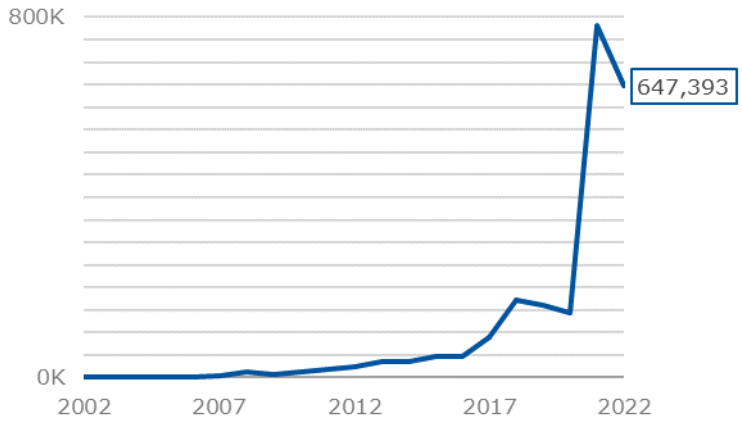


Figure 10. Number of ICSRs by European patients and consumers through the NCAs and MAHs.

Table 1. Number of EVPM ICSRs and unique cases transmitted in 2022 related to or excluding COVID-19 vaccines. Counts for 2021 are provided for comparison.

	2022			2021
	Total count	**Count related to COVID-19 vaccines**	**Count excluding COVID-19 vaccines**	**Total count**
ICSRs processed	2,908,262	1,140,599 (39%)	1,767,663 (61%)	3,525,975
ICSRs originated in EEA	1,451,946	885,216 (61%)	566,730 (39%)	1,743,238
Non-serious ICSRs	1,016,397	639,970 (63%)	376,427 (37%)	1,312,952
ICSRs submitted by European patients and consumers through the NCAs and MAHs	647,393	551,716 (85%)	95,677 (15%)	781,632
Individual cases submitted by European patients and consumers through the NCAs and MAHs	580,669	503,834 (87%)	76,835 (13%)	672,932

E-reporting status for MAHs and sponsors of clinical trials

- 1,906 MAHs (at headquarter level) have sent reports to EVPM in 2022, a 2% decrease compared to 2021.
- 655 sponsors of clinical trials (at headquarter level) have sent reports to EVCTM in 2022, a 8% increase compared to 2021.
- A total of 20,219 individual MAH users and 10,698 sponsors of clinical trials are registered in EudraVigilance.

Table 2 below shows the total number of individual cases and ICSRs transmitted by MAHs and sponsors to EVPM and EVCTM and Figure 11 shows the 15-day and 90-day reporting compliance of MAHs when reporting to EVPM.

15-day reporting compliance is calculated by subtracting the date the ICSR was received by the EudraVigilance Gateway (EV Message Gateway Date) from the date of receipt of the most recent information (Receipt Date – ICH E2B(R2) A.1.7/E2B(R3) C.1.5). The receipt date is treated as day 0, giving the MAH 15 days from that day to transmit the reports.

Nullification, amendment and error reports are excluded from the compliance calculations.

In 2022, 304,706 ICSRs and 88,882 SUSARs (total 393,588) were rerouted to NCAs following receipt of the reports from MAHs and Sponsors in EudraVigilance. 1,479,328 ICSRs were forwarded to WHO. A total of 197,066 download requests were made by MAHs, resulting in 6,608,929 ICSRs downloaded from the EudraVigilance database.

Table 2. Number of ICSRs and unique cases transmitted by MAHs and sponsors to EVPM and EVCTM in 2022

EV Module	Transmission type	Count
EVPM	ICSRs	1,860,032
	Individual cases	1,154,439
EVCTM	ICSRs	133,624
	Individual cases	38,957

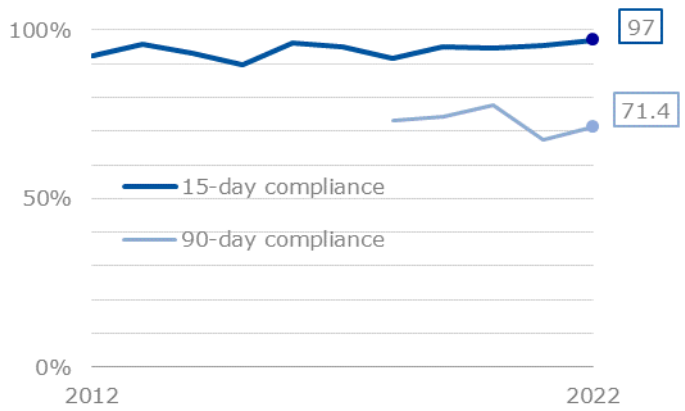


Figure 11. Compliance rate for serious (15-days) and non-serious (90-days) ICSRs to EVPM for all MAHs and sponsors by year. Non-serious ICSRs need to be submitted only since November 2017.

E-reporting status for NCAs

- All NCAs in the EEA are authorised to transmit safety reports to EudraVigilance.
- All NCAs reported ICSRs to EVPM, except for Liechtenstein; all ICSRs occurring in Liechtenstein are transmitted to EudraVigilance by MAHs. A total of 1,435 individual NCA users are registered in EudraVigilance.

Table 3 below shows the total number of individual cases and ICSRs transmitted by NCAs to EVPM and EVCTM and Figure 12 shows 15-day reporting compliance of NCAs when reporting serious cases to EVPM and 90-day reporting compliance for non-serious cases.

15-day reporting compliance is calculated by subtracting the date the ICSR was received by the EudraVigilance Gateway (EV Message Gateway Date) from the date of receipt of the most recent information (Receipt Date – ICH E2B(R2) A.1.7/E2B(R3) C.1.5). The receipt date is treated as day 0, giving the NCA 15 days following that day to transmit the reports. Nullification, amendment and error reports are excluded from the compliance calculations.

Table 3. Number of ICSRs and unique cases transmitted by NCAs to EVPM and EVCTM during 2022

EV Module	Transmission type	Count
EVPM	ICSRs	1,048,230
	Individual cases	995,164
EVCTM	ICSRs	630
	Individual cases	1,858

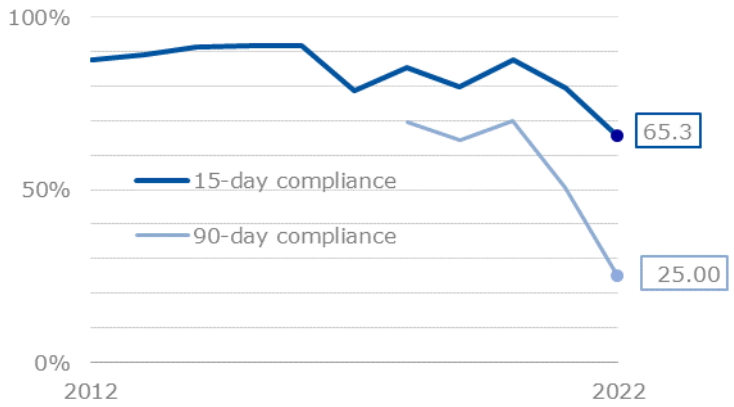


Figure 12. Compliance rate for serious (15-days) and non-serious (90-days) ICSRs to EVPM for all NCAs by year. Non-serious ICSRs need to be submitted only since November 2017.

During 2022, the following nine NCAs transmitted SUSARs to EVCTM (SUSARs from other countries were received directly from sponsors of clinical trials):

- Croatia (Agency for Medicinal Products and Medical Devices of Croatia)
- Denmark (Danish Medicines Agency)
- Germany (Federal Institute for Drugs and Medical Devices)
- Iceland (Icelandic Medicines Agency)
- Ireland (Health Products Regulatory Authority)
- Luxembourg (Le Ministère de la Santé Division de la Pharmacie et des Médicaments)
- Netherlands (Central Committee on Research Involving Human Subjects)
- Netherlands (Medicines Evaluation Board)
- Sweden (Medical Products Agency)

EudraVigilance database and support of signal management process

A total of 23,281 eRMRs were generated in 2022 to facilitate the continuous monitoring of the safety of medicines by the Agency and NCAs in the EEA. Of these,

- 10,704 were routine eRMRs, produced monthly
- 2,616 were 3-monthly eRMRs
- 1,481 were 6-monthly eRMRs
- 8,480 were additional eRMRs – produced fortnightly.

The frequency of eRMR was changed in the third quarter of 2022, moving to less frequent monitoring: monthly for medicinal products subject to additional monitoring (instead of every two weeks) and every 3 months for routinely monitored products (instead of monthly).

Annex III - Total number of medicinal product submissions by MAHs

In 2014, the Agency published an updated format for medicinal product information and updated the XEVMPD, in order to ensure that the database could meet the following objectives:

- facilitating data analysis and signal detection to support better safety monitoring for patients;
- provision of access to EudraVigilance data:
    - reactively in accordance with the revised EudraVigilance Access Policy,
    - proactively:
        - to MAHs to enable the performance of signal detection activities
        - to healthcare professionals and the public via the www.adrreports.eu website
- reliably identifying medicinal products that fall within the scope of the PSUR submissions and referral procedures;
- supporting literature monitoring activities;
- facilitating NCAs' inspections (e.g. sharing information on Pharmacovigilance Master File location);
- computing pharmacovigilance fees.

These data are validated by the Agency (see Annex IV for a summary of the validations performed in 2021). Table 4, below and Figures 13 and 14 provide a summary of the data submitted as of 04 January 2023.

Table 4. Summary of medicinal product submissions to the XEVMPD

Total number of medicinal product submissions by MAHs by 31 December 2022 in accordance with Article 57(2), second subparagraph of Regulation (EC) 726/2004	
Total number of medicinal product submissions (counted on the basis of EudraVigilance codes).	998,060
Total number of MAHs (legal entities) established in the EU (corresponding to EudraVigilance codes).	6,101

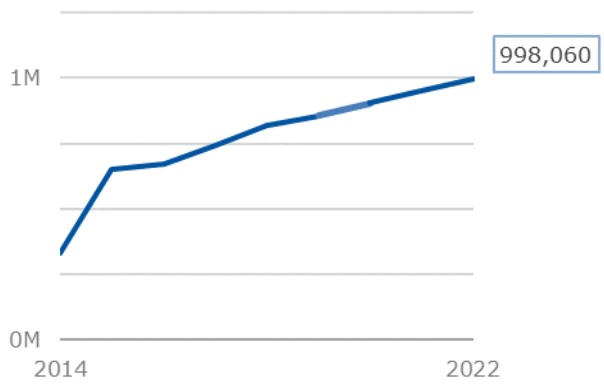


Figure 13. Total number of medicinal products (counted based on EudraVigilance codes) submitted (cumulative by year)

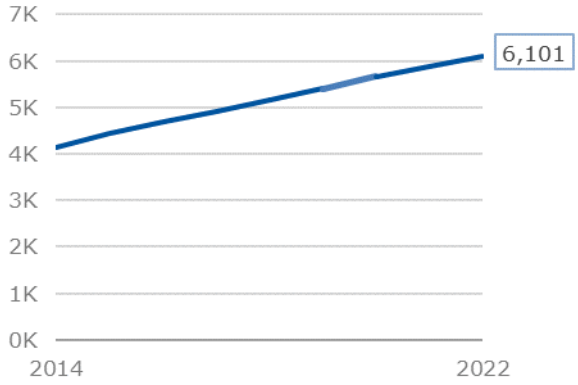


Figure 14. Total number of marketing authorisation holders (legal entities) established in the EU (corresponding to EudraVigilance codes) (cumulative by year)

The EudraVigilance code is the level to which a product is defined in the context of the XEVMPD.

It encompasses the following parameters:

- Name of the medicinal product;
- MAH;
- Authorising National Competent Authority;
- Country;
- Active ingredient(s);
- Strength(s);
- Pharmaceutical form;
- Authorisation number;
- Authorisation procedure;
- Pack size (only if Competent Authority assigns unique marketing authorisation number at package level).

Annex IV - EudraVigilance data quality activities

In accordance with Regulation (EC) No 726/2004, Article 24(3), the Agency operates procedures to ensure the quality and integrity of the information collected in EudraVigilance in collaboration with the EU medicines regulatory network. This includes identifying duplicate individual cases, performing the coding of the reported medicinal products and reported active substances, and providing feedback on the quality of both ADR reports and medicinal product information sent by NCAs, MAHs and sponsors. Table 5 below refers to the data quality activities performed by the Agency in 2022 and provides 2021 and 2020 data for comparison.

Table 5. Summary of EudraVigilance data quality activities in 2022

Data quality area	Activities performed	2022	2021	2020
Identifying and managing duplicate individual cases	Duplicate couples assessed	147,875	144,883	160,047
	Master reports generated based on duplicated data	41,728	81,360	85,168
Coding of reported medicines and active substances	Reported medicinal products and active substance terms recoded	147,054	1,068,728	54,366
	ADR reports recoded (ICSRs)	130,619	959,665	76,990
Providing feedback on data quality	Organisations subject to ICSR data quality review	32	119	120
	Medicinal products in XEVMPD quality reviewed (and corrected if necessary)	138,350	139,053	145,320

Annex V – Signal detection

Signal detection by EMA

A signal refers to information on one or more observed suspected adverse reactions potentially caused by a medicine and that warrant further investigation. In 2022, EMA's signal management team reviewed in detail the information on 1,605 potential signals (i.e. drug-event pairs from screening of the EudraVigilance database, medical literature or information received from other regulatory authorities). This figure includes 230 potential signals reviewed as part of the enhanced monitoring plan for COVID-19 vaccines, for which further details are provided below. This represents an approximately 12% decrease compared to the previous year (see Table 6). In addition to 1,605 potential signals, 405 vTMEs were reviewed for COVID-19 vaccines on an ongoing basis in 2022. Excluding potential signals associated with COVID-19 vaccines (new total, n=1,375) would result in a 7% drop in the number of potential signals reviewed compared to 2021.

Table 6. Potential signals reviewed

Potential signals reviewed	2022**	2021*	2020	2019	2018	2017	2016	2015
Total	1605**	1829*	1888	1,806	2,204	2,062	2,076	2,372
Change from previous year	-224	-59	+82	-398	+142	-14	-296	+342
% change from previous year	-12%	-3%	+4%	-18%	+7%	-1%	-12%	+17%

*1,485 signals which are not related to Covid-19 vaccines and 344 signals for Covid-19 vaccines (not including 648 vTMEs, was presented as cumulative total 2477 in 2021 annual report on EudraVigilance)
**1,375 signals which are not related to Covid-19 vaccines and 230 signals for Covid-19 vaccines (not including 405 vTMEs)

A specific monitoring strategy was created for COVID-19 vaccines in 2021 and this was followed in 2022 also, with some modifications. With more experience gained with vaccine safety, a dedicated vaccine eRMR was moved from weekly monitoring to bi-weekly and finally to monthly eRMR in the third quarter of 2022. Specifically for COVID-19 vaccines 230 signals were reviewed and a conclusion was reached by EMA's signal management team (344 in 2021): 151 from the eRMR, 42 from excel Validation Perpetual Report (eVPR) monitoring, 27 from literature monitoring, 4 from MS communications and 3 from other regulators and 3 as part of pregnancy monitoring (thus 83% of reviewed COVID-19 vaccine signals originating from EudraVigilance, however all other signals e.g. originating from literature, were also supported with EudraVigilance data). In addition to vaccine eRMRs, serious adverse events that are more likely to be vaccine related (vTME) are under constant monitoring for each vaccine in eVRP enabling in-stream review of every such new case report. Number of vTMEs continuously reviewed for COVID-19 vaccines on an ongoing basis in 2022 was 405 (648 in 2021).

For other products, EudraVigilance screening also continues to be the major source of EMA's potential signals with 83% of reviewed potential signals in 2022 originating from EV screening (compared to 89% in 2021). Scientific literature screening gave rise to 14.8% of potential signals in 2021 (9% in 2020). Additionally, cooperation with other regulatory authorities worldwide accounted for 1.5% of potential signals (1% in 2020), including notifications from World Health Organisation/Uppsala Monitoring Centre (WHO-UMC), United States Food and Drug Administration (FDA), Japan Pharmaceuticals and Medical Devices Agency (PMDA)/Ministry of Health, Labor and Welfare (MHLW) and Health Canada. Remaining 0.7% of signals were from other sources, including notifications from

MAHs and internal EMA meetings. The breakdown of action taken by potential signals opened by EMA has been relatively constant over time with 2-3% of signals reviewed being validated for further PRAC assessment (see Table 7).

Table 7. Overview of potential signals by action taken is shown below

Action taken	Number of potential signals - 2022	% of total	Number of potential signals - 2021	% of total	Number of potential signals - 2020	% of total
Not validated (closed)	1,103	80.2%	1157	77.9%	1,530	81.0%
Monitored	89	6.5%	97	6.5%	138	7.3%
Ongoing	152	11.1%	193	13%	181	9.6%
Prioritised and assessed by PRAC	31* (39 combined)	2.3%	40* (55 combined)	2.7%	39	2.1%
Total	1,375	100.0%	1,485	100.0%	1,888	100.0%

*excluding COVID-19 vaccines, number in brackets shows total number of signals validated by Agency (COVID-19 vaccines and other products combined).

Overview of signals prioritised and assessed by the PRAC

All detected validated signals which are confirmed by the Rapporteur or LMS are brought to the attention of the PRAC for initial analysis and prioritisation and assessment. The number of confirmed signals prioritised and assessed by the PRAC in 2022 was 64, compared with 86 in 2021, representing a 26% decrease compared to 2021, but a similar number as in 2020. Of these 64, 39 were validated by the Agency (8 for COVID-19 vaccines and 31 for other products) and 25 were validated by the MSs (8 for COVID-19 vaccines and 17 for other products) in the course of ongoing safety monitoring through screening of reaction monitoring reports, ADR reports, medical literature and other safety data. Overall, 86% of the signals included data from EudraVigilance among their sources (87% in 2021).

Sixteen of the assessed signals (25%) resulted in a recommendation for an update of the product information for patients and healthcare professionals, thus providing updated guidance on the safe and effective use of the medicines. For 21 signals (33%) continuing with routine safety monitoring of the medicine was considered sufficient. The evaluation of 26 signals (41%) is ongoing in 2022, including 16 via a follow-up signal procedure and 10 in upcoming PSURs/PSUSAs. One signal resulted in a referral procedure and no signals resulted in PASS studies. See Figure 15 for a summary and tables 8 and 9 lists all the signals noting the latest status or outcome as of 31 December 2022.

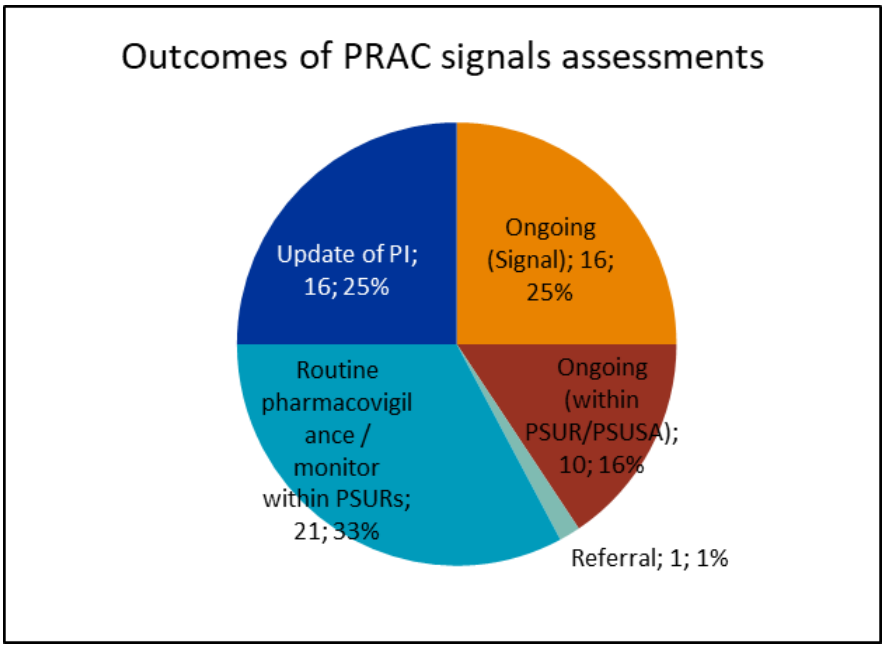


Figure 15. Outcomes of PRAC signal assessments (2022). PI: product information, PSUR: Periodic Safety Update Report, PSUSA: Periodic Safety Update Single Assessment.

Table 8. A list of all COVID-19 vaccine signals prioritised and assessed by the PRAC in 2022 is provided below, noting the latest status or outcome as of 31 December 2022, by chronological order of signal

COVID-19 vaccine	Issue/signal	Status or outcome
Comirnaty (BioNtech/Pfizer)	Capillary Leak Syndrome	routine pharmacovigilance / monitor within PSURs
Spikevax (Moderna)	Capillary Leak Syndrome	Update of PI
Comirnaty (BioNtech/Pfizer)	Autoimmune hepatitis	ongoing (within PSUR/PSUSA)
Spikevax (Moderna)	Autoimmune hepatitis	ongoing (within PSUR/PSUSA)
Comirnaty (BioNtech/Pfizer)	Amenorrhoea	ongoing (within PSUR/PSUSA)
Spikevax (Moderna)	Amenorrhoea	ongoing (within PSUR/PSUSA)
Vaxzevria (COVID-19 vaccine AZ)	Corneal graft rejection	routine pharmacovigilance / monitor within PSURs
Comirnaty (BioNtech/Pfizer)	Corneal graft rejection	routine pharmacovigilance / monitor within PSURs
Spikevax (Moderna)	Corneal graft rejection	routine

COVID-19 vaccine	Issue/signal	Status or outcome
		pharmacovigilance / monitor within PSURs
Comirnaty (BioNtech/Pfizer)	Histiocytic necrotizing lymphadenitis	ongoing (within PSUR/PSUSA)
Comirnaty (BioNtech/Pfizer)	Vulval ulceration	ongoing (Signal)
Comirnaty (BioNtech/Pfizer)	Heavy menstrual bleeding	update of PI
Spikevax (Moderna)	Heavy menstrual bleeding	update of PI
Vaxzevria (COVID-19 vaccine AZ)	Pemphigus and pemphigoid	ongoing (Signal)
Comirnaty (BioNtech/Pfizer)	Pemphigus and pemphigoid	ongoing (Signal)
Spikevax (Moderna)	Pemphigus and pemphigoid	ongoing (Signal)

Table 9. A list of all other signals prioritised and assessed by the PRAC in 2021 is provided below, in alphabetical order, noting the status or outcome as of 31 December 2021

Drug	Issue/signal	Status or outcome
3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins): atorvastatin; fluvastatin; lovastatin; pitavastatin; pravastatin; rosuvastatin; simvastatin and other relevant fixed dose combinations; pravastatin, fenofibrate; simvastatin, fenofibrate	Myasthenia gravis	ongoing (Signal)
Abatacept	Acute Respiratory Distress Syndrome (ARDS)	routine pharmacovigilance / monitor within PSURs
Adalimumab; etanercept; infliximab	Menstrual disorder	ongoing (Signal)
Alemtuzumab	Vitiligo	update of PI
Apixaban	Masking of acquired haemophilia	routine pharmacovigilance / monitor within PSURs
Atezolizumab	Optic neuritis	routine pharmacovigilance / monitor within PSURs
Bosutinib	Interstitial lung disease	ongoing (Signal)
Cabozantinib	Tumour lysis syndrome	ongoing (within PSUR/PSUSA)
Cannabidiol; Calcineurin inhibitors: ciclosporin, tacrolimus; Mammalian	Signal of drug interaction with	update of PI

Drug	Issue/signal	Status or outcome
target of rapamycin (mTOR) inhibitors: everolimus, sirolimus; temsirolimus	cannabidiol leading to calcineurin inhibitors and mTOR inhibitors serum levels increased and toxicity	
Ceftriaxone	Risk of factor V inhibition	ongoing (Signal)
Cetuximab	Nephrotic syndrome	routine pharmacovigilance / monitor within PSURs
CGRP antagonists: Erenumab, Fremanezumab, Galcanezumab, Eptinezumab	Raynaud's phenomenon	routine pharmacovigilance / monitor within PSURs
Codeine, ibuprofen	Renal tubular acidosis and hypokalaemia	update of PI
Colistin / colistimethate sodium (IV use)	Pseudo-Bartter syndrome	ongoing (Signal)
Dabrafenib; trametinib	Haemophagocytic lymphohistiocytosis (HLH)	ongoing (Signal)
Diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated) vaccine (adsorbed); diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated) vaccine (adsorbed, reduced antigen(s) content)	Immune thrombocytopenia	routine pharmacovigilance / monitor within PSURs
Durvalumab	Arthralgia	update of PI
Durvalumab	Myelitis transverse	update of PI
Enfortumab vedotin	Interstitial lung disease	ongoing (within PSUR/PSUSA)
Enzalutamide	Erythema multiforme	update of PI
Evolocumab	Weight increased and abnormal weight gain	ongoing (Signal)
Gemtuzumab ozogamicin	Atypical haemolytic reactions	routine pharmacovigilance / monitor within PSURs
Human normal immunoglobulin	Thrombocytopenia	routine pharmacovigilance / monitor within PSURs
Ipilimumab; nivolumab	Aplasia pure red cell and aplastic anaemia	routine pharmacovigilance / monitor within PSURs
Nivolumab	Morphoea	ongoing (Signal)
Obinutuzumab	Non-overt disseminated	update of PI

Drug	Issue/signal	Status or outcome
	intravascular coagulation (DIC)	
Olaparib	Hepatocellular damage and hepatitis	ongoing (Signal)
Osimertinib	Aplastic anaemia	update of PI
Pneumococcal polysaccharide vaccine containing 23 serotypes	Extensive swelling of vaccinated limb	update of PI
Pregabalin	Toxic epidermal necrolysis	update of PI
Propofol	Medication errors that could potentially lead to life-threatening/fatal cases	ongoing (Signal)
Regorafenib	Thrombotic microangiopathy	ongoing (Signal)
Rivaroxaban	Pemphigoid	routine pharmacovigilance / monitor within PSURs
Roxadustat	Central Hypothyroidism	update of PI
Sacubitril Valsartan	Vasoplegia Syndrome	routine pharmacovigilance / monitor within PSURs
Selective serotonin reuptake transporter inhibitors (SSRIs): citalopram; escitalopram; fluoxetine; fluvoxamine; paroxetine; sertraline; and Serotonin-norepinephrine reuptake inhibitors (SNRIs): desvenlafaxine; duloxetine; milnacipran; venlafaxine; and Mirtazapine; vortioxetine	Pulmonary Hypertension	routine pharmacovigilance / monitor within PSURs
Selpercatinib	Hypothyroidism	ongoing (within PSUR/PSUSA)
Sorafenib	Tumour lysis syndrome	update of PI
Temozolomide	Progressive multifocal leukoencephalopathy (PML)	routine pharmacovigilance / monitor within PSURs
Tildrakizumab	Herpes zoster	routine pharmacovigilance / monitor within PSURs
Tocilizumab	Pancreatitis	ongoing (within PSUR/PSUSA)
Tocilizumab	Sarcoidosis	routine pharmacovigilance / monitor within PSURs
Tocilizumab	Drug reaction with eosinophilia	routine

Drug	Issue/signal	Status or outcome
	and systemic symptoms (DRESS)	pharmacovigilance / monitor within PSURs
Tocilizumab	Encephalopathy including posterior reversible encephalopathy syndrome (PRES)	routine pharmacovigilance / monitor within PSURs
Topiramate	Neurodevelopmental disorders due to in utero exposure	referral
Tranexamic acid	Incorrect route of product administration	update of PI
Voriconazole	Drug interaction with flucloxacillin leading to subtherapeutic voriconazole levels	ongoing (Signal)
Voxelotor	Drug reaction with eosinophilia and systemic symptoms (DRESS)	ongoing (within PSUR/PSUSA)

Annex VI - Signal management process and methods

The Signal Management Review Technical Working Group (SMART) is a collaboration between Member States and EMA with the objective to strengthen and simplify the signal management process in the EU. Its two work streams are focused on signal management tools and processes (SMART Processes) and methodological guidance and signal detection methods (SMART Methods). SMART reports to PRAC. The progress achieved in 2022 is summarised below.

In line with the established role of SMART Processes to support the overall signal management process, the group has continued to provide guidance and clarifications as regards the importance of precisely defining the scope of PRAC recommendations to facilitate a clear identification of concerned products and as regards criteria and considerations underpinning the confirmation of signals. Updates to the signal assessment report template to reflect the above have been implemented.

SMART processes have also provided a platform to share information and experiences within the network as regards the validation of COVID-19 signals and the coordination of their assessment with the objective of promoting efficiency in the use of resources and a harmonised approach.

Building on the experience gathered with the signal management process and after considering an analysis of signal detection kinetics within product lifecycles, as well the evidence from the literature, the group supported screening the eRMR for intensively monitored Centrally Authorised Products (CAPs) and for routinely monitored CAPs with a monthly (as opposed to bimonthly) and quarterly (as opposed to monthly) frequency, respectively. This revision is expected to further promote efficiency and has been agreed for a 1-year pilot, after which an analysis of signal detection performances will be carried out to inform future steps. The frequency of literature monitoring has been left unaltered.

The group also discussed the complexity deriving from the inclusion of unpublished data from studies within signal assessment reports, which may need to be shared with Marketing Authorisation Holders (MAHs) and, in certain cases, may need to be published. In those cases, confidentiality commitments may need to be drafted and signed by the relevant MAHs and a careful redaction is needed, with consequent risk of delaying the assessment timetable. SMART Processes agreed that unpublished data should only be included within signal assessment reports in exceptional cases, e.g. when they are essential for urgent regulatory actions.

In line with the established role of SMART Methods, the group worked on the following research topics:

- Lessons learnt on the use of Observed to expected (O/E) analyses and steps considered beneficial based on the experienced gained during the COVID-19 pandemic: 1) Enhanced preparedness prior to deployment of the vaccines (i.e. calculation of background incidence rates, identification of Adverse Events of Special Interests (AESIs) etc.); 2) Establishment of a multidisciplinary team of epidemiologists and pharmacovigilance (PV) experts for the selection of the key parameters and the interpretation of the results; 3) Implementation of different sensitivity analyses to adjust for potential under-reporting, heterogeneity between background incidence rates, etc.; 4) Increased efficiency by automating the process thereby enabling routine production which had multiple applications; 5) Independent tool for Pharmacovigilance which is not subject to some of the limitations of the ROR(-) (e.g., masking); 6) Implementation of descriptive analyses of the reported cases to EudraVigilance to inform strategy in terms of identification of risk periods and the selection of relevant Medical Dictionary for Regulatory Activities (MedDRA) terms.
- The following challenges were also identified: 1) O/E analyses are useful for signal detection but are not indicative of a causal association, thus results must be interpreted cautiously 2) Alignment of the case definition utilized for ascertainment of both the observed and expected is often not

straight forward, 3) Heterogeneity of background rates is prominent between databases and/or time intervals, therefore identification of the most appropriate source is complex 4) The validity of assumptions used within the analysis requires careful consideration (e.g., risk periods) 5) Spontaneous reports are subject to several limitations which may introduce bias to the analysis.

- European Union's product information Entity extraction and Knowledge acquisition tool (EUREKA), which is a Modular application to extract and expose Adverse Drug Reaction (ADR) data from the Summary of Product Characteristics. Since 2011, the Protect ADR database received manual updates, however, considering the intense manual work involved, an assessment of its usefulness was performed. Five use cases were identified: 1) public facing dataset, 2) support signal detection, 3) real-world data analyses identifying possible comparators; 4) support Committees, 5) harmonise the description of listed reactions for similar products.
  The plan is to create a web application to expose the data for use, allow users to edit the list of ADRs and apply a modular approach that is easy to update potentially expanding to Nationally Authorised Products (NAPs).

- COVID-19 vaccines and potential masking effects in EudraVigilance. The analyses performed aimed to quantify the impact of the high volume of cases received in EudraVigilance for COVID-19 vaccines. The data in EudraVigilance up to 7 October 2022 showed an over-representation of cases related to COVID-19 vaccines since their authorisation, accounting for approximately 18% of ADRs in EudraVigilance. This large proportion of reports could have an impact on signal detection, particularly for important medical events (IMEs), given that these are prioritised for review based on signals of disproportionality (SDRs), specifically the Reporting Odds Ratio (ROR(-)). Drug-ADR pairs potentially subject to masking effect by COVID-19 vaccines were identified as influential outliers using the approach developed by Juhlin et al., 2013[14]. As a short-term action to mitigate the impact of masking effect, the events will be flagged as potentially masked. As a long-term approach, published and novel methods will be tested to take into account masking effects including and beyond those caused by COVID-19 vaccines.

[14] Juhlin K, Ye X, Star K, Norén GN. Outlier removal to uncover patterns in adverse drug reaction surveillance - a simple unmasking strategy. Pharmacoepidemiol Drug Saf. 2013 Oct;22(10):1119-29. doi: 10.1002/pds.3474. Epub 2013 Jul 7. PMID: 23832706.

Annex VII - Requests for information and documents

In 2022, EMA responded to 29 requests for EudraVigilance (EV) data, where requests for information (involving aggregated data) and/or documents (line listings) were provided. Whilst this number of requests is a decrease compared to 2021 (39 requests), this in line with the two years before 2021 (28 in 2020 and 32 in 2019, respectively). EMA continues to receive significantly less EV data requests, owing to the adverse reaction data provided through the publicly available www.adrreports.eu website. The portal continues to fulfil most general public queries. In 2022, EMA supplied an additional 30 responses to requests for clarifications concerning this website or general aspects of EV data.

The figure of 29 requests mentioned above corresponds to internal requests from the EU regulatory network (13) in addition to external requests (16) which could not be answered with the information provided via www.adrreports.eu and for which a detailed, tailored EV search was required. These requests include queries for data from the general public, including patients and not-for-profit organisations, or requests from academia.

Of the 29 requests for EV data, 16 (55%) were requests for information (involving aggregated data), whilst 11 (38%) involved requests for documents (line listings). The remaining 2 requests (7% of the total) concerned requests for both information and documents. The majority of the requests were related to centrally authorised products (CAPs), all of them concerning COVID-19 vaccines, accounting for almost 80% of the total number of requests, whilst nationally authorised products (NAPs) accounted for 10%. Requests concerning both CAPs and NAPs accounted for the remaining 10%.

The median response time for external requests in 2022 was 16 days (range 1 – 170 days). Two requests (7%) were responded to past the deadline due to their complexity.

COVID-19 related queries

As mentioned above, a high proportion of the requests for EV data in 2022 were relating to one or more of the centrally authorised COVID-19 vaccines (23 out of 29 requests). This is the same total number as in the previous year (23 requests in 2021). Thirteen (13) out of these 23 requests (56.5%) originated within EMA, either for the safety updates on COVID-19 vaccines published monthly on the EMA website or for press conferences. Five (5) requests were from not-for-profit organisations (22%), followed by two (2) requests from academia (9%), 2 requests from patients (9%) and one (1) request from a healthcare professional (4%). There weren't any requests from journalists in 2022, whilst EMA had received eleven (11) such queries in 2021.

Figures 16 and 17 below provide an overview by type of request, authorisation type of concerned product(s), requester type and origin country (for external requests only).

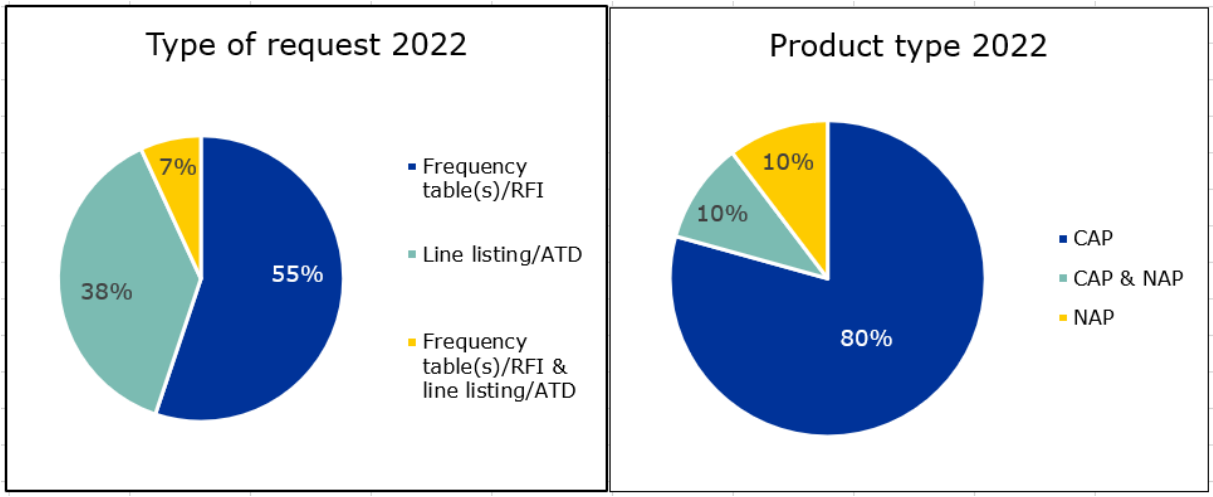
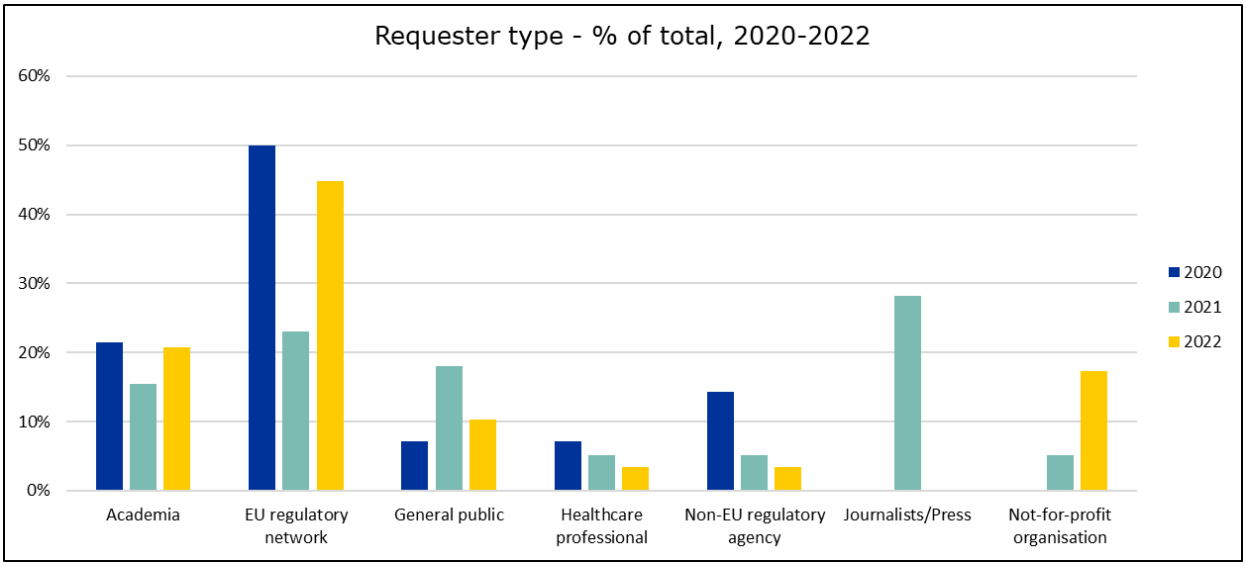


Figure 16 Overview of requests for EV data in 2022 by type of request (right) and product type (left).



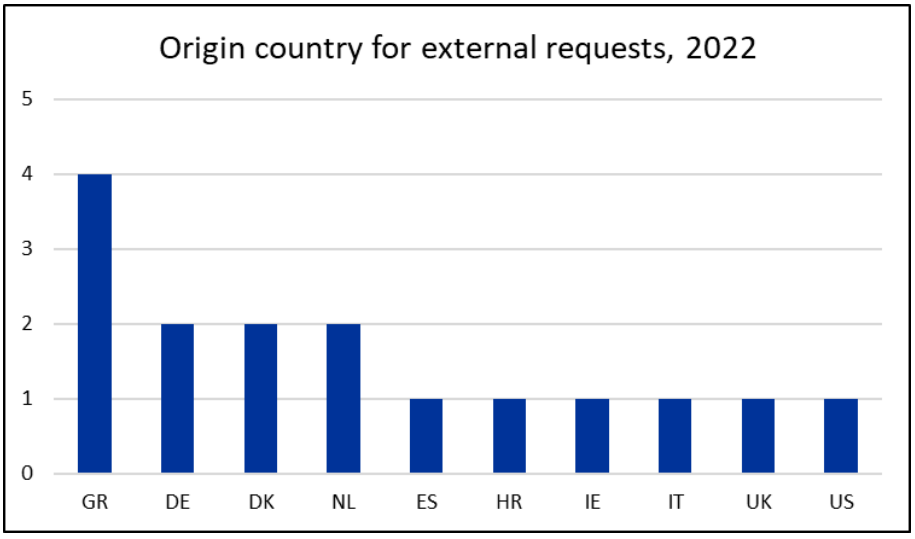


Figure 17 Overview of requests for EV data in 2022 by requester type (top) and country or region of origin for external requests (bottom).

Table 10 Overview of requests responded to in 2022

Type of requester	Substance/product	Issue	Type of request
Academia	Various	ADRs related to medication errors for 2002-2020	Line listing/ATD
Academia	Covid-19 vaccines	Musculoskeletal ADRs	Line listing/ATD
EU regulatory network	Covid-19 vaccines	All ADRs	Frequency table(s)/RFI
Not-for-profit organisation	Covid-19 vaccines	Country of origin for requested cases	Line listing/ATD
General public	Covid-19 vaccines/Comirnaty	All ADRs per batch	Line listing/ATD
Not-for-profit organisation	Covid-19 vaccines	All ADRs per batch	Line listing/ATD
Academia	Covid-19 vaccines/Comirnaty and Spikevax	All ADRs reported by country and batch number	Line listing/ATD
EU regulatory network	Covid-19 vaccines	All ADRs	Frequency table(s)/RFI
EU regulatory network	Covid-19 vaccines	All ADRs	Frequency table(s)/RFI
Non-EU regulatory agency	Tramadol	Respiratory depression	Frequency table(s)/RFI
General public	Quadrivalent influenza vaccination split virion inactivated	Post viral fatigue syndrome	Line listing/ATD
EU regulatory network	Covid-19 vaccines	All ADRs	Frequency table(s)/RFI
Not-for-profit organisation	Covid-19 vaccines	Country of origin for requested cases	Frequency table(s)/RFI + Line listing/ATD
General public	Covid-19 vaccines / Comirnaty	All ADRs for requested clinical trials	Frequency table(s)/RFI
Academia	List of 64 products	All ADRs	Line listing/ATD
EU regulatory network	Covid-19 vaccines	All ADRs	Frequency table(s)/RFI
Not-for-profit organisation	Covid-19 vaccines	Country of origin for requested cases	Frequency table(s)/RFI + Line listing/ATD
EU regulatory network	Covid-19 vaccines	All ADRs	Frequency table(s)/RFI
Academia	Clozapine	All ADRs	Line listing/ATD
EU regulatory network	Covid-19 vaccines	All ADRs	Frequency table(s)/RFI

Type of requester	Substance/product	Issue	Type of request
Healthcare professional	Covid-19 vaccines	All ADRs	Frequency table(s)/RFI
EU regulatory network	Covid-19 vaccines	All ADRs	Frequency table(s)/RFI
Academia	Various	ADRs related to medication errors in 2021	Line listing/ATD
EU regulatory network	Covid-19 vaccines	All ADRs	Frequency table(s)/RFI
Not-for-profit organisation	Covid-19 vaccines	All ADRs by country of origin	Line listing/ATD
EU regulatory network	Covid-19 vaccines	All ADRs	Frequency table(s)/RFI
EU regulatory network	Covid-19 vaccines	All ADRs	Frequency table(s)/RFI
EU regulatory network	Covid-19 vaccines	All ADRs	Frequency table(s)/RFI
EU regulatory network	Covid-19 vaccines	All ADRs	Frequency table(s)/RFI