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2023 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 medicine 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 medicine, even if it is unclear whether the medicine 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 routine benefit-risk re-evaluation of authorised medicines 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).

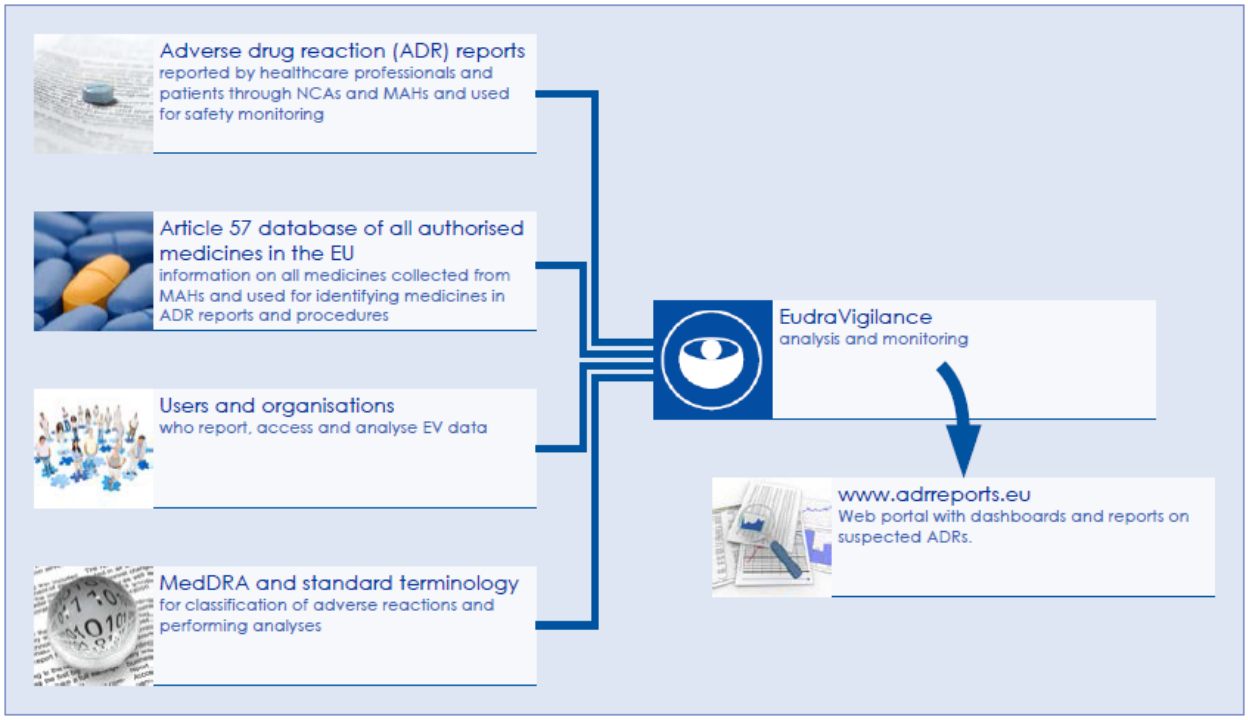


Figure 1. EudraVigilance users, data sources and data use.

The EudraVigilance database currently holds over 27.4 million individual case safety reports (ICSRs) relating to 15.9 million unique suspected ADR case reports[1] related to medicines for human use 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 for medicines for human use performed in 2023, notably:

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

- ***Operation of EudraVigilance including its new functionalities.*** EudraVigilance continued to be maintained by EMA on behalf of the EU medicines regulatory network, with further functional improvements in data analysis and signal detection delivered, including the first phase of the Signal and Safety Analytics (SSA) project. The objective of this project is to review the EudraVigilance data analytics platform and tools and enable the Agency and the Network to deliver evidence more effectively and efficiently from data-driven interrogation of ADR reports.
- ***Collecting and processing suspected adverse drug reaction reports***. In 2023, 1.9 million ICSRs related to suspected ADRs occurring after authorisation were collected and managed in EudraVigilance (a 34% decrease compared to the previous year). The number of ICSRs originating from the European Economic Area (EEA) decreased by 49% and non-serious reports by 50%. This decrease indicates a return to the pre-pandemic levels, as 2021 and 2022 showed an unprecedented increase in reporting due to the authorisation and roll-out of the first COVID-19 vaccines. A proportion of the reports received in 2023 were related to COVID-19 vaccines, which accounted for 11% (215,960) of all ICSRs and 19% (137,251) of reports originated from the EEA (39% of all ICSRs in 2022 were related to COVID-19 vaccines).
- ***Screening for, and review of, potential signals***. In 2023, EMA's signal management team reviewed in detail 1,364 potential signals[2], including 79 for COVID-19 vaccines, related to 998 substances from screening the EudraVigilance database and other sources (a 14% overall decrease versus 2022). For active substances contained in nationally authorised products (NAPs), the monitoring of ADR reports is shared between the NCAs. Lead Member States (LMSs) have been appointed to monitor the current list of 1,690 active substances. NCAs also monitor all medicines authorised nationally in their country for which no LMS has been appointed. COVID-19 vaccines were monitored together with other intensively monitored products (through monthly eRMRs).
- ***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 2023, the PRAC prioritised and assessed 71 confirmed signals (an 11% increase versus 2022). About 94% of them included data from EudraVigilance among their sources. Of the 71 confirmed signals, 39 were validated by the Agency and 32 were validated by the Member States (MSs); 47 were for CAPs, 15 for NAPs and 9 for both CAPs and NAPs. Of the 71 signals assessed by the PRAC, 13% were related to COVID-19 vaccines (compared to 25% in 2021 and 2022).
- ***Transparency and public access to aggregated EudraVigilance data***. The public has access to data on all spontaneous reports of suspected side effects from EudraVigilance through the public *European database of suspect adverse drug reactions reports*. By the end of 2023, this database included information on 4,351 active substances, 917 of which were contained in CAPs and 3,434 in NAPs. ADR data were also available to the general public on all 14 COVID-19 vaccines (original and adapted vaccines).
- ***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 highlighted the major enhancements of the system which were launched on 22 November 2017 and provided benefits in terms of simplified reporting, data access, analysis tools, quality and scalability of the system.

The key activities undertaken in 2023 are summarised here:

The EMA Multi-factor Authentication (MFA) was enabled first on the production EVWEB & XEVMPD systems on 28 March 2023. Communications were issued requesting users to check and set up the MFA credentials in advance of this functionality being implemented. The MFA in EVDAS is expected to be implemented in 2024.

The EudraVigilance terms and conditions of use and access were updated and users were required to accept these new terms and conditions before being able to access the EudraVigilance systems. All users were encouraged to read the updated terms and conditions carefully when implemented in Test (XCOMP) System on Monday 27 March 2023 and in the production system on 12 April 2023.

In June 2023, the EMA account management portal was updated to include a required systematic review by the QPPV/Responsible Person (RP) user (or trusted deputy) of the list of users within their organisation and the EudraVigilance access role that has been assigned to them. The initial demonstration run was completed by mid-July and EMA confirmed that 90% of all the user registrations were successfully reviewed on time.

Following the first review, the QPPV/RP users of the organisations that did not complete (or fully complete) the review of their users were contacted to remind them of their obligations to protect the EudraVigilance data by ensuring that access is restricted to individuals that have a valid reason to have that access. For the subsequent reviews, the default action is to revoke any roles that have not been assessed within one month of the review process starting. The system will send out regular reminders to complete the assessments before the deadline is passed. The reviews are triggered in a 6-month review cycle, set in March and September. The regular review of users and the removal of unnecessary user roles plays an important part in ensuring that the data held in EudraVigilance are protected.

EMA and the European Commission (EC) extended until the end of 2024 the pilot on the mandatory monitoring by MAHs of selected active substances in EudraVigilance and related transitional arrangements. 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. It is expected that the updated Commission Implementing Regulation 52/2012 will be published during 2024.

On 23 July 2023 the EMA Portfolio Board approved the first phase of the Signal and Safety Analytics project. The objective is to review the EudraVigilance data analytics platform and tools to enable the

Agency and the Network to deliver evidence from data-driven interrogation of ADR reports more effectively and efficiently. The first phase of the project will be based on a minimum viable product covering the core functionalities for signal detection and validation by the EMA pharmacovigilance service and the national competent authorities.

Following the publication of Regulation (EU) 2023/1182 of 14 June 2023 and the change in the framework created by the Protocol on Ireland/Northern Ireland with regard to the authorisation and supervision of current CAPs for human use that will be done by the UK authorities under UK law, EMA has started to work on the implementation of the above-mentioned Regulation. The Regulation will become applicable on 1 January 2025.

EMA has started a project to implement EudraVigilance compliance notifications of ICSRs adherence to reporting timelines. These compliance reports are intended to support the legislative requirements established in Regulation (EC) No 726/2004 Article 24 (3) and the Commission Implementing Regulation (EU) No 520/2012- Articles 11 and 15 on collaboration between EMA, NCAs and MAHs to ensure EV data quality and adherence to the reporting timelines. These reports will be based on the serious and non-serious cases submitted to the post-marketing module and the clinical trials module. In the preparation steps a six-month pilot was initiated in October 2023 including stakeholders from MAHs, commercial and non-commercial sponsors and National Competent Authorities. Once the results of the pilot phase are analysed, the compliance reports will be generated for all stakeholders during 2024. Further communications and engagement with stakeholders and inspectors are foreseen to ensure an adequate implementation.

As defined in the Pharmacovigilance Plan of the EU Regulatory Network for COVID-19 Vaccines issued in 2020, EudraVigilance continued to play a crucial role during 2023 in facilitating the early detection of emerging risks with the COVID-19 vaccines and therapeutics.

With the authorisation of the new adapted COVID-19 vaccines in 2023, EMA engaged with the Member States and the concerned 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 adapted vaccines and safety topics to be closely monitored. This dashboard was updated in 2023 to accommodate business needs, including the monitoring of signals together with transparency and communication activities.

Within the Medical Literature Monitoring (MLM) service, EMA, together with the service provider, reviewed the results of the satisfaction surveys conducted every six months. Preparations for significant service enhancements, which will take place in 2024, have been made. 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.

The EudraVigilance Expert Working group (EV-EWG) met twice in 2023, on 7 March and 11 October. The work programme for 2023-2024 of the EV-EWG was published in March 2023. The EMA-MSs Pharmacovigilance Business team met quarterly in 2023 to discuss, agree on, and issue guidance for the different EudraVigilance operations.

The EudraVigilance training page has been updated to launch a training course on the enhanced EudraVigilance system and a course for clinical trial sponsors, which will be available in 2024.

In March 2023 the European Data Protection Supervisor (EDPS) audited the EudraVigilance system at the EMA premisses. At the time of the preparation of this annual report, the Agency was still awaiting the audit report from the EDPS. The audit recommendations will be analysed and implemented as required.

3. Data collection and data quality

Medicinal product information

In the database of all medicines authorised in the EU (the "Article 57 database"), the total number of medicinal product entries provided by MAHs in the eXtended EudraVigilance Medicinal Product Dictionary (XEVMPD) was 1,037,442 as of 31 December 2023, 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 2023, 1,908,381 ICSRs were collected and managed in EudraVigilance. This figure represents a 34% decrease compared to the numbers recorded in 2022 and is characterised by a marked decrease in EEA reports (-49%) and in non-serious reporting (-50%), showing a downward trend towards pre-pandemic figures. The proportion of reports related to COVID-19 vaccines accounted for 11% (215,960) of all the ICSRs and for 19% (137,251) of the ICSRs originating in the EEA.

The number of reports submitted directly by patients and consumers through the NCAs and MAHs (176,044) saw a 73% decrease compared to the previous year. This significant decrease indicates a return to the pre-pandemic levels, as 2021 and 2022 showed an unprecedented increase in reporting due to the authorisation and roll-out of the first COVID-19 vaccines (See Figure 2). In 2023, reports associated with COVID-19 vaccines accounted for 39% (67,994) of the reports submitted directly by patients and consumers through the NCAs and MAHs.

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

[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.

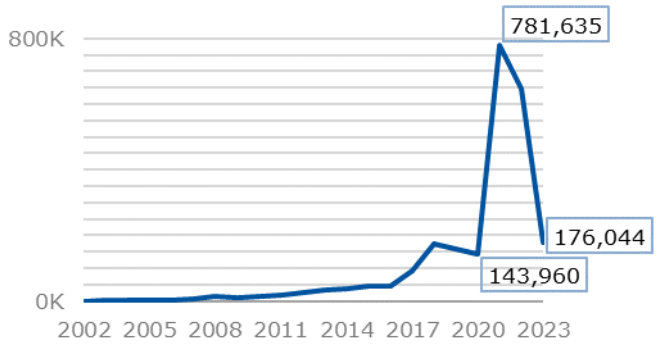


Figure 2. Trend of ADR reports from patients and consumers received in the EEA by NCAs and MAHs and reported to EudraVigilance.

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 using 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 validating the signal of suicidal ideation associated with GLP-1 receptor agonists, and EudraVigilance analysis plays a central role in the assessment of this signal. The PRAC assessment started in 2023 and is expected to finalise in April 2024. The network also validated a signal of postmenopausal haemorrhage with COVID-19 vaccines Comirnaty and Spikevax, this assessment was also still ongoing at the end of 2023.

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 2023, over 17,000 eRMRs were generated for NCAs and EMA's signal management team. These were produced on a monthly, three-monthly, or six-monthly basis.

[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

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: 1,364 potential signals were reviewed by the Agency in 2023, including 79 relating to COVID-19 vaccines (see Annex V for further breakdown).

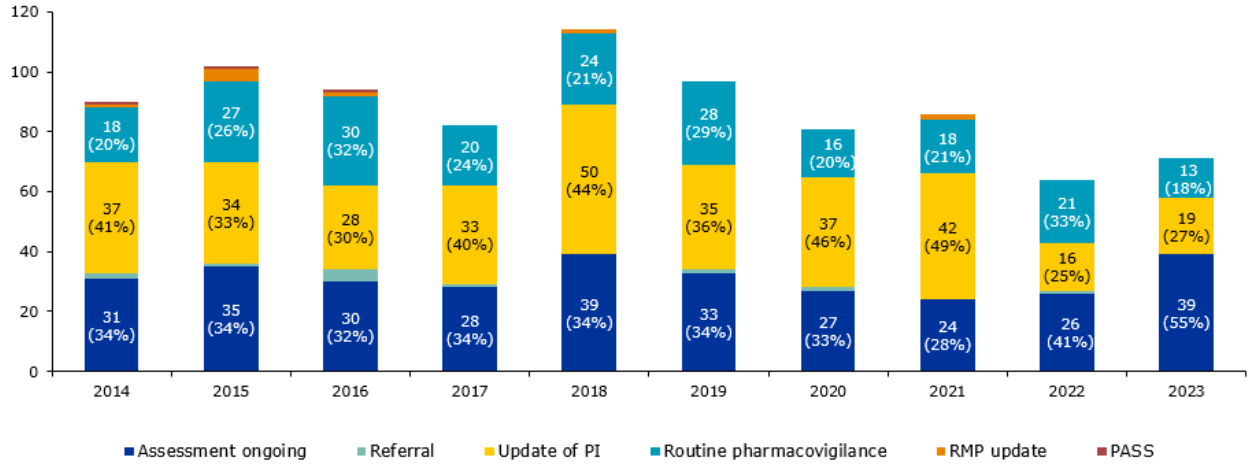
For active substances contained in NAPs, the monitoring of ADR reports in EudraVigilance and in national databases is shared between the NCAs, in line with the 'List of substances and products subject to worksharing for signal management'[6] which defines a LMS for each active substance included. Following changes in the marketing authorisation status throughout the EU and in the LMS for Periodic Safety Update Single Assessment (PSUSA), an extensive revision of the signal management worksharing list was finalised end of 2023. It currently includes 1,690 active substances. NCAs also monitor all medicines authorised nationally in their country for which no LMS has been appointed. Substances and combination of substances no longer eligible for worksharing or substances no longer authorised in the Member States were removed from eRMR monitoring.

All detected and validated signals that are confirmed by the Rapporteur or LMS are brought to the attention of the PRAC for initial analysis, prioritisation and assessment. In 2023, the PRAC prioritised and assessed 71 confirmed signals (a 11% increase compared to 2022, see Figure 3). Of the signals assessed by the PRAC in 2023, 13% were related to COVID-19 vaccines (25% in 2022 and also in 2021).

Of the 71 signals assessed by the PRAC, 67 (94%) included data from EudraVigilance. Nineteen of the assessed signals (27%) 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 13 signals (18%) continuing with routine safety monitoring of the medicine was considered sufficient. The evaluation of 39 signals (55%) was ongoing at the end of 2023, including 16 via a follow-up signal procedure and 23 as part of upcoming PSURs/PSUSAs (for 2 of these signals, the MAHs have additionally been requested to follow up in ongoing PASS studies). No signals led to a referral procedure.

[6] https://www.ema.europa.eu/system/files/documents/regulatory-procedural-guideline/ws-list-publication-2023-en.xlsx

Figure 3. Overview of signals assessed by the PRAC



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 2023 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 since February 2018 whereby MAHs must monitor selected active substances[7] in EudraVigilance and inform EMA and NCAs of validated signals with their medicines.[8] Since February 2018 up until December 2023, the Network had received 56 standalone signal notifications from MAHs. Of these, 13 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 2023). All other MAHs also have access to cases for their medicinal products and can therefore integrate EudraVigilance data into their own signal management processes. In July 2023, the European Commission decided to further extend the pilot until the end of 2024, pending the update of the Commission Implementing Regulation[9] based on the experience gained with the pilot.

5. Transparency, communication and training

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.

As for all medicines authorised in the EU, monitoring and timely assessment of emerging safety data continued for the COVID-19 vaccines. Any major safety-related changes to the existing product information were communicated in the PRAC highlights, together with dedicated public health

[7]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

[8] https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:159:0005:0025:EN:PDF

[9] 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

communications as needed. For each medicine, all identified side effects are listed in the relevant product information which is available in all the languages of the EU/EEA (see section 1). The European database of suspected drug reaction reports (https://www.adrreports.eu/) will continue to be updated weekly, for vaccines and all other substances.

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 (https://www.adrreports.eu/) and was further improved in November 2017 by providing additional outputs, such as line listings and ICSR forms. By the end of 2023, the website provided information on a total of 4,351 active substances, of which 917 were contained in CAPs and 3,434 in NAPs. ADR data were also available to the general public on all 14 COVID-19 vaccines (original and adapted 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, 20 requests were answered (9 fewer than in 2022). This corresponds to internal requests from the EU regulatory network (6) in addition to external requests (14) which could not be answered with the information provided via www.adrreports.eu and for which a detailed, tailored EudraVigilance search was required. More details are provided in Annex VII.

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

- 10 training sessions on EudraVigilance ICSR submissions, with 208 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)
- 3 training sessions on EudraVigilance ICSR submissions for clinical trial sponsors, with 62 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)
- PRAC assessors training took place in October 2023 and was focussed on PASS assessment. Over 240 assessors registered for the event.
- 1 EudraVigilance Information Day took place in 2023 with 128 participants.

6. Conclusion

EudraVigilance continued to play a crucial role in 2023 and it remains a central pillar for pharmacovigilance activities in the EEA.

In 2023, 1.9 million ICSRs were collected and managed in EudraVigilance, a 34% decrease compared to the previous year. A proportion of the reports were related to COVID-19 vaccines, which accounted for 11% of all ICSRs collected in EudraVigilance. The number of reports submitted directly by patients and consumers through NCAs and MAHs (176,044) saw a 73% decrease compared to the previous year. This significant decrease indicates a return to the pre-pandemic levels, as 2021 and 2022 showed an unprecedented increase in reporting due to the authorisation and roll-out of the first COVID-19 vaccines.

Based on these reports, over 17,000 statistical outputs were produced to facilitate the continuous monitoring of the safety of medicines by the Agency and EU NCAs and the identification of signals which were subsequently assessed by the PRAC.

EudraVigilance currently contains over 27.4 million ICSRs, corresponding to 15.9 million unique suspected ADR case reports. It is being used by EMA, EU NCAs and MAHs, and plays a key role in global surveillance of medicines authorised in the EEA.

Significant enhancements to the database implemented in previous years are now in routine operation and several new improvements were started or implemented in 2023.

In 2023 the EMA Portfolio Board approved the first phase of the Signal and Safety Analytics project. This project aims to review the EudraVigilance data analytics platform and tools, in order to enable the Agency and the Network to deliver evidence from data-driven interrogation of ADR reports more effectively and efficiently.

EMA has also started a project to implement EudraVigilance compliance notifications of ICSRs adherence to reporting timelines. This aims to ensure data quality and adherence to the reporting timelines. These reports will be based on the serious and non-serious cases submitted to the post-marketing module and the clinical trials module. A six-month pilot was initiated in 2023. Once the results of the pilot phase are analysed, the compliance reports will be implemented for all stakeholders during 2024.

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 2023.
Data quality review and duplicate management of adverse reaction reports in EudraVigilance. [*Legal basis:* Regulation (EC) 726/2004, Article 24(3)]	Continued during 2023.
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 2023.
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 2023.
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 2023.
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 2023.
Operation of the Medical Literature Monitoring service [*Legal basis:* Regulation (EC) 726/2004, Article 27]	Continued during 2023.

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 availability exceeded the required 98% availability throughout the years[10].

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 2023, the EudraVigilance database held a total of 27,403,870 ICSRs, referring to 15,913,303 individual cases (Figure 5). The EudraVigilance post-authorisation module (EVPM) contained 25,574,697 ICSRs (15,425,867 individual cases) and the EudraVigilance clinical trial module (EVCTM) contained 1,829,173 ICSRs (487,436 individual cases).

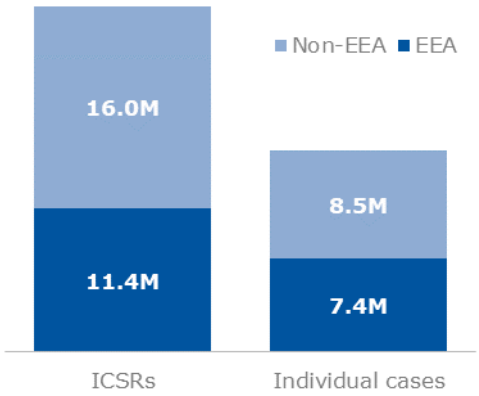


Figure 4. Number of ICSRs versus individual cases received in the EudraVigilance database from its inception in December 2001 until 31 December 2023, split by origin of the report (in or outside the EEA).

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 2023, compared to the number of individual cases they are referring to.

[10] Only unplanned downtime is taken into consideration

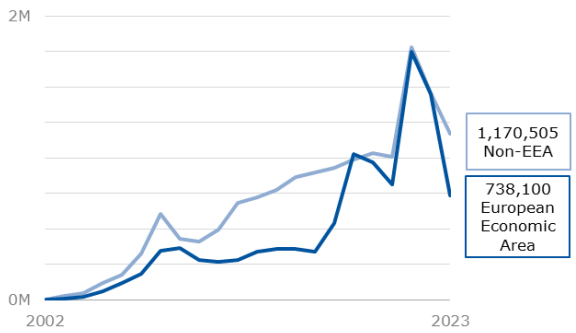


Figure 5. Number of ICSRs processed per year in EVPM split by cases occurred inside and outside the EEA.[11]

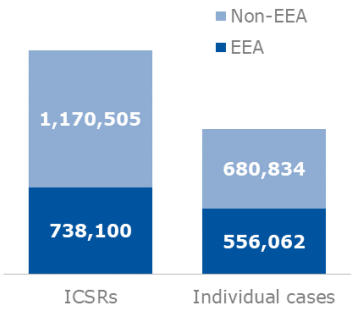


Figure 6. Number of ICSRs versus the number of individual cases in 2023 in EVPM.

The numbers presented in Figures 8 and 9 refer to the ICSRs received in EVPM. A total of 25,574,697 EVPM ICSRs were processed over the years up to the end of 2023, of which 1,908,605 EVPM ICSRs were processed in 2023. This represents a 34% decrease compared to the numbers recorded in 2022, and it is characterised by a decrease in EEA (-49%, Figure 6) and non-serious (-50%) reporting. The downward trend for EEA and non-serious is tightly linked with the decrease in the number of reports related to COVID-19 vaccines (-84% compared to 2022 in both EEA and non-serious categories). ICSRs are subsequently made available for signal detection and data analysis by the Agency and NCAs in the Member States.

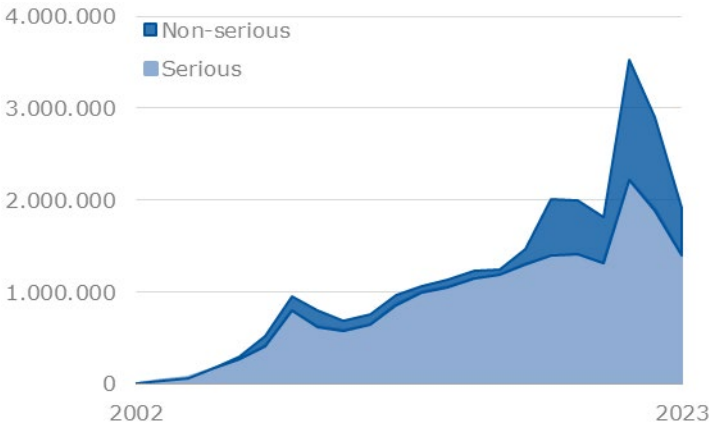


Figure 7. Number of ICSRs processed per year in EVPM.

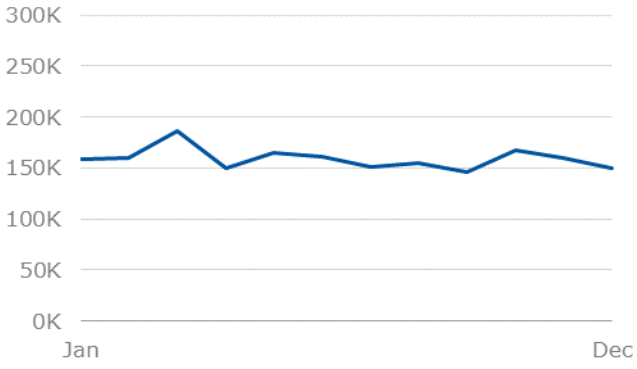


Figure 8. Number of ICSRs processed per month in EVPM in 2023.

In 2023, 176,044 ICSRs were submitted by European patients and consumers through the NCAs and MAHs, referring to 146,680 individual cases. This is a decrease of 73% in the number of such reports compared to the previous year (Figure 10). A large proportion of these reports continues to be related to COVID-19 vaccines, which account for 41% of the individual cases (Table 1). The mandatory

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

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 6 years.

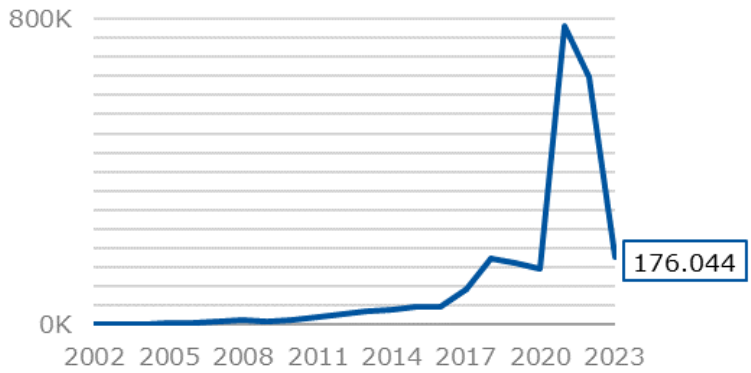


Figure 9. Number of ICSRs by European patients and consumers through the NCAs and MAHs.

Table 1. Number of EVPM ICSRs and unique cases transmitted in 2023 related to or excluding COVID-19 vaccines. Counts for 2022 are provided for comparison.

	2023			2022
	Total count	**Count related to COVID-19 vaccines**	**Count excluding COVID-19 vaccines**	**Total count**
ICSRs processed	1,908,605	215,960 (11%)	1,692,645 (89%)	2,908,262
ICSRs originated in EEA	738,100	137,251 (19%)	600,849 (81%)	1,451,946
Non-serious ICSRs	505,203	99,728 (20%)	405,475 (80%)	1,016,397
ICSRs submitted by European patients and consumers through the NCAs and MAHs	176,044	67,994 (39%)	108,050 (61%)	647,393
Individual cases submitted by European patients and consumers through the NCAs and MAHs	146,680	59,773 (41%)	86,907 (59%)	580,669

E-reporting status for MAHs and sponsors of clinical trials

- 1,157 MAHs (at headquarter level) sent reports to EVPM in 2023, a 6% increase compared to 2022.
- 721 sponsors of clinical trials (at headquarter level) sent reports to EVCTM in 2023, a 11% increase compared to 2022.
- A total of 22,631 individual MAH users and 12,553 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 ('Date of Most Recent Information for This Report'– ICH 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 2023 280,214 ICSRs and 151,596 SUSARs (total 431,810) were rerouted to NCAs following receipt of the reports from MAHs and sponsors in EudraVigilance. A total of 759,260 ICSRs were forwarded to WHO. A total of 201,210 download requests were made by MAHs, resulting in 6,592,679 ICSRs downloaded from the EudraVigilance database while adhering to the EudraVigilance access policy.

Table 2. Number of ICSRs and unique cases transmitted by MAHs and sponsors to EVPM and EVCTM in 2023.

EV Module	Transmission type	Count
EVPM	ICSRs	1,573,916
	Individual cases	895,356
EVCTM	ICSRs	150,745
	Individual cases	43,240

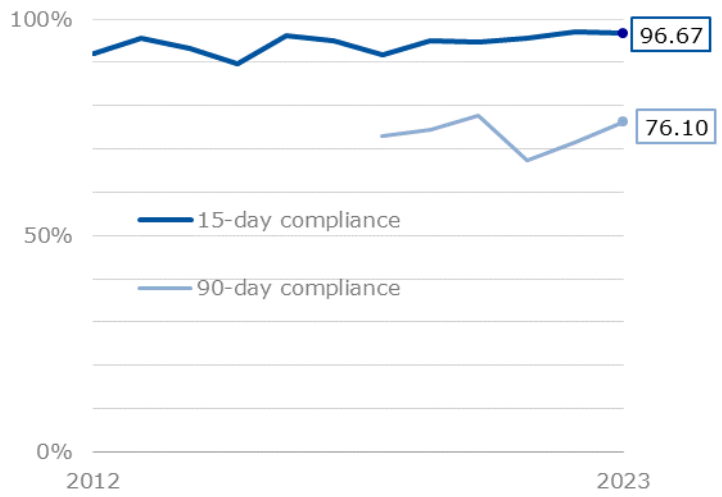


Figure 10. Compliance rate for serious (15-day) and non-serious (90-day) ICSRs to EVPM for all MAHs and sponsors by year. Non-serious ICSRs need to be submitted since November 2017.

EudraVigilance database and support of signal management process

A total of 17,006 eRMRs were generated in 2023 to facilitate the continuous monitoring of the safety of medicines by the Agency and NCAs in the EEA. Of these,

- 11,241 were monthly eRMRs,
- 4,205 were 3-monthly eRMRs
- 1,560 were 6-monthly eRMRs

In Q3, an ad-hoc review was conducted to identify substances related to withdrawn CAPs with the aim of stopping their eRMR monitoring. In Q3 and Q4, a high number of changes to the eRMR frequency of numerous substances were implemented as per the Lead Member State requests, mostly moving from 1 to 3 and 6-monthly production frequency.

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 1,514 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 ('Date of Most Recent Information for This Report'– ICH 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 2023

EV Module	Transmission type	Count
EVPM	ICSRs	334,689
	Individual cases	295,001
EVCTM	ICSRs	214
	Individual cases	72

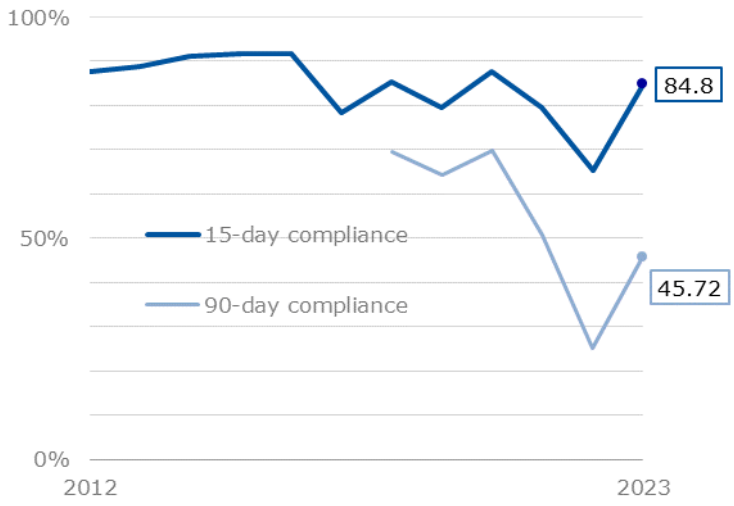


Figure 11. Compliance rate for serious (15-day) and non-serious (90-day) ICSRs to EVPM for all NCAs by year. Non-serious ICSRs need to be submitted since November 2017.

During 2023, the following nine NCAs transmitted SUSARs to EVCTM (SUSARs from other countries were received directly from sponsors of clinical trials):

- Denmark (Danish Medicines Agency)
- Finland (Finnish Medicines Agency)
- Germany (Federal Institute For Drugs And Medical Devices)
- Iceland (Icelandic Medicines Agency)
- Ireland (Health Products Regulatory Authority)
- Netherlands (Central Committee On Research Involving Human Subjects)
- Netherlands (Medicines Evaluation Board)
- Sweden (Swedish Medical Products Agency)

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 better support safety monitoring for patients;
- providing 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 2023). Table 4 below and Figures 13 and 14 provide a summary of the data submitted.

Table 4. Summary of medicinal product submissions to the XEVMPD

Total number of medicinal product submissions by MAHs by 31 December 2023 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

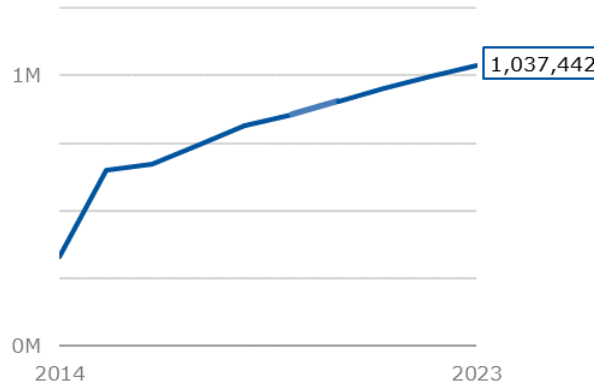


Figure 12. Total number of medicinal products (counted based on EudraVigilance codes) submitted (cumulative by year).

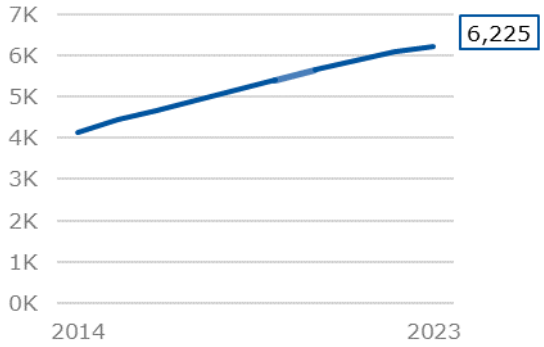


Figure 13. Total number of marketing authorisation holders (legal entities) established in the EU (corresponding to EudraVigilance codes) (cumulative by year).

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 2023 and provides 2022 and 2021 data for comparison.

Table 5. Summary of EudraVigilance data quality activities in 2023.

Data quality area	Activities performed	2023	2022	2021
Identifying and managing duplicate individual cases	Duplicate couples assessed	190,689	147,875	144,883
	Master reports generated based on duplicated data	105,033	41,728	81,360
Coding of reported medicines and active substances	Reported medicinal products and active substance terms recoded	77,598	147,054	1,068,728
	ADR reports recoded (ICSRs)	66,461	130,619	959,665
Providing feedback on data quality	Organisations subject to ICSR data quality review	160	32	119
	Medicinal products in XEVMPD quality reviewed (and corrected if necessary)	163,013	138,350	139,053

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 2023, EMA's signal management team reviewed in detail the information on 1,364 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 79 potential signals reviewed for COVID-19 vaccines. This represents an approximately 14% decrease in the total number of reviewed signals compared to the previous year (see Table 6) and a 34% decrease in the number of COVID-19 signals that were reviewed.

Table 6. Potential signals reviewed

Potential signals reviewed	2023	2022**	2021*	2020	2019	2018
Total	1364***	1605**	1829*	1888	1,806	2,204
Change from previous year	-241	-224	-59	+82	-398	+142
% change from previous year	-14%	-12%	-3%	+4%	-18%	+7%

*1,485 signals that are not related to Covid-19 vaccines and 344 signals related to COVID-19 vaccines (not including 648 vaccine Targeted Medical Events (vTMEs), was presented as cumulative total 2,477 in 2021 annual report on EudraVigilance)
**1,375 signals that are not related to Covid-19 vaccines and 230 signals related to COVID-19 vaccines (not including 405 vTMEs)
*** 1,364 includes 79 potential signals reviewed for COVID-19 vaccines.

A specific monitoring strategy was created for COVID-19 vaccines in 2021 and this was still followed in 2022 also, with some modifications. With more experience gained with vaccine safety, a dedicated vaccine eRMR was gradually moved to monthly eRMR (together with other intensively monitored products). Additionally, EMA ceased to use excel Validation Perpetual Reports (eVPRs) in 2023, enabling in-stream review of every new case report of interest. These eVPRs were extensively used in 2022 and 2021 (the number of vTMEs continuously reviewed was 405 in 2022 and 648 in 2021); however they proved to be most useful only in the earlier stages of safety monitoring.

EudraVigilance screening continues to be the major source of EMA's potential signals with 74% of reviewed potential signals in 2023 originating from EudraVigilance screening (compared to 83% in 2022). Scientific literature screening gave rise to 25% of potential signals in 2023 (14.8% in 2022). Additionally, cooperation with other regulatory authorities worldwide accounted for 1% of potential signals (1.5% in 2022), 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. The breakdown of actions taken by potential signals opened by EMA has been relatively stable 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 - 2023	% of total	Number of potential signals - 2022	% of total	Number of potential signals - 2021	% of total
Not validated (closed)	1091	80.0%	1,103	80.2%	1157	77.9%
Monitored	90	6.6%	89	6.5%	97	6.5%
Ongoing	144	10.6%	152	11.1%	193	13%
Prioritised and assessed by PRAC	39	2.9%	31* (39 combined)	2.3%	40* (55 combined)	2.7%
Total	1364	100.0%	1,375	100.0%	1,485	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 that 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 2023 was 71, compared with 64 in 2022, representing an 11% increase compared to 2022. Of these, 39 were validated by the Agency (6 for COVID-19 vaccines and 33 for other products) and 32 were validated by the MSs (3 for COVID-19 vaccines and 29 for other products) during ongoing safety monitoring through screening of reaction monitoring reports, ADR reports, medical literature and other safety data. Of the signals assessed by the PRAC, 13% were related to COVID-19 vaccines (25% in 2022 and also in 2021). Overall, 94% of the signals included data from EudraVigilance among their sources (86% in 2022).

Nineteen of the assessed signals (27%) 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 13 signals (18%) continuing with routine safety monitoring of the medicine was considered sufficient. The evaluation of 39 signals (55%) was ongoing at the end of 2023, including 16 via a follow-up signal procedure and 23 as part of upcoming PSURs/PSUSAs. No signals led to a referral procedure and 2 signals resulted in PASS studies (as the outcome was within evaluation in PSUR/PSUSA and PASS, these 2 signals are merged with ongoing (within PSUR/PSUSA) in Figure 15 below).

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 2023.

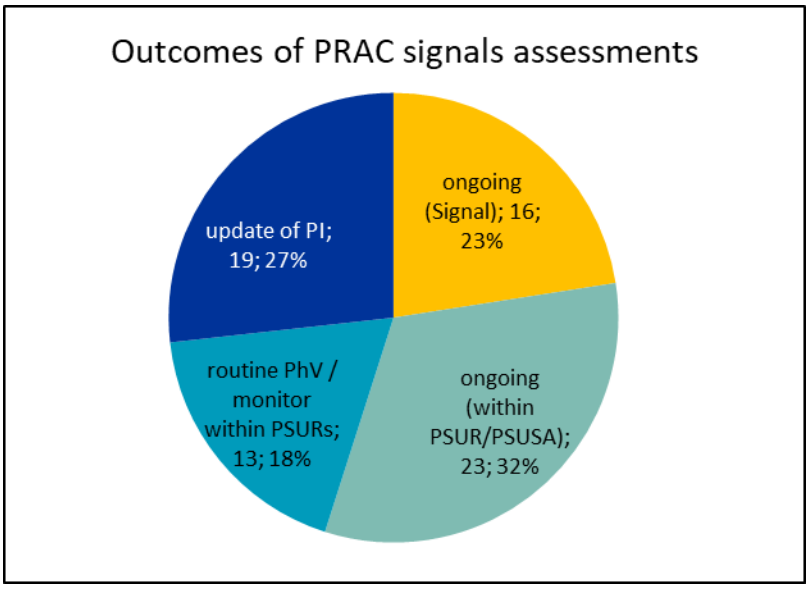


Figure 14. Outcomes of PRAC signal assessments (2023). PI: product information, PSUR: Periodic Safety Update Report, PSUSA: Periodic Safety Update Single Assessment, PhV: pharmacovigilance.

Table 8. A list of all COVID-19 vaccine signals prioritised and assessed by the PRAC in 2023 is provided below, noting the latest status or outcome as of 31 December 2023, by chronological order of signal

COVID-19 vaccine	Issue/signal	Status or outcome
Comirnaty (BioNtech/Pfizer)	Vulval ulceration	ongoing (within PSUR/PSUSA)
Vaxzevria (COVID-19 vaccine AZ)	Pemphigus and pemphigoid	routine pharmacovigilance / monitor within PSURs
Comirnaty (BioNtech/Pfizer)	Pemphigus and pemphigoid	ongoing (within PSUR/PSUSA)
Spikevax (Moderna)	Pemphigus and pemphigoid	ongoing (within PSUR/PSUSA)
Vaxzevria (COVID-19 vaccine AZ)	Myositis	routine pharmacovigilance / monitor within PSURs
Comirnaty (BioNtech/Pfizer)	Myositis	ongoing (within PSUR/PSUSA and PASS)
Spikevax (Moderna)	Myositis	ongoing (within PSUR/PSUSA and PASS)
Comirnaty (BioNtech/Pfizer)	Postmenopausal haemorrhage	ongoing (Signal)
Spikevax (Moderna)	Postmenopausal haemorrhage	ongoing (Signal)

Table 9. A list of all other signals prioritised and assessed by the PRAC in 2023 is provided below, in alphabetical order, noting the status or outcome as of 31 December 2023

Drug	Issue/signal	Status or outcome
Adalimumab; etanercept; infliximab	Menstrual disorder	routine pharmacovigilance / monitor within PSURs
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	update of PI
Dabrafenib; trametinib	Haemophagocytic lymphohistiocytosis (HLH)	update of PI
Regorafenib	Thrombotic microangiopathy	update of PI
Bosutinib	Interstitial lung disease	update of PI
Nivolumab	Morphoea	routine pharmacovigilance / monitor within PSURs
Colistin / colistimethate sodium (IV use)	Pseudo-Bartter syndrome	update of PI
Olaparib	Hepatocellular damage and hepatitis	update of PI
Voriconazole	Drug interaction with flucloxacillin leading to subtherapeutic voriconazole levels	update of PI
Propofol	Medication errors that could potentially lead to life-threatening/fatal cases	update of PI
Ceftriaxone	Risk of factor V inhibition	ongoing (within PSUR/PSUSA)
Evolocumab	Weight increased and abnormal weight gain	routine pharmacovigilance / monitor within PSURs
Progesterone	Meningioma	routine pharmacovigilance / monitor within PSURs
Glucagon-like peptide-1 (GLP-1) receptor agonists: dulaglutide; exenatide; insulin degludec, liraglutide; liraglutide; lixisenatide; insulin glargine, lixisenatide; semaglutide	Thyroid cancer	routine pharmacovigilance / monitor within PSURs

Drug	Issue/signal	Status or outcome
Lenvatinib	Adrenal insufficiency	update of PI
Ipilimumab; nivolumab; pembrolizumab	Capillary leak syndrome (OPDIVO, YERVOY, KEYTRUDA) and cytokine release syndrome (OPDIVO)	update of PI
Tofacitinib	Acnes	update of PI
Nusinersen	Arachnoiditis	ongoing (within PSUR/PSUSA)
Dupilumab	Weight decreased, abnormal loss of weight, cachexia, body mass index decreased	ongoing (within PSUR/PSUSA)
Pramipexole	Intestinal obstruction	routine pharmacovigilance / monitor within PSURs
Enoxaparin	Angiokeratoma	ongoing (within PSUR/PSUSA)
Apalutamide	Interstitial Lung disease (ILD)	update of PI
Baricitinib	Interstitial lung disease (ILD)	routine pharmacovigilance / monitor within PSURs
Rituximab	Oral lichenoid reaction	routine pharmacovigilance / monitor within PSURs
Mepolizumab	Arthralgia	ongoing (within PSUR/PSUSA)
Pirfenidone	Drug reaction with eosinophilia and systemic symptoms (DRESS)	update of PI
Megestrol	Meningioma	routine pharmacovigilance / monitor within PSURs
Acetazolamide	Choroidal effusion and choroidal detachment	update of PI
Efgartigimod alfa	Anaphylactic reaction	update of PI
Amivantamab	Anaphylactic reaction	routine pharmacovigilance / monitor within PSURs
Azacitidine	Cutaneous vasculitis	update of PI

Drug	Issue/signal	Status or outcome
Leuprorelin	Severe cutaneous adverse reactions (SCARs)	ongoing (within PSUR/PSUSA)
Dapagliflozin; dapagliflozin, metformin; dapagliflozin, saxagliptin	Acquired phimosis and phimosis	update of PI
Latanoprost	Choroidal detachment and choroidal effusion	ongoing (within PSUR/PSUSA)
Axicabtagene Ciloleucel	Progressive multifocal leukoencephalopathy (PML)	update of PI
Encorafenib; Binimetinib	Tumour lysis syndrome	ongoing (within PSUR/PSUSA)
Glucagon-like peptide-1 (GLP-1) receptor agonists: dulaglutide; exenatide; liraglutide; insulin degludec, liraglutide; lixisenatide; insulin glargine, lixisenatide; semaglutide	Suicidal ideation and self-injurious ideation	ongoing (Signal)
Dabrafenib; Trametinib	Peripheral neuropathy	update of PI and monitor within PSURs
Liraglutide	Drug-Induced Liver Injury	ongoing (within PSUR/PSUSA)
Ixazomib	Angioedema and anaphylactic reaction	ongoing (within PSUR/PSUSA)
Minoxidil (topical formulation)	Hypertrichosis in children following accidental exposure via patients	ongoing (within PSUR/PSUSA)
Avatrombopag	Antiphospholipid syndrome	ongoing (Signal)
Atezolizumab; avelumab; cemiplimab; dostarlimab; durvalumab; ipilimumab; nivolumab; nivolumab, relatlimab; pembrolizumab; tislelizumab; tremelimumab	Pancreatic failure	ongoing (Signal)
Atezolizumab; avelumab; cemiplimab; dostarlimab; durvalumab; ipilimumab; nivolumab; nivolumab, relatlimab; pembrolizumab; tislelizumab; tremelimumab	Coeliac disease	ongoing (Signal)
Osimertinib	Anaphylactic reaction	ongoing (within PSUR/PSUSA)
Cefotaxime	Drug reaction with eosinophilia and systemic symptoms (DRESS)	ongoing (Signal)
Cobimetinib Vemurafenib	Aphthous ulcer, mouth ulceration, stomatitis	ongoing (Signal)
Palbociclib	Rhabdomyolysis by interaction with statins	ongoing (within PSUR/PSUSA)

Drug	Issue/signal	Status or outcome
Amphotericin B	Hyperkalaemia	ongoing (Signal)
Chlorhexidine (di)gluconate, isopropyl alcohol	Product caught fire	routine pharmacovigilance / monitor within PSURs
Chlorhexidine	Persistent corneal injury and significant visual impairment	ongoing (Signal)
Teriparatide	Alopecias	ongoing (Signal)
Abemaciclib; palbociclib; ribociclib	Erythema multiforme	ongoing (Signal)
Exenatide; liraglutide; dulaglutide; semaglutide; lixisenatide; tirzepatide	Aspiration, pneumonia aspiration	ongoing (Signal)
Esomeprazole; omeprazole	Erectile dysfunction	ongoing (within PSUR/PSUSA)
Osimertinib	Progressive multifocal leukoencephalopathy	ongoing (within PSUR/PSUSA)
Afatinib	Growth of eyelashes	ongoing (within PSUR/PSUSA)
Glatiramer acetate	Anaphylaxis with a long latency	ongoing (within PSUR/PSUSA)
Doxycycline	Suicidality	ongoing (Signal)
Elexacaftor, tezacaftor, ivacaftor; ivacaftor; lumacaftor, ivacaftor; tezacaftor, ivacaftor	Intracranial pressure increased	ongoing (Signal)
Brolucizumab	Scleritis	ongoing (within PSUR/PSUSA)
Ethambutol	Drug reaction with eosinophilia and systemic symptoms (DRESS)	ongoing (Signal)
Brolucizumab	Scleritis	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 2023 is summarised below.

The SMART Processes group has continued to support the signal management process by providing guidance and clarifications as regards the definition of signals, in line with GVP IX. Issues that are not covered in the product information of some Member States but are adequately reflected in the product information of others, may suggest a possible need to harmonise labels, but do not qualify as safety signals, because they do not highlight a new potential causal association or a new aspect of a known association.

The group also discussed some practicalities to facilitate the smooth management of signals whose scope includes the entire therapeutic class, e.g. possibility to have a preparatory meeting to identify the Rapporteur for the signal, ideal time for discussion during plenary PRAC meeting, timelines for circulation of the consolidated assessment report within the Network.

The SMART processes group has provided a platform to share information and experiences within the Network, e.g. on signals for which PRAC requests MAHs to update the product information directly after the first plenary discussion, without a prior request for a cumulative review. Although those instances are not frequent, the group acknowledged that PRAC recommendations are driven by science, hence a review by the MAH may not be necessary in case the Committee establishes, after the first plenary discussion, that enough evidence in support of a product information update is already available. In those instances, the concerned MAHs would normally be given the opportunity to provide comments on the proposed product information update.

The group also discussed the significant update to the Member State signal management work-sharing list carried out during the year. By releasing capacity at Member States level, it was possible to allocate an excess of 200 active substances.

The SMART Methods group continued its work in 2023 and made marked progress in accordance with its 2022 – 2025 workplan. A new addition to the way of working of the group was the creation of focus groups which meet quarterly to work intensively on specific topics of interest and provide feedback on progress and activities in the quarterly SMART Methods meetings.

Research topics include:
A pregnancy algorithm developed in EudraVigilance was fine-tuned to identify maternal exposure to a medicinal product during pregnancy associated with a suspected adverse reaction. The algorithm is built upon expert knowledge using structured data elements that have the potential to hold pregnancy-related information. Meetings in 2023 facilitated knowledge sharing between EMA and the Uppsala Monitoring Centre on this field. Following the algorithm's finalisation, a publication was underway in 2023 and the implementation in EVDAS is foreseen for the second quarter of 2024. The focus group will continue to have a key role in validating the algorithm and evaluating its performance.

The masking effect focus group has explored the impact of the COVID-19 vaccine reports on signal detection practices and regulatory decision-making. Following its kick-off meeting in September 2023, members have been working on identifying key questions to explore and defining the scope. Masking is a long-known issue in quantitative signal detection methods based on disproportionality. To that end, since the impact of the volume of reports generated by the COVID-19 vaccination campaigns has

affected most national spontaneous reporting systems, a survey was circulated to gather information on the masking effect, including any remediation methods implemented related to COVID-19 vaccines.

Further updates on tools and methodologies discussed within SMART Methods in 2023:

Restricted Reporting Odd Ratio (ROR) analyses in comparison with the crude ROR calculation, has been explored as a potential tool for investigating causal association or mitigating masking in COVID-19 vaccine safety monitoring. The case studies discussed focused on similar target populations, and if carefully designed ad-hoc subgroup analyses may be a useful addition to current armamentarium to contextualize crude ROR.

Observed/Expected (O/E) analysis: The use of O/E analysis beyond COVID-19 vaccines to other medicinal products remained a topic of investigation. Results from the utilisation of O/E analysis on national patient register data provided additional practical insights, highlighting the strengths and limitations of this methodology. EMA followed up with a commentary on pharmacoepidemiological considerations for O/E analysis on COVID-19 vaccines. Overall, based on the experience gathered so far, while O/E analysis is viewed as a supportive tool that can facilitate contextualization of data during extreme circumstances, its limitations must be considered on a case-by-case basis.

European Union's product information Entity extraction and Knowledge acquisition tool (EUREKA): The EurEKA project aims to develop a database of Adverse Drug Reactions (ADRs) using current summary of product characteristics (SmPCs). Following an overview of the different models tested so far and lessons learnt from their respective performance, the project roadmap includes: i) developing a rule-based algorithm, ii) developing a web-application to expose the data for use iii) involvement of human in the loop to allow ADR editing and iv) modular approach easy to update and expand to National Competent Authority (NCA) SmPCs.

Signal and Safety Analytics (SSA) project: The first phase of the implementation of the SSA project aims to create a minimal viable product for signal detection and validation for EMA and NCA users, with additional functionalities for Marketing Authorisation Holders and other stakeholders in phase two. The selected tool will feature built-in algorithms and AI-based functionalities that will be assessed by the SMART Methods group. The first phase of the project is expected to finish by the end of 2024.

Website update for SMART working groups

The EMA corporate website was updated to include information on SMART working groups, to enhance visibility on their work and promote collaboration. Information can be found at www.ema.europa.eu under Committees > Working parties and other groups.

Annex VII - Requests for information and documents

In 2023, EMA responded to 20 requests for EudraVigilance (EV) data, where requests for information (involving aggregated data) and/or documents (line listings) were provided. This number of requests is a decrease compared to 2022 (29 requests). EMA continues to receive significantly fewer 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 2023, EMA supplied an additional 65 responses to requests for clarifications concerning this website or general aspects of EV data. This is more than double the number of responses sent out in 2022.

Of the 20 requests for EV data, 13 (65%) were requests for information (involving aggregated data), whilst 7 (35%) involved requests for documents (line listings). The majority of the requests (15) were related to centrally authorised products (CAPs), accounting for 75% of the total number of requests. There were 5 requests concerning both CAPs and nationally authorised products (NAPs), accounting for the remaining 25% (see figure 16).

The figure of 20 requests corresponds to internal requests from the EU regulatory network (6) in addition to external requests (14) 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 EU institutions (3), the general public including patients (2), not-for-profit organisations (1), non-EU regulatory authorities (2) or requests from academia (6) (see figure 17).

As regards the geographic origin of the queries, 17 (85%) originated from the EU, while only 3 (15%) originated from outside of the EU (see figure 18).

COVID-19 related queries

A high proportion of the requests for EV data in 2023 were still relating to one or more of the centrally authorised COVID-19 vaccines (13 out of 20 requests, accounting for 65% of the requests). This is lower than the previous year (23 requests in 2022, accounting for 79% of the requests). Eight out of these 13 requests (61.5%) originated within the regulatory network/EU institutions, followed by two requests from academia, two from patients and one request from a not-for-profit organisation (15%). There were no requests from journalists in 2023.

For more details on the requests for EV data responded to in 2023, please refer to Table 10.

Figures 16, 17 and 18 below provide an overview by authorisation type of concerned products, type of request, requester type and geographic origin.

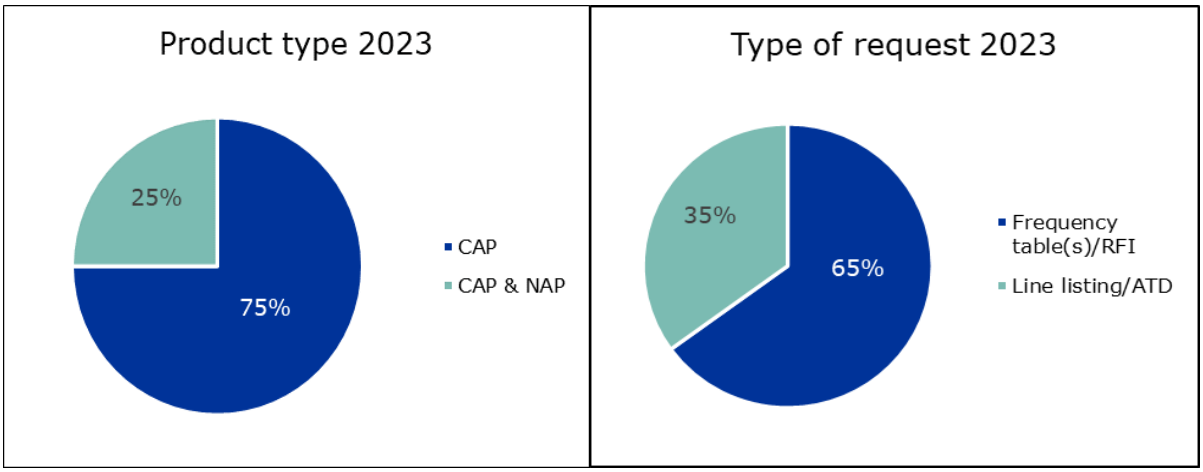


Figure 16 Overview of requests for EV data in 2023 by product type (left) and type of request (right).

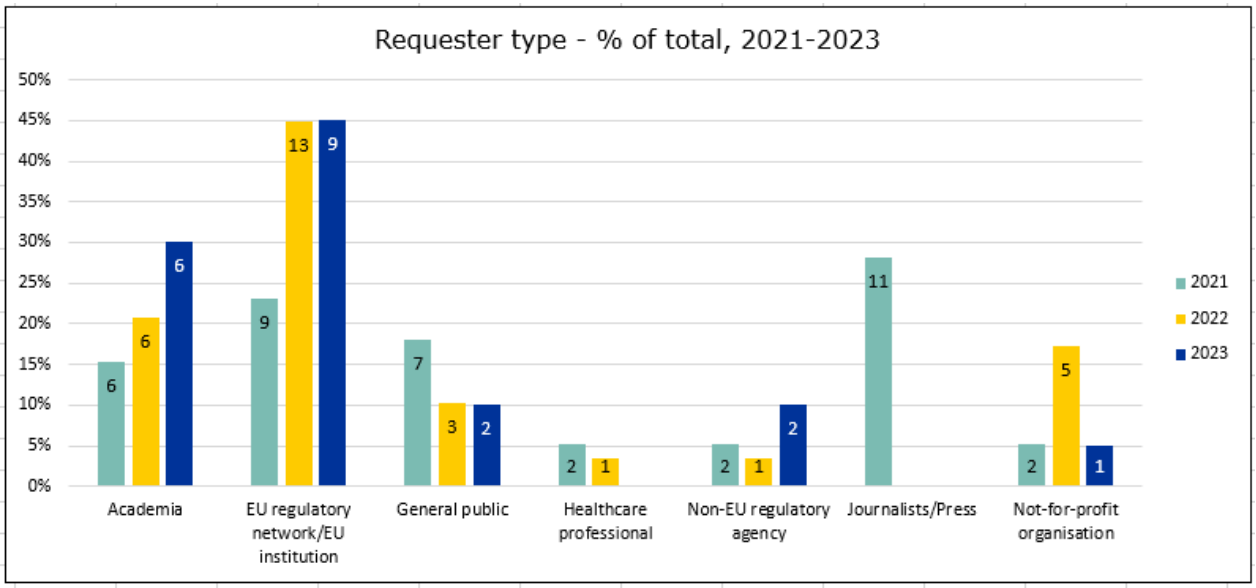


Figure 17 Overview of requests for EV data in 2023 by requester type.

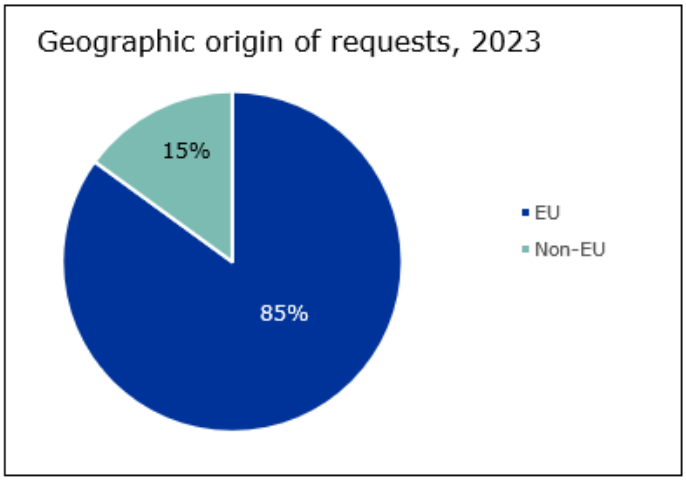


Figure 18 Overview of requests for EV data in 2023 by geographic origin.

Table 10 Overview of requests responded to in 2023

Type of requester	Substance/ product	Issue	Type of request
Academia/research institute	All medicinal products	All ADRs reported in patients aged 0-18 for requested period	Line listing/ATD
Non-EU regulatory agency	Bimekizumab	Suicide/self-injury	Frequency table(s)/RFI
EU regulatory network/EU institution	Covid-19 vaccines	All ADRs	Frequency table(s)/RFI
EU regulatory network/EU institution	Covid-19 vaccines	Country of origin for requested cases	Line listing/ATD
EU regulatory network/EU institution	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	All ADRs per batch	Line listing/ATD
Academia/research institute	Covid-19 vaccines	All ADRs reported by country, batch number, administration date, ADR onset date	Line listing/ATD
Academia/research institute	Covid-19 vaccines	All ADRs reported by country, batch number, administration date, ADR onset date	Line listing/ATD
EU regulatory network/EU institution	Covid-19 vaccines	All ADRs	Frequency table(s)/RFI
General public	Covid-19 vaccines	All ADRs for requested period	Frequency table(s)/RFI
EU regulatory network/EU institution	Covid-19 vaccines	All ADRs	Frequency table(s)/RFI
EU regulatory network/EU institution	Covid-19 vaccines	All ADRs	Frequency table(s)/RFI
EU regulatory network/EU institution	Covid-19 vaccines	All fatal ADRs	Frequency table(s)/RFI
Non-EU regulatory agency	Gadolinium based contrast agents	All ADRs for requested period	Frequency table(s)/RFI
Academia/research institute	Methotrexate	All ADRs	Line listing/ATD

Type of requester	Substance/ product	Issue	Type of request
EU regulatory network/EU institution	mRNA Covid-19 vaccines	All ADRs	Frequency table(s)/RFI
EU regulatory network/EU institution	Seasonal flu vaccines (Fluenz Tetra, Intanza/IDflu, Optaflu)	All ADRs for requested period	Frequency table(s)/RFI
Academia/research institute	Various	All ADRs related to counterfeit, adulterated and falsified medicines	Frequency table(s)/RFI
Academia/research institute	Various	Nephrotoxicity for requested substances	Frequency table(s)/RFI