20 March 2025
EMA/559856/2024 - Noted
Human Medicines Division

2024 Annual Report on EudraVigilance for the European Parliament, the Council and the Commission

Reporting period: 1 January to 31 December 2024

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List of abbreviations

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 and analysing reports of medical events and problems that occur following the use of a medicine are the pillars of the European Union (EU) safety monitoring system. Healthcare professionals and patients play a critical role and are encouraged to continue to report suspected adverse reactions individuals may have experienced after administration of a medicine.

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 performed by EMA's Pharmacovigilance Risk Assessment Committee (PRAC) through the assessment of periodic safety update reports (PSURs) and risk management plans (RMPs). EudraVigilance is therefore one of the cornerstones of EU pharmacovigilance (See Figure 1).

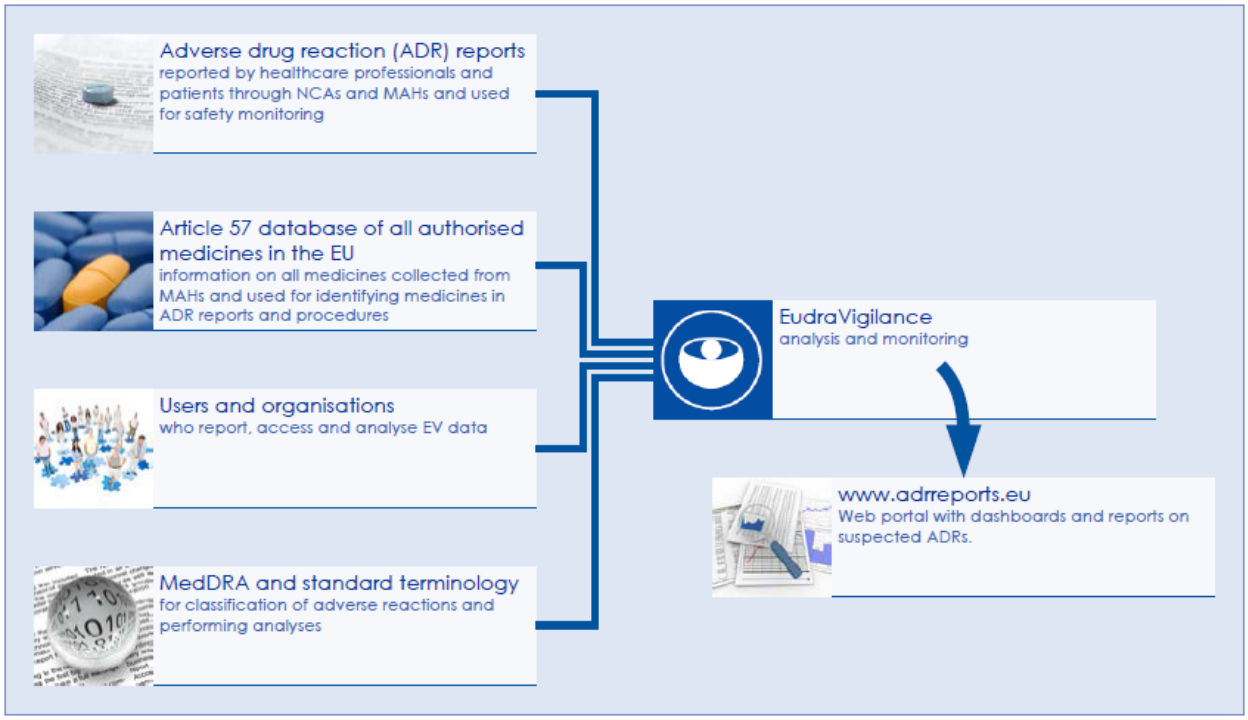

Figure 1. EudraVigilance users, data sources and data use.

The EudraVigilance database currently holds over 29.3 million individual case safety reports (ICSRs) relating to 16.9 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 2024, notably:

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

- ***Operation of EudraVigilance, including its new functionalities.*** EudraVigilance is maintained by EMA on behalf of the EU medicines regulatory network. Further functional improvements in data analysis and signal detection were delivered, including works with an external vendor on the Signal and Safety Analytics project; the first User Acceptance Test of the new system took place in October 2024. 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 2024, nearly 1.8 million ICSRs related to suspected ADRs occurring after authorisation were collected and managed in EudraVigilance (a 7.9% decrease compared to 2023). The number of ICSRs originating from the European Economic Area (EEA) decreased by 14.15% and non-serious reports by 17.76%.
- ***Screening for, and review of, potential safety signals***. In 2024, EMA's signal management team reviewed in detail 1,254 potential safety signals[2] related to 990 substances (an 8% overall decrease versus 2023). The review followed routine screening the EudraVigilance database and other sources. 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 is 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 safety signals which are confirmed by a Rapporteur or LMS are brought to the attention of the PRAC for initial analysis, prioritisation and assessment. In 2024, the PRAC prioritised and assessed 71 confirmed signals (the same number as in 2023). About 92% of them included data from EudraVigilance among their sources. Of the 71 confirmed signals, 39 were validated by EMA and 32 were validated by the Member States (MSs), exactly like in 2023; 42 were for CAPs, 19 for NAPs and 10 for both CAPs and NAPs.
- ***Transparency and public access to aggregated EudraVigilance data***. The public has access to data on all spontaneous reports of suspected adverse reactions in EudraVigilance through the public European database of suspected adverse drug reactions reports. By the end of 2024, this database included information on 4,448 active substances, 990 of which were contained in CAPs and 3,458 in NAPs.
- ***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 safety 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 the detection of risks related to medicines, and 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 in 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 2024 are summarised here:

The EMA multi-factor authentication (MFA) was enabled and implemented in the EudraVigilance Data Analysis System (EVDAS) during the first quarter of 2024. Communications were issued with instructions for users to check and set up the MFA credentials in advance of this functionality being implemented.

The 6-monthly systematic review of the list of EudraVigilance users and the verification of their access role was performed in March 2024 and in September 2024 through the EMA account management system. The review was performed by the QPPV/Responsible Person (RP) user (or trusted deputy) without major incidents and any roles that were not assessed within one month of the review process starting were revoked. This process, which was first implemented in 2023, can now be considered well-established and suitable to ensure that the data held in EudraVigilance is protected.

During 2024, a technical analysis documenting the current consuming systems using XEVMPD data was conducted; several options to modernise the current dictionary and move towards an ISO IDMP compliant database were proposed. A decision on the preferred solution is expected in 2025, followed by the start of activities aiming to enhance the use of the XEVMPD and make it ISO IDMP compliant.

Following the extension to the end of 2024 of the pilot on the mandatory monitoring of data in EudraVigilance by marketing authorisation holders (MAHs) and the related transitional arrangements, the EC published the draft updated Commission Implementing Regulation 520/2012 on pharmacovigilance activities for public consultation. Stakeholders and the general public had until 15th January 2025 to provide comments and feedback. It is expected that the updated Commission Implementing Regulation 520/2012 will be published in 2025, and with that the pilot for monitoring EudraVigilance by the MAHs of selected active substances that was initiated in February 2018 will come to an end. The EMA issued a communication and an announcement to indicate that the pilot on signal detection by MAHs in EudraVigilance will be extended beyond the end of 2024 in its current form and will be terminated as of the entry into force of the amended Commission Implementing Regulation 520/2012.

During the course of 2024, EMA started working with an external vendor on the Signal and Safety Analytics project. The objective of this project 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 in a more effective and efficient way. The first phase of the project will be the delivery of a minimum viable product covering the core functionalities for signal detection and validation by the EMA pharmacovigilance service and the NCAs. The first User Acceptance Test of the new system took place

in October 2024. The EMA and the EU network will continue with the next phases of the project during 2025.

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 United Kingdom authorities under UK law, EMA has published a questions and answers document on the implications of the above referenced regulation. The document describes the consequences for the safety reporting into EudraVigilance and access to EudraVigilance data. Regulation (EU) 2023/1182 came into force on 1st January 2025.

During 2024, EMA has continued the work on the development of 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 EudraVigilance data quality and adherence to the reporting timelines. These reports will be based on the serious and non-serious cases submitted to the EudraVigilance post-marketing module and the EudraVigilance clinical trials module. The results of the pilot conducted with stakeholders (including MAHs, commercial and non-commercial sponsors and NCAs) have been analysed, and the required technical improvements have been initiated. Further communication and engagement with stakeholders and inspectors are foreseen.

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 2024 in facilitating the early detection of emerging risks with COVID-19 vaccines and therapeutics.

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 authorised during 2024.

Following the publication of the Data Quality Framework for EU medicine regulation, EMA organised on 1st March 2024 a multi-stakeholder workshop on Data Quality Framework for Adverse Drug Reaction reporting. The aim of this workshop was to bring together experts in the field to build on their extensive experience and knowledge relating to ADR data quality. The workshop was attended online by approximately 160 people from various stakeholder groups. A high-level summary of the workshop presentations, as well as highlights from the discussions with stakeholders, were published in August 2024.

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

EMA 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 2024, on 21st March and 10th October. The new EV-EWG work programme for 2025-2026 will be published during Q1 2025. The EMA-MSs Pharmacovigilance Business team met quarterly in 2024 to discuss, agree on, and issue guidance for the different EudraVigilance operations.

The EudraVigilance training page was updated to launch a training course on the enhanced EudraVigilance system and a course for clinical trial sponsors, which will be available in 2025.

In March 2023 the European Data Protection Supervisor (EDPS) audited the EudraVigilance system at the EMA premises. In May 2024, the EMA received the EDPS audit report and started working on the

relevant actions and recommendations. Within these actions, EMA together with NCAs and in consultation with the MAHs is developing a masking guideline to be implemented by the senders of ICSRs to EudraVigilance. It is expected that the masking guideline will be adopted and published in 2025.

3. Data collection and data quality

Medicinal product information

In the database of all medicines authorised in the EU (the so-called "Article 57 database"), the total number of medicinal product entries provided by MAHs in the eXtended EudraVigilance Medicinal Product Dictionary (XEVMPD) was 1,139,255 (as of 31 December 2024), regardless of authorisation status (e.g. valid, withdrawn). These entries relate to both CAPs and NAPs. 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

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 2024, 1,757,524 ICSRs were collected and managed in EudraVigilance. This figure represents a 7.9% decrease compared to the numbers recorded in 2023 and is characterised by a decrease in EEA reports (-14.1%) and in non-serious reporting (-17.8%).

The number of reports submitted directly by patients and consumers through the NCAs and MAHs (127,329) saw a 27.7% decrease compared to the previous year.

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

EudraVigilance also continued to support the reporting of SUSARs that occurred during clinical trials, in accordance with the Clinical Trials Regulation[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 aimed at protecting 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 suspected adverse reactions,

[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.
[5] On 31 January 2022, the Regulation repealed the Clinical Trials Directive (EC) No. 2001/20/EC and national implementing legislation in the EU Member States, which regulated clinical trials in the EU until the Regulation's entry into application.

removing duplicate reports, ensuring timely submission of serious and non-serious suspected 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

The EU pharmacovigilance system has been efficient in detecting issues and dealing with them. For example, the EU network identified the safety signal of suicidal ideation associated with GLP-1 receptor agonists, and EudraVigilance analysis played a central role in the assessment of this signal. The PRAC assessment started in 2023 and was finalised in April 2024. The network also evaluated the signal of secondary malignancies of T-cell origin with chimeric antigen receptor (CAR) T-cell medicines: this assessment was finalised in June 2024 resulting in a labelling update and a direct healthcare professional communication (DHPC).

EudraVigilance data monitoring is a collaborative effort between NCAs and EMA. The safety information contained in EudraVigilance is continuously screened through statistical reports called electronic reaction monitoring reports (eRMRs). In 2024, over 14,000 eRMRs were generated for NCAs and EMA's signal management team, for a total of 2,758 substances. These were produced on a monthly, three-monthly, or six-monthly basis.

Screening of these outputs is one of the principal sources of validated safety signals, i.e. information on observed ADRs potentially caused by a medicine that warrant further investigation. For CAPs, EMA leads this monitoring: 1,254 potential safety signals were reviewed by the Agency in 2024 (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. 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 combinations of substances no longer eligible for worksharing or substances no longer authorised in the Member States were removed from eRMRs monitoring work-sharing.

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 2024, the PRAC assessed 71 confirmed signals (same as in 2023, see Figure 2).

[6] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/list-substances-products-subject-worksharing-signal-management_en.xlsx

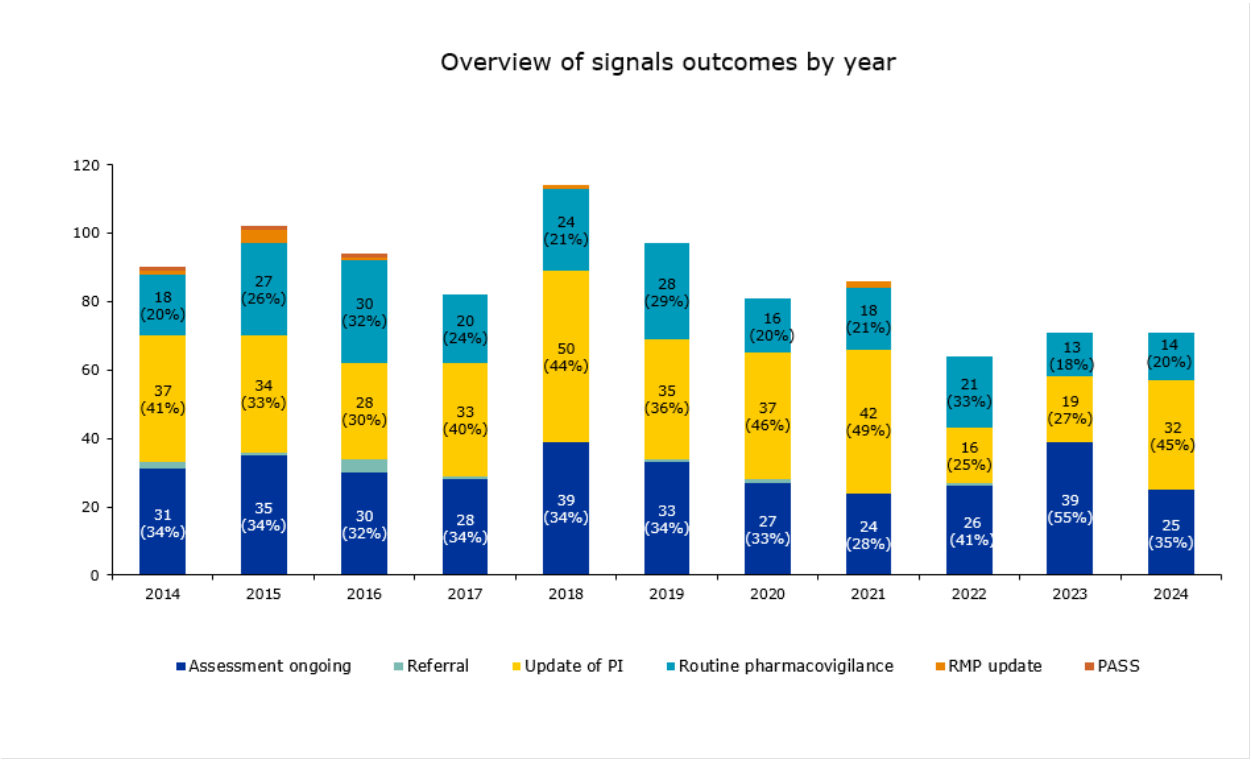

Figure 2. Overview of signals assessed by the PRAC

Of the 71 signals assessed by the PRAC, 67 (92%) included data from EudraVigilance. Thirty-two of the assessed signals (45%) 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 affected medicines (27% in 2023). For 14 signals (20%), continuing with routine safety monitoring of the medicine was considered sufficient. The evaluation of 25 signals (35%) was ongoing at the end of 2024, including 12 via a follow-up signal procedure and 13 as part of upcoming PSURs/PSUSAs. No signals led to a referral procedure and 2 signals resulted in a DHPC (as the outcome was update of PI and DHPC, these 2 signals are merged with "update of PI" in Figure 2 above).

EudraVigilance monitoring thus facilitated detection and 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 2024 can be found in Annex V. The progress of process improvements and simplifications in signal management is detailed in Annex VI.

From February 2018 up until December 2024, the network received 57 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 nor 2024).

5. Transparency, communication and training

PRAC agendas, minutes and signal recommendations, including the translation 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 (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 2024, the website provided information on a total of 4,448 active substances, of which 990 were contained in CAPs and 3,458 in NAPs.

The Agency also continued responding to requests for information related to EudraVigilance and requests for access to EudraVigilance documents, in line with the current EudraVigilance Access Policy. In total, 24 requests were answered (4 more than in 2023). This corresponds to internal requests from the EU regulatory network (4) in addition to external requests (20) 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:

- 9 training sessions on EudraVigilance ICSR submissions, with 212 users trained in total
- 3 training sessions on EudraVigilance ICSR submissions for clinical trial sponsors, with 64 users trained in total.

6. Conclusion

EudraVigilance continued to play a crucial role in 2024 and it remains a central pillar for pharmacovigilance activities in the EEA.

In 2024, nearly 1.76 million ICSRs were collected and managed in EudraVigilance, a 7.9% decrease compared to the previous year. Approximately 7.2% of the ICSRs received in 2024 were submitted directly by patients and consumers through NCAs and MAHs.

Based on these reports, 14,000 statistical outputs were produced to facilitate the continuous monitoring of the safety of medicines by the Agency and NCAs and the detection of signals which were subsequently assessed by the PRAC.

EudraVigilance currently contains over 29.3 million ICSRs, corresponding to 16.9 million unique suspected ADR case reports and it is being used by EMA, NCAs and MAHs.

In 2024 there were several technical developments for EudraVigilance. The Agency actively prepared for the implementation on 1st January 2025 of Regulation (EU) 2023/1182. This relates to 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 in the territory of Northern Ireland that will be done by the United Kingdom authorities under UK law.

The results from the European Data Protection Supervisor (EDPS) audit conducted in 2023 on the EudraVigilance system were another milestone. After receiving these results in May 2024, the Agency started working on remedial measures.

Finally, the Agency continued the work started in 2023 on reviewing the EudraVigilance data analytics platform and tools for more effective and efficient ADR report analysis. The first user acceptance

testing was conducted in October 2024. This is a complex and impactful project which will continue in 2025.

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.

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 safety signals validated and notified by MAHs based on EudraVigilance monitoring. [*Legal basis:* Commission Implementing Regulation (EU) 520/212, Article 18 and 21]	Started 22 February 2018. Continued during 2024.
Data quality review and duplicate management of suspected adverse reaction reports in EudraVigilance. [*Legal basis:* Regulation (EC) 726/2004, Article 24(3)]	Continued during 2024.
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 2024.
Provision of 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 2024.
Operation of the signal management processes based on EudraVigilance data, including the monthly provision of eRMRs to LMSs 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 2024.
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 2024.
Operation of the medical literature monitoring service. [*Legal basis:* Regulation (EC) 726/2004, Article 27]	Continued during 2024.

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 suspected ADR reports between the Agency, NCAs and MAHs for all medicines authorised in the EEA. This network, known as the EudraVigilance gateway, has been in continuous operation since December 2001.

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 the initial and follow-up ICSRs, constitute a unique suspected ADR case report.

By 31 December 2024, the EudraVigilance database held a total of 29,317,644 ICSRs, referring to 16,902,323 individual cases (Figure 3). The EudraVigilance post-authorisation module (EVPM) contained 27,332,221 ICSRs (16,384,464 individual cases) and the EudraVigilance clinical trial module (EVCTM) contained 1,985,423 ICSRs (517,859 individual cases of Suspected Unexpected Serious Adverse Reactions (SUSARs)).

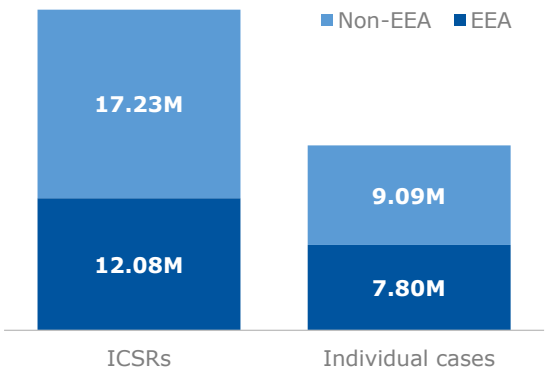

Figure 3. Number of ICSRs versus individual cases received in the EudraVigilance database (EVPM and EVCTM) from its inception in December 2001 until 31 December 2024, split by origin of the report (in or outside the EEA).

Figure 4. presents the number of ICSRs processed per year in EVPM split by cases occurring within and outside the EEA. **Figure 5.** presents the total number of ICSRs received in EVPM for 2024, compared to the number of individual cases they are referring to.

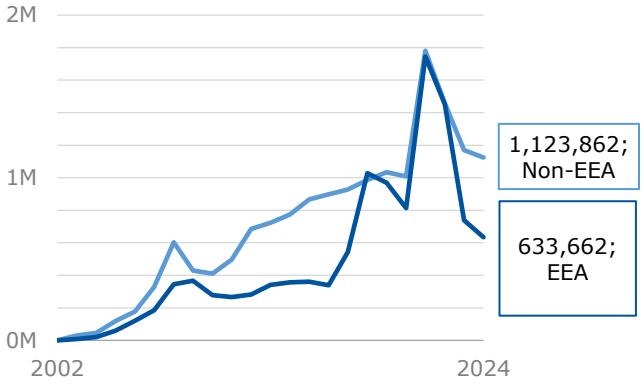

Figure 4. Number of ICSRs processed per year in EVPM split by cases occurred inside and outside the EEA.[7]

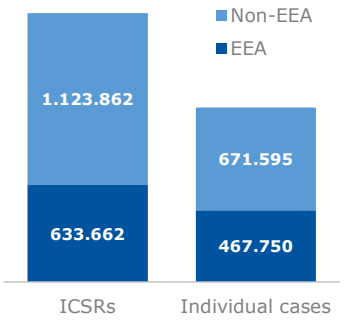

Figure 5. Number of ICSRs versus the number of individual cases in 2024 in EVPM.

The numbers presented in **Figure 6.** and **Figure 7.** refer to the ICSRs received in EVPM. A total of 27,332,221 EVPM ICSRs were processed over the years up to the end of 2024, of which 1,757,524 EVPM ICSRs were processed in 2024. This represents a 7.9% decrease compared to the numbers recorded in 2023, and it is characterised by a decrease in EEA (-14.15%) and non-serious (-17.76%) reporting. ICSRs are subsequently made available for signal detection and data analysis by the Agency and NCAs in the Member States.

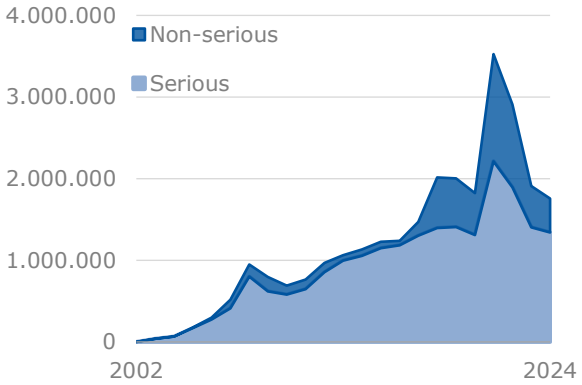

Figure 6. Number of ICSRs processed per year in EVPM.

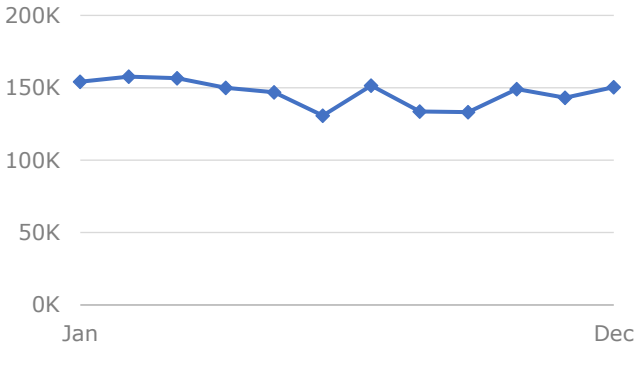

Figure 7. Number of ICSRs processed per month in EVPM in 2024.

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

In 2024, 127,329 ICSRs were submitted by European patients and consumers through the NCAs and MAHs, referring to 103,147 individual cases. This is a decrease of 27.67%% in the number of such reports compared to the previous year (**Figure 8**).

In 2024, 831,365 spontaneous ICSRs (EEA and non-EEA) were processed, a very similar figure compared to the previous year (0.4% decrease, **Figure 9**).

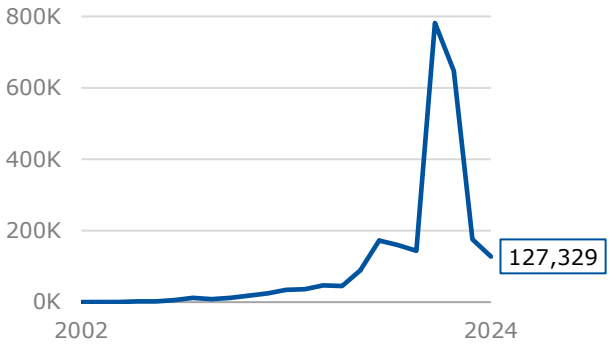

Figure 8. Number of ICSRs reported by European patients and consumers through the NCAs and MAHs.

Figure 9. Number of spontaneous ICSRs per year (EEA + non-EEA).

Table 1. Number of EVPM ICSRs and unique cases transmitted in 2024. Counts for 2023 are provided for comparison.

	2024	2023
	Total count	**Total count**
ICSRs processed	1,757,524	1,908,605
ICSRs originated in EEA	633,662	738,100
Non-serious ICSRs	415,462	505,203
ICSRs reported by European patients and consumers through the NCAs and MAHs	127,329	176,044

E-reporting status for MAHs and sponsors of clinical trials

- 1,141 MAHs (at headquarter level) sent reports to EVPM in 2024, a 0.6% decrease compared to 2023.
- 731 sponsors of clinical trials (at headquarter level) sent reports to EVCTM in 2024, a 2% increase compared to 2023.
- A total of 19,621 individual MAH users and 10,394 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; **Figure 10.** 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 2024, 271,927 ICSRs and 209,311 SUSARs (total 481,238) were rerouted to NCAs following receipt of the reports from MAHs and sponsors in EudraVigilance. A total of 653,961 ICSRs were forwarded to WHO. A total of 220,734 download requests were made by MAHs, resulting in 6,437,670 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 2024.

EV Module	Transmission type	Count
EVPM	ICSRs	1,507,708
	Individual cases	873,336
EVCTM	ICSRs	155,864
	Individual cases	45,401

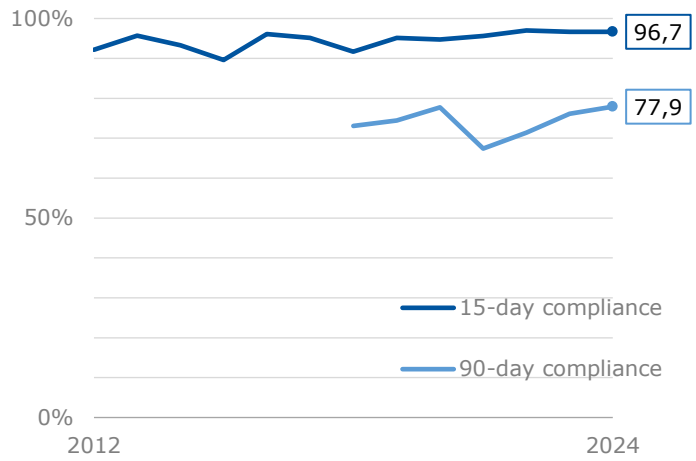

Figure 10. Compliance rate for serious (15-day) and non-serious (90-day) ICSRs to EVPM for all MAHs and sponsors by year. Non-serious ICSRs need to be submitted since November 2017.

EudraVigilance database and support of signal management process

In 2024, a total of 14,307 eRMRs were generated, concerning 2,758 substances, to facilitate the continuous monitoring of the safety of medicines by the Agency and NCAs in the EEA. Of these:

- 7,505 were monthly eRMRs,
- 5,083 were 3-monthly eRMRs,
- 1,719 were 6-monthly eRMRs.

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 1,380 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 11.** 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. Summary of medicinal product submissions to the XEVMPD

Number of ICSRs and unique cases transmitted by NCAs to EVPM and EVCTM during 2024

EV Module	Transmission type	Count
EVPM	ICSRs	249,816
	Individual cases	214,868
EVCTM	ICSRs	104
	Individual cases	38

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 2024, the following eight 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)
- Netherlands (Central Committee On Research Involving Human Subjects)
- Netherlands (Medicines Evaluation Board)
- Norway (Norwegian Medical Products Agency)
- 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 2024). **Table 4.** and **Figure 12.** below 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 2024 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).	1,139,255
Total number of MAHs (legal entities) established in the EU (corresponding to EudraVigilance codes).	6,399

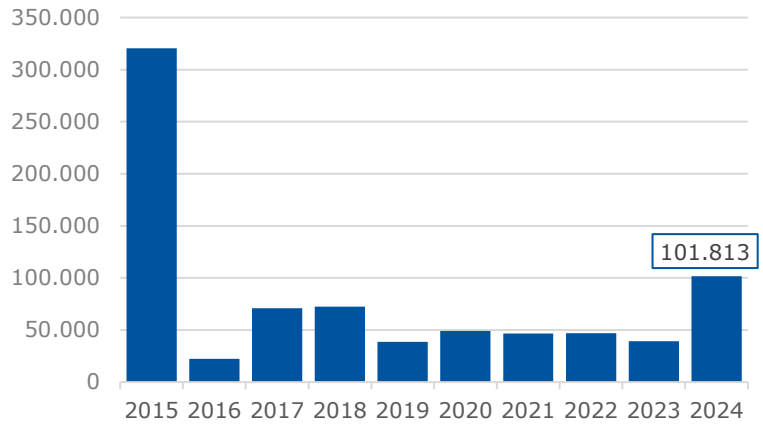

Figure 12. Yearly number of medicinal product submissions (counted on the basis of EudraVigilance codes) since 2015.

A surge in medicinal product submissions was observed in 2024 due to pack size submission from xEVMPD to product management service (PMS). Starting in the second half of 2024, each new product record must make reference to one pack size. This will support the European Shortages Monitoring Platform (ESMP).

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 2024 and provides 2023 and 2022 data for comparison.

Table 5. Summary of EudraVigilance data quality activities in 2024.

Data quality area	Activities performed	2024	2023	2022
Identifying and managing duplicate individual cases	Duplicate couples assessed	205,187	190,689	147,875
	Master reports generated based on duplicated data	52,661	105,033	41,728
Coding of reported medicines and active substances	Reported medicinal products and active substance terms recoded	137,335	77,598	147,054
	ADR reports recoded (ICSRs)	109,037	66,461	130,619
Providing feedback on data quality	Organisations subject to ICSR data quality review	186	160	32
	Medicinal products in XEVMPD quality reviewed (and corrected if necessary)	187,381	163,013	138,350

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 2024, EMA's signal management team reviewed in detail the information on 1,254 potential signals (i.e., drug-event pairs from screening of the EudraVigilance database, medical literature or information received from other regulatory authorities). This represents an approximately 8% decrease in the total number of reviewed signals compared to the previous year (see **Table 6**).

Table 6. Potential signals reviewed

Potential signals reviewed	2024	2023	2022	2021	2020	2019
Total	1254	1364	1605	1829	1888	1,806
Change from previous year	-110	-241	-224	-59	+82	-398
% change from previous year	- 8%	-14%	-12%	-3%	+4%	-18%

EudraVigilance screening continues to be the major source of EMA's potential signals, with 76% of reviewed potential signals in 2024 originating from EudraVigilance screening (compared to 74% in 2023). Scientific literature screening accounted for 22% of potential signals in 2023 (25% in 2023). Additionally, cooperation with other regulatory authorities worldwide accounted for 1% of potential signals (also 1% in 2023), including notifications from the World Health Organisation - Uppsala Monitoring Centre (WHO-UMC), the 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 approx. 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 - 2024	% of total	Number of potential signals - 2023	% of total
Not validated (closed)	953	76.0%	1091	80.0%
Monitored	83	6.6%	90	6.6%
Ongoing	179	14.3%	144	10.6%
Prioritised and assessed by PRAC	39	3.1%	39	2.9%
Total	**1,254**	100.0%	**1,364**	100.0%

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 2024 was 71, the same number as in 2023. Of these 71, 39 were validated by the Agency and 32 were validated by the MSs during ongoing safety monitoring through screening of reaction monitoring reports, ADR reports, medical literature and other safety data.

Thirty-two of the assessed signals (45%) 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 affected medicines. For 14 signals (20%), continuing with routine safety monitoring of the medicine was considered sufficient. The evaluation of 25 signals (35%) was ongoing at the end of 2024, including 12 via a follow-up signal procedure and 13 as part of upcoming PSURs/PSUSAs. No signals led to a referral procedure and 2 signals resulted in a DHPC (as the outcome was update of PI and DHPC, these 2 signals are merged with "update of PI" in Figure 13 below).

See Figure 13 for a summary, and Table 8 listing all the signals noting the latest status or outcome as of 31 December 2024.

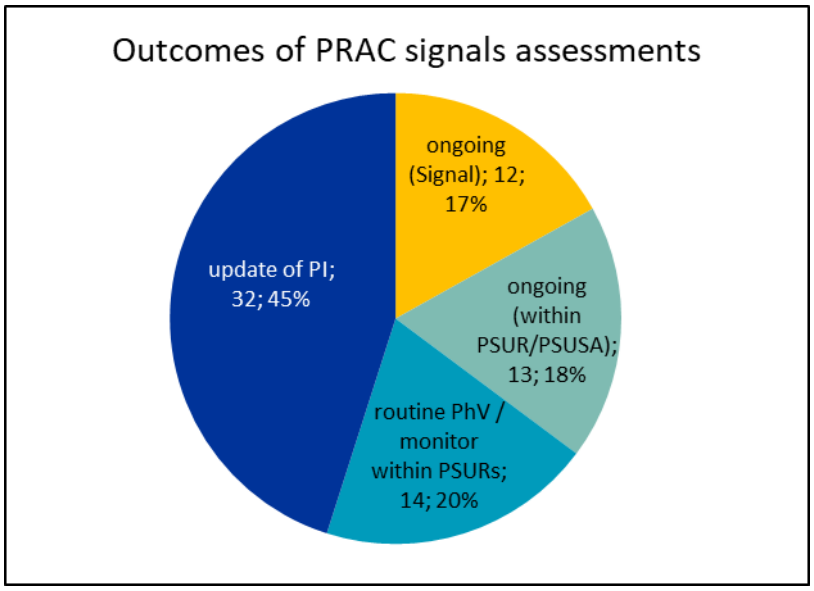

Figure 13. Outcomes of PRAC signal assessments (2024). PI: product information, PSUR: Periodic Safety Update Report, PSUSA: Periodic Safety Update Single Assessment, PhV: pharmacovigilance.

Table 8. A list of signals prioritised and assessed by the PRAC in 2024 is provided below, in alphabetical order, noting the status or outcome as of 31 December 2024.

Medicine	Issue	Status or outcome
Abemaciclib; palbociclib; ribociclib	Erythema multiforme	update of PI
Acetazolamide	Pulmonary oedemas	update of PI
Adagrasib	Febrile neutropenia	ongoing (within PSUR/PSUSA)
Adagrasib	Serious cutaneous adverse reactions (SCARs)	update of PI and monitor within PSURs
Adagrasib	Thrombocytopenia	ongoing (Signal)
Adalimumab	Paradoxical hidradenitis	ongoing (Signal)
Aflibercept	Nephropathy toxic after intravitreal administration	ongoing (within PSUR/PSUSA)
Amphotericin B	Hyperkalaemia	update of PI
Anakinra	Amyloidosis	update of PI
Angiotensin II receptor blockers: amlodipine, valsartan; amlodipine, valsartan, hydrochlorothiazide; azilsartan medoxomil; irbesartan; irbesartan, hydrochlorothiazide; telmisartan, sacubitril, valsartan; telmisartan; telmisartan, amlodipine; telmisartan, hydrochlorothiazide; sacubitril, valsartan; olmesartan; candesartan; eprosartan; losartan; other relevant fixed dose combinations containing angiotensin II receptor blockers	Intestinal angioedema	update of PI
Apalutamide	Lichenoid keratosis	update of PI
Atezolizumab; avelumab; cemiplimab; dostarlimab; durvalumab; ipilimumab; nivolumab; nivolumab, relatlimab; pembrolizumab; tislelizumab; tremelimumab	Coeliac disease	update of PI
Atezolizumab; avelumab; cemiplimab; dostarlimab; durvalumab; ipilimumab; nivolumab; nivolumab, relatlimab; pembrolizumab; tislelizumab; tremelimumab	Pancreatic failure	update of PI
Atezolizumab; avelumab; cemiplimab; dostarlimab; durvalumab; ipilimumab;	Scleroderma, systemic scleroderma, morphea	ongoing (Signal)

Medicine	Issue	Status or outcome
nivolumab; pembrolizumab; retifanlimab; tislelizumab; toripalimab; tremelimumab		
Atezolizumab; avelumab; cemiplimab; dostarlimab; durvalumab; ipilimumab; nivolumab; pembrolizumab; retifanlimab; tislelizumab; tremelimumab	Thrombotic microangiopathy	ongoing (Signal)
Avatrombopag	Antiphospholipid syndrome	update of PI
Axicabtagene ciloleucel; idecabtagene vicleucel; lisocabtagene maraleucel; ciltabtagene autoleucel; tisagenlecleucel; brexucabtagene autoleucel	Secondary malignancy of T-cell origin	update of PI and RMP and DHPC
Azathioprine	Non-cirrhotic portal hypertension / Portosinusoidal vascular disease	update of PI
Baricitinib	Hypoglycaemia in diabetic patients	update of PI
Bumetanide	Toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS)	update of PI
Canagliflozin, dapagliflozin, empagliflozin and ertugliflozin-containing mono products and their combinations	Sarcopenia	ongoing (Signal)
Canagliflozin; dapagliflozin; empagliflozin; empagliflozin, metformin	Polycythaemia	update of PI
Cefotaxime	Drug reaction with eosinophilia and systemic symptoms (DRESS)	update of PI
Ceftriaxone	Precipitation when administered with calcium-containing solutions in infants between 29 days and 1 year	routine pharmacovigilance / monitor within PSURs
Chlorhexidine	Persistent corneal injury and significant visual impairment	update of PI
Clobazam	Drug reaction with eosinophilia and systemic symptoms (DRESS)	routine pharmacovigilance / monitor within PSURs
Cobimetinib; vemurafenib	Aphthous ulcer, mouth ulceration, stomatitis	update of PI

Medicine	Issue	Status or outcome
COVID-19 mRNA vaccines (nucleoside-modified) (Comirnaty)	Postmenopausal haemorrhage	routine pharmacovigilance / monitor within PSURs
COVID-19 mRNA vaccines (nucleoside-modified) (Spikevax)	Postmenopausal haemorrhage	routine pharmacovigilance / monitor within PSURs
Dabrafenib; trametinib	Acute febrile neutrophilic dermatosis	update of PI
Domperidone	Hypertension in patients with a phaeochromocytoma	ongoing (within PSUR/PSUSA)
Doxycycline	Suicidality	routine pharmacovigilance / monitor within PSURs
Dupilumab	Thrombocytopenia	ongoing (within PSUR/PSUSA)
Elexacaftor, tezacaftor, ivacaftor; ivacaftor; lumacaftor, ivacaftor; tezacaftor, ivacaftor	Intracranial pressure increased	routine pharmacovigilance / monitor within PSURs
Emtricitabine, tenofovir disoproxil	Trigeminal neuralgia	ongoing (Signal)
Entrectinib	Myocarditis	ongoing (within PSUR/PSUSA)
Epcoritamab	Progressive multifocal leukoencephalopathy (PML)	update of PI
Eptinezumab; erenumab; fremanezumab; galcanezumab	Insomnia	routine pharmacovigilance / monitor within PSURs
Eptinezumab; erenumab; galcanezumab	Erectile dysfunction	routine pharmacovigilance / monitor within PSURs
Erenumab	Hypertension	ongoing (within PSUR/PSUSA)
Esketamine	Bradycardia	update of PI
Ethambutol	Drug reaction with eosinophilia and systemic symptoms (DRESS)	update of PI
Exenatide, liraglutide, dulaglutide, semaglutide, lixisenatide, tirzepatide	Aspiration and pneumonia aspiration	update of PI
Glofitamab	Immune effector cell-associated neurotoxicity syndrome (ICANS)	update of PI and RMP and monitor within PSURs

Medicine	Issue	Status or outcome
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	routine pharmacovigilance / monitor within PSURs
Human papillomavirus 9-valent vaccine (recombinant, adsorbed); human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)	Granuloma	update of PI
Ixazomib	Vasculitis	routine pharmacovigilance / monitor within PSURs
Ixekizumab	Demyelinating disorders	ongoing (Signal)
Lenvatinib	Tumour lysis syndrome	ongoing (Signal)
Lisocabtagene maraleucel	Progressive multifocal leukoencephalopathy (PML)	ongoing (within PSUR/PSUSA)
Manidipine	Ascites	update of PI
Medroxyprogesterone acetate	Meningioma	update of PI and DHPC
Methotrexate	Hyperhomocysteinaemia	ongoing (within PSUR/PSUSA)
Mogamulizumab	Colitis	ongoing (Signal)
Montelukast	Persistent neuropsychiatric events	ongoing (within PSUR/PSUSA)
Nitric oxide	Pulmonary oedema in patients with veno-occlusive disease	update of PI
Oxytetracycline hydrochloride / hydrocortisone acetate / polymyxin B sulfate (ear/eye drops / suspension / ointment)	Hearing and vestibular disorders	ongoing (Signal)
Paracetamol (single ingredient and fixed dose combinations)	High anion gap metabolic acidosis (HAGMA) due to pyroglutamate acidosis	update of PI
Pirfenidone	Lichenoid drug eruption	routine pharmacovigilance / monitor within PSURs
Posaconazole	Photosensitivity reaction	update of PI
Propofol	Hepatic failure	update of PI
Regorafenib	Nephrotic syndrome	ongoing (Signal)
Risperidone oral solution	Medication errors associated with accidental overdoses in children and adolescents treated with risperidone 1 mg/mL oral solution	update of PI

Medicine	Issue	Status or outcome
Rosuvastatin	Tubulointerstitial nephritis	routine pharmacovigilance / monitor within PSURs
Roxadustat	Thrombocytopenia	ongoing (within PSUR/PSUSA)
Sacubitril, valsartan	Myoclonus	ongoing (within PSUR/PSUSA)
Semaglutide	Appendicitis	ongoing (within PSUR/PSUSA)
Semaglutide	Tubulointerstitial nephritis	ongoing (within PSUR/PSUSA)
Tegafur, gimeracil, oteracil	Hyperammonaemia	ongoing (Signal)
Teriparatide	Alopecias	routine pharmacovigilance / monitor within PSURs
Valaciclovir	Acute hepatitis	routine pharmacovigilance / monitor within PSURs

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 2024 is summarised below.

The SMART process group continued to support the signal management process by providing guidance aimed at promoting a harmonised approach while querying pharmacovigilance databases in the context of the assessment of safety signals raised for an entire therapeutic class. In those instances, several MAHs may be asked to perform cumulative reviews of safety data for the substances under their responsibility. It was observed that if the PRAC recommendation did not include more granular information on the search strategy to be used for the analysis, there was a significant risk that different MAHs would query safety databases using different MedDRA terms. This made it challenging for Rapporteurs to compare and assess the various data output received.

In order to mitigate this risk, the group recommended that, whenever possible, PRAC recommendations should specify which MedDRA terms, as a minimum, should be used by MAHs while performing their queries. Those could include one or more MedDRA preferred term(s), higher levels of the MedDRA hierarchy or a standardised MedDRA query, as applicable. The group acknowledged that even though the minimum search strategy is defined in the PRAC recommendation, MAHs would always have the freedom to broaden their search, if and as considered warranted. The template used to draft PRAC recommendations has been amended accordingly, in order to foster implementation of this guidance.

The group also discussed opportunities to optimise the process to integrate real-world evidence (RWE) into signal procedures. Although the conduct of RWE studies has proved to be of value in supporting the assessment of a number of signals, some challenges have also been identified. A RWE study can only be conducted after completion of a successful feasibility analysis and the finalisation of the study protocol, which require time. Because of that, Rapporteurs may receive the study report only shortly before the conclusion of the signal procedure, which leaves them with little time to adequately consider and reflect the impact of the RWE study results in the signal assessment report. One possibility to optimise the process would be to deliver the study report to Rapporteurs sooner by anticipating the feasibility analysis. However, this possible approach needs to be balanced with efficiency considerations, since RWE studies may not be required for each and every signal and, for some signals, the necessity of a RWE study may only become evident at a later stage. The group discussed that having criteria for the signals for which RWE studies are expected to be beneficial would be helpful. For instance, RWE studies might support the assessment of signals evaluating conditions with long latency or high prevalence, for which spontaneous reports may not be an ideal source of evidence. Another option to optimise the process might be to consider adopting longer timelines for the assessment of signals for which a RWE study is requested. The group agreed that further reflection is needed to ensure that whenever the PRAC has agreed on the need for a RWE study to support the assessment of a signal, sufficient time is available for Rapporteurs to consider the RWE study report and its impact on the outcome of the signal.

The SMART methods group continued its work in 2024 and made marked progress in accordance with its 2022 – 2025 workplan. A new addition to the way of working 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 published (https://link.springer.com/article/10.1007/s40264-024-01448-y) and implemented in EVDAS to identify maternal exposure to a medicinal product during pregnancy associated with a suspected adverse reaction. A new dashboard was created and shared with the network to enable an initial triage of cases, screening of different populations using tables and visualisation by age group and geographic regions. Collaboration with Uppsala Monitoring Centre is ongoing in this field, and the Pregnancy focus group will continue to play a key role in future research to evaluate the effectiveness of disproportionality methods on a more refined subset of pregnancy-related ADR reports.

The **masking effect** focus group explored the impact of the COVID-19 vaccine reports on signal detection practices and regulatory decision-making. 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 in relation to COVID-19 vaccines. Influential outlier removal and crude removal methods were tested in both large and small databases and show some value in unmasking important ADRs associated with COVID-19 vaccines. Further studies are needed to gather as much evidence as possible before implementing any interventions in EudraVigilance, to ensure that the methodology is sufficiently robust for routine signal detection.

Observed/expected (O/E) analysis: The use of O/E analysis beyond COVID-19 vaccines to other medicinal products remained a topic of investigation. EMA published lessons learned on O/E using spontaneous reports to generate real-time evidence on emerging safety concerns during mass vaccination (https://link.springer.com/article/10.1007/s40264-024-01422-8). The use of O/E to support the safety monitoring of COVID-19 vaccines has provided valuable insights on its design and interpretability, emphasising the importance of stratified and harmonised data collection, the need for alignment between coding dictionaries and the crucial role of accurate background incidence rates for adverse events of special interest.

A new stream following the EMA's DigiLab innovation framework, called the **Health Data Lab,** was created and is being piloted to provide a service to the Agency for experimentation with healthcare data, including with novel digital technologies. Ongoing initiatives include automated adjudication of case reports, handling of ICSRs from the literature to avoid duplication, a semi-automated literature screening, extract and explore product information listed ADRs and prioritisation of signals to review based on cumulative information on signals.

Website update for SMART working groups

Information on SMART working groups can be found at www.ema.europa.eu under Committees > Working parties and other groups.

Annex VII - Requests for information and documents

In 2024, EMA responded to 24 requests for EudraVigilance data, where requests for information (aggregated data) and/or documents (line listings/cases) were provided. This number of requests is a small increase compared to 2023 (20 requests). In two cases, EMA also provided a detailed descriptive analysis of the EV data.

EMA continues to receive significantly fewer EudraVigilance data requests than a few years ago, 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 2024, EMA supplied an additional 19 responses to requests for clarifications concerning this website or general aspects of EudraVigilance data.

Of the 24 requests for EudraVigilance data, 12 (50%) were requests for documents (line listings/cases), 9 (38%) were requests for information (aggregated data), whilst 3 (12%) involved a mix of both types. As for the type of medicinal products concerned, the requests were almost equally distributed between CAPs, accounting for 29% of the total number of requests; NAPs, accounting for 33% of the total; and a mix of CAPs and NAPs, accounting for the remaining 38% (see **Figure 14**).

The number of 24 requests corresponds to internal requests from the EU regulatory network (4) in addition to external requests (20) which could not be answered with the information provided via www.adrreports.eu and for which a detailed, tailored EudraVigilance search was required. These requests include queries for data from academia (12), non-EU regulatory authorities (4), the general public including patients (2), an EU agency outside the EMA network (1) and a journalist (1) (see **Figure 15**). Queries from academia have doubled compared to previous years (6 queries respectively in 2023, 2022, 2021 and 2020).

As regards the geographic origin of the queries, 14 (70%) originated from the EU, while 6 (30%) originated from outside of the EU (see **Figure 16**).

A small proportion of the requests for EudraVigilance data in 2024 were still relating to one or more of the centrally authorised COVID-19 vaccines (3 out of 24 requests, accounting for 12% of the requests). This is lower than the previous year (13 requests in 2023, accounting for 65% of the requests).

For more details on the requests for EudraVigilance data responded to in 2024, please refer to **Table 9**.

Figures 14, **15** and **16** below provide an overview by authorisation type of concerned products, type of request, requester type and geographic origin.

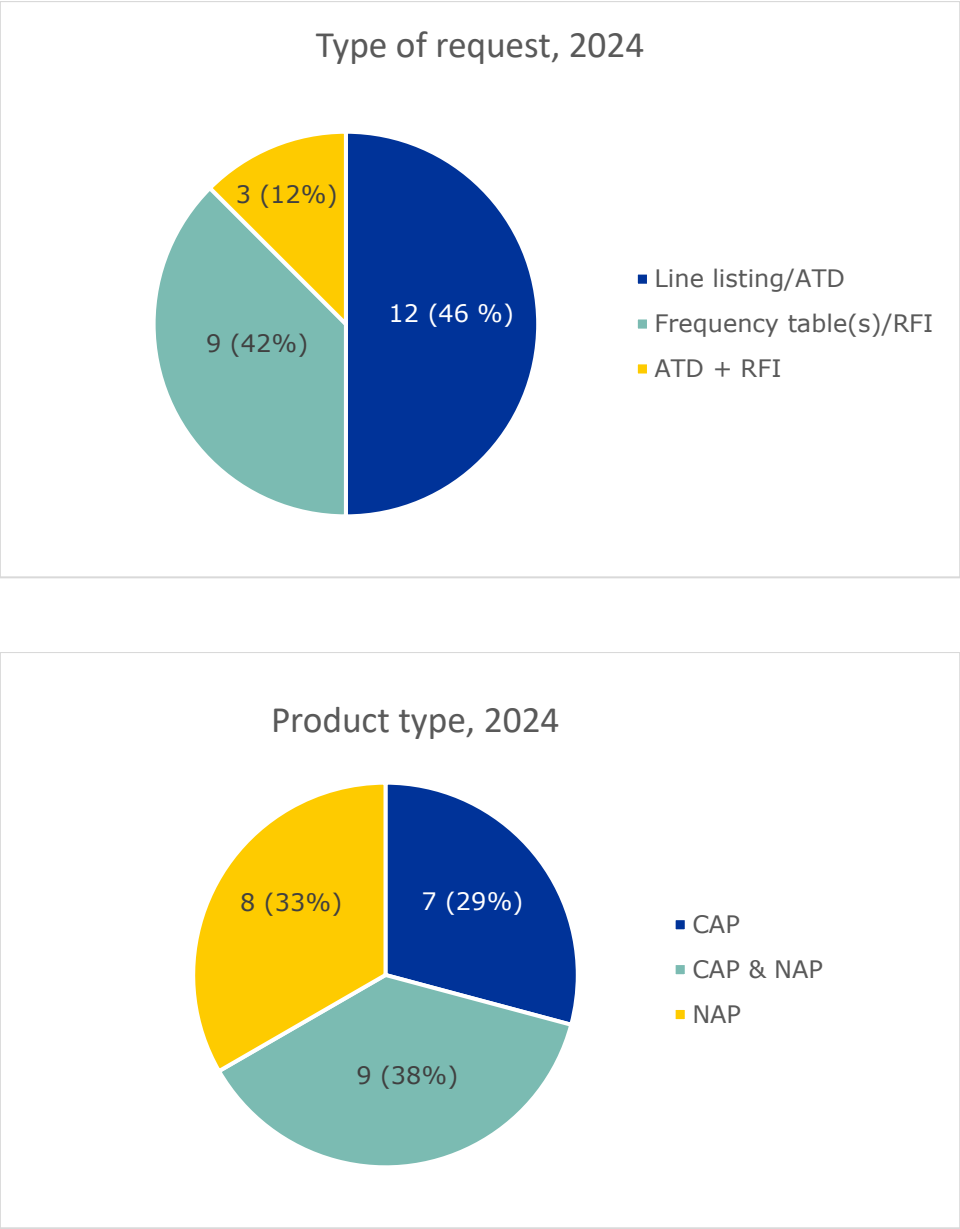

Figure 14. Overview of requests for EudraVigilance data in 2024 by product type (top) and type of request (down).

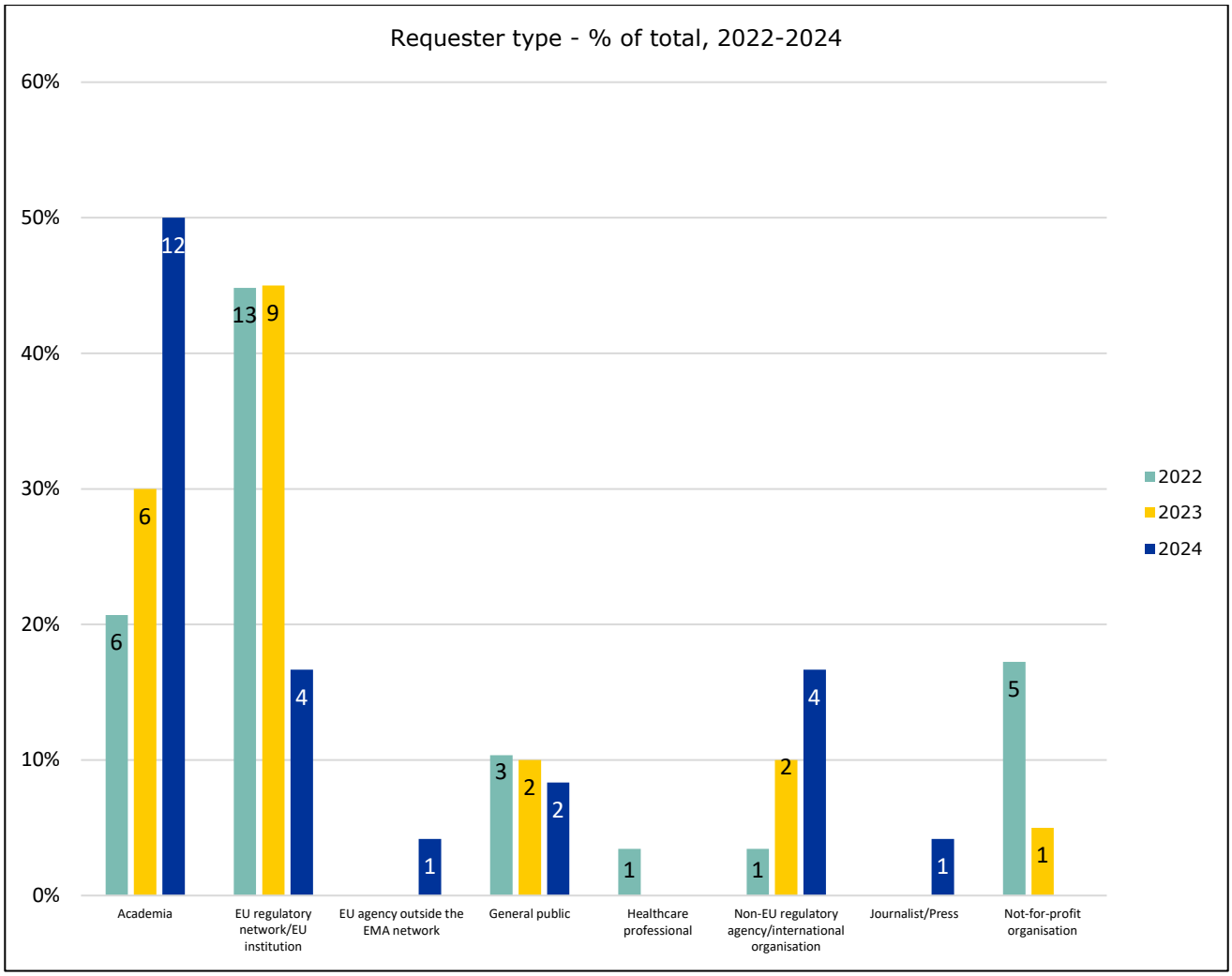

Figure 15. Overview of requests for EV data in 2024 by requester type.

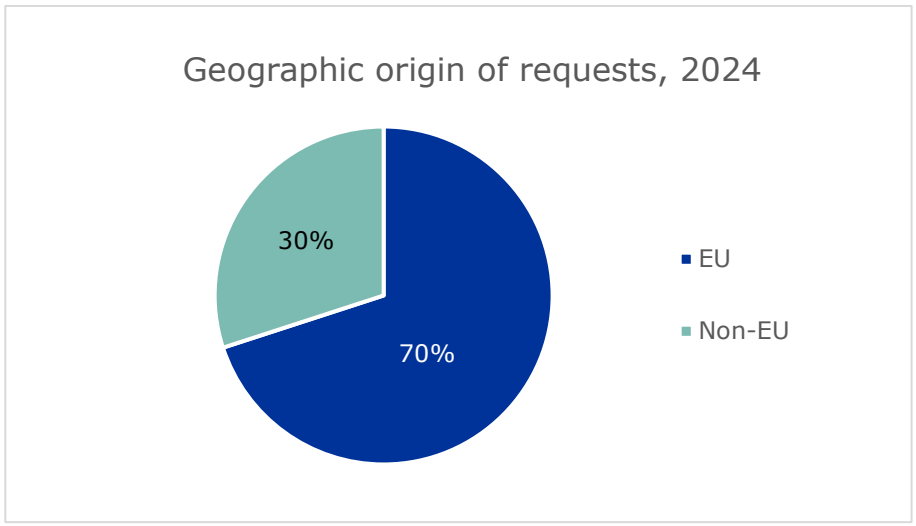

Figure 16. Overview of requests for EV data in 2024 by geographic origin.

Table 9. Overview of requests responded to in 2024.

Type of requester	Substance/ product	Issue	Type of request
Academia/research institute	Antipsychotics	Myocarditis	Line listing/ATD
Non-EU regulatory agency/international organisation	Calcium carbonate containing products indicated for heartburn relief	Hypercalcaemia	Frequency table(s)/RFI
Patient or consumer	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
Academia/research institute	Covid-19 vaccines and influenza vaccines	All ADRs for requested period	Line listing/ATD
EU agency outside the EMA network	Dimethicon and simethicon	All ADRs for selected age group	Frequency table(s)/RFI
Academia/research institute	DPP-4 inhibitors	Bullous pemphigoid	Line listing/ATD
EU regulatory network/EU institution	Finasteride; dutasteride	Suicide	Line listing/ATD
EU regulatory network/EU institution	Maralixibat	All ADRs	Frequency table(s)/RFI + line listing/ATD
Academia/research institute	Medicines used off-label in obesity and weight control	All ADRs for requested period	Line listing/ATD
EU regulatory network/EU institution	Metamizole	Agranulocytosis	Frequency table(s)/RFI + line listing/ATD
Academia/research institute	Methylphenidate	Abuse, misuse, dependence	Line listing/ATD
Patient or consumer	Paroxetine and cyamemazine	Specific case	Line listing/ATD
Academia/research institute	Pneumococcal vaccines	All ADRs for requested period	Line listing/ATD
Academia/research institute	Pneumococcal vaccines	Additional information	Line listing/ATD
Academia/research institute	Quetiapine	All ADRs in specific country	Line listing/ATD
Non-EU regulatory agency/international organisation	Respiratory syncytial virus vaccine (bivalent, recombinant) [Abrysvo]	Guillain-Barre Syndrome	Frequency table(s)/RFI + line listing/ATD

Type of requester	Substance / product	Issue	Type of request
Non-EU regulatory agency/international organisation	Respiratory syncytial virus vaccine (bivalent, recombinant) [Abrysvo]	Hypertension in pregnancy	Frequency table(s)/RFI
Academia/research institute	Tolperisone	Selected ADRs	Line listing/ATD
Academia/research institute	Various	All ADRs for requested period in selected EU countries	Frequency table(s)/RFI
Press	Various	Specific ICSRs	Line listing/ATD
Non-EU regulatory agency/international organisation	Various	All ADRs for requested period	Frequency table(s)/RFI
Academia/research institute	Various	Interstitial lung disease	Frequency table(s)/RFI
Academia/research institute	Various	All ADRs	Frequency table(s)/RFI