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2021 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
BCP	Business Continuity Plan
CAP	Centrally Authorised Product
DHPC	Direct Healthcare Professional Communication
E2B(R3)	ICH Guideline 'Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports', revision 3
EC	European Commission
EEA	European Economic Area
EMA	European Medicines Agency
eRMR	electronic Reaction Monitoring 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)
IAM	Identity and Access Management
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICSR	Individual Case Safety Report
IDMP	Identification of Medicinal Products
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
PI	Product information
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
WHO	World Health Organization
xEVMPD	eXtended EudraVigilance Medicinal Product Dictionary

1. Executive summary

Collecting reports of medical events and problems that occur following the use of a medicinal product is one of the pillars of the EU safety monitoring system. Healthcare professionals and patients are encouraged to report all suspected adverse reactions individuals may have experienced even if it is unclear whether the medicine or vaccine was the cause. EudraVigilance, the European database of suspected adverse drug reaction (ADR) reports, is the tool that the European Medicines Agency (EMA) and national competent authorities (NCAs) use for monitoring the safety of all authorised medicines in the EU as well as medicines studied in clinical trials. Timely detection and assessment of safety signals from sources such as EudraVigilance complements the benefit-risk evaluation of medicinal products via assessment of periodic safety update reports (PSURs) and risk management plans (RMPs) by the Pharmacovigilance Risk Assessment Committee (PRAC). EudraVigilance is therefore one of the cornerstones of EU pharmacovigilance.

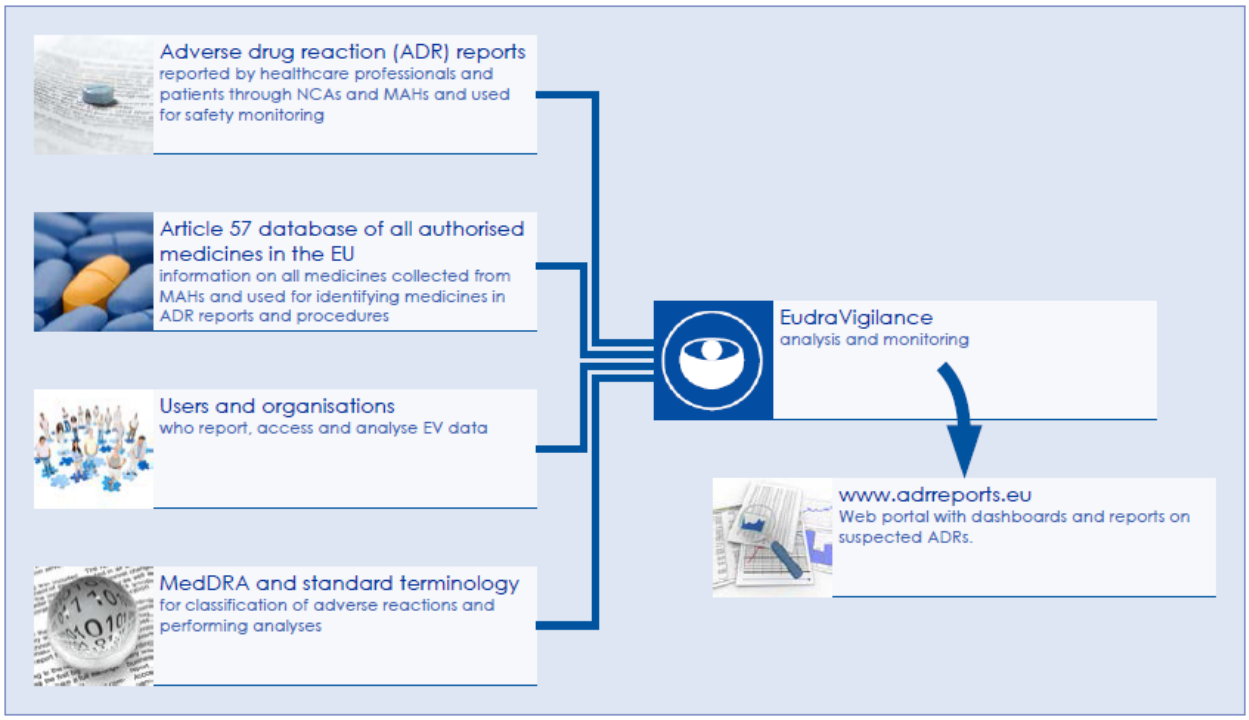


Figure 1. EudraVigilance users, data sources and data use.

The database currently holds over 22.3 million individual case safety reports (ICSRs) relating to 12.9 million unique suspected adverse drug reaction case reports[1] and is one of the largest pharmacovigilance databases in the world. It has undergone significant development in recent years, and this has delivered enhanced functionalities allowing for a better support of pharmacovigilance activities and the protection of public health.

This annual report is produced in accordance with Regulation (EC) No. 726/2004, Article 24(2), paragraph 2 and summarises the EudraVigilance-related activities performed in 2021, notably:

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

- ***EMA's pharmacovigilance system*** has been particularly efficient in detecting safety issues and dealing with them: for example, the EU was at the forefront in dealing with the novel thrombosis with thrombocytopenia syndrome (TTS) risk and analysis of Eudravigilance data was central to the assessment. PRAC and the European network identified and mitigated the risk for Vaxzevria and was proactive in dealing with the same potential risk for COVID-19 Vaccine Janssen – acting before the vaccine was rolled out.
- ***Collecting and processing suspected adverse drug reaction reports***. In 2021, 3.5 million ICSRs related to suspected adverse reactions occurring after authorisation were collected and managed in EudraVigilance (a 93% increase compared to the previous year and the largest annual total recorded). This increase is largely explained by the reports related to COVID-19 vaccines (1.68 million), which account for 48% of the annual ICSRs. Some 50% of overall reports originated from the EEA (a 114% increase). The number of reports submitted directly by European patients and consumers through the NCAs and MAHs increased significantly (781 thousand, an increase of 443%), again driven by COVID-19 vaccine reporting.
- ***Screening for, and review of, potential signals***. In 2021, EMA's signal management team reviewed in detail 2,477 potential signals[2] (a 31% overall increase versus 2020, including 992 from enhanced COVID-19 vaccine monitoring) for 796 centrally authorised products (CAPs) from screening the EudraVigilance database and other sources. Regarding nationally authorised products (NAPs); for 1,878 substances, a Lead Member State (LMS) is appointed to monitor safety data.
- ***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 the Rapporteur or LMS are brought to the attention of the PRAC for initial analysis, prioritisation and assessment. In 2021, the PRAC prioritised and assessed 86 confirmed signals (a 6% increase versus 2020). 85% of them included data from EudraVigilance. Of the 86 confirmed signals, 55 were validated by the Agency, 31 were validated by the MSs; 63 were for CAPs, 17 for NAPs and 6 for both CAPs and NAPs. 25% of the signals assessed by PRAC related to COVID-19 vaccines and many of these required extraordinary PRAC meetings to be convened for timely assessments.
- ***Transparency and public access to aggregated EudraVigilance data***. In November 2017, public access to EudraVigilance data via www.adrreports.eu, the European database of suspect adverse drug reactions reports, was further improved by providing additional outputs such as line listings and individual case report forms. By the end of 2021, the website included information on a total of 4,202 active substances, of which 831 were contained in CAPs and 3,371 in NAPs. This included timely and transparent data on the authorised COVID-19 vaccines.
- ***Enhanced communications.*** Safety updates for the COVID-19 vaccines were published on a monthly basis as were the full assessment reports for signals of public health interest. Regular stakeholder meetings for the public and press briefings were convened to keep the public informed on the latest COVID-19 developments and how the European regulatory system is working to protect public health.
- ***Training and support activities***. Extensive training offerings are available face-to-face or online as e-learning for all stakeholders and training for the EU network is available through the EU Network Training Centre[3]. Some of the training and support activities organised by the EMA were suspended or made on-line only during 2021 due to the COVID-19 pandemic.

[2] A signal refers to information on one or more observed adverse reactions potentially caused by a medicine and that warrant further investigation
[3] https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance/eudravigilance-training-support

2. Operation of EudraVigilance including its further development

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

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

Following the launch of an enhanced system in 2017, EMA published the first EudraVigilance operational plan in 2018 to describe the subsequent technical and operational activities driven by the routine system maintenance and the evolution of EU and international pharmacovigilance activities. This plan was updated on 23 March 2020 to cover the period 2020-2022.

The key activities undertaken in 2021 are summarised here:

- The departure of the UK from the EU had consequences on the operation of EudraVigilance. The implementation of Brexit in the database took place from 1 January 2021, including the implementation of the Northern Ireland protocol as determined in the Notice to Stakeholders on the Withdrawal of the United Kingdom and EU rules for medicinal products for human use and veterinary medicinal products published on 13th March 2020. The relevant changes include amongst others, the categorisation of UK cases as non-EEA cases from 1 January 2021 and the possibility to use the country code 'XI' to identify the cases from Northern Ireland within the United Kingdom, thus facilitating the ICSR reporting requirements. Cases with country code 'XI' are considered EEA cases in the database.
- In line with the Northern Ireland protocol a new country [Northern Ireland (UK)] has been implemented in the public European database of suspect adverse drug reactions reports in order to provide full transparency to the general public on the cases submitted in this territory.
- The EVDAS manuals (for MAHs and NCAs) were updated in 2021 to reflect the changes in the database driven by Brexit and the Northern Ireland protocol.
- The revision of the EU ICSR Implementation guide took place in March 2021. This revision should support the mandatory use of the ISO Individual Case Safety Report standard and the ISO terminology on pharmaceutical dose forms and routes of administration along with other updates related to the data protection and clinical trials legislation.
- Regarding the ESTRI Gateway (Electronic Standards for the Transfer of Regulatory Information), software upgrades occurred as required by the EMA IT strategy. AS1 is officially decommissioned and all AS1 organisations have been transferred to AS2 or are using EVWEB/EVPOST.
- To support the integration of the EV Human XCOMP (external testing system) registration process and the improvements within the Agency's identity and access management (IAM) components, the EMA EudraVigilance registration manual was updated with a new version available in April 2021.
- EMA and the European Commission extended until the end of 2022 the pilot for the obligation and transitional arrangements regarding monitoring of EudraVigilance by MAHs. In parallel, the

European Commission launched a targeted stakeholder consultation on the Commission Implementing Regulation 520/2012 on pharmacovigilance activities seeking feedback on the proposed amendments, including MAH requirements for EudraVigilance monitoring. The deadline for the consultation was 15 October 2021.

- EMA has issued a monthly publication of spreadsheets providing information on nullified ICSRs to facilitate case reconciliation by NCAs and MAHs.
- Regarding the Medical Literature Monitoring (MLM) service, a call for a service provider was launched in 2021 and the results are to be announced in 2022. In 2021, an audit of the MLM service was performed, the results were fully evaluated by EMA and a corrective action plan has been put in place.
- As defined in the Pharmacovigilance Plan of the EU Regulatory Network for COVID-19 Vaccines issued in 2020, EudraVigilance is playing a crucial role facilitating the early detection of emerging risks with the COVID-19 vaccines and therapeutics.
- New guidance for companies was issued on adaptations to the regulatory framework, including ADR reporting to EudraVigilance, to address challenges arising from the COVID-19 pandemic, with a particular focus on crucial medicines for use in COVID-19 patients In the context of the COVID-19 pandemic (Questions and Answers on regulatory expectations for medicinal products for human use during the Covid-19 pandemic).
- A dedicated COVID-19 dashboard was made available to NCAs and EMA staff in EVDAS in 2020 to support the monitoring of ADR reports related to COVID-19 vaccines. This dashboard was updated several times in 2021 to accommodate the business needs including the monitoring of signals together with the transparency and communication activities.
- The public European database of suspect adverse drug reactions reports was updated to incorporate COVID-19 related important messages in order to respond to the high demand for data and clarifications from the public and to explain how data from spontaneous reports should be interpreted and understood in the context of the pandemic.
- The data management activities have been carried out as described in the guide on EudraVigilance data management activities by the European Medicines Agency.
- In order to implement the requirements established by the Commission Implementing Regulation (EU) 2022/20 of 7 January 2022 laying down rules for the application of Regulation (EU) No 536/2014 of the European Parliament and of the Council in relation to the cooperation between Member States in the safety assessment of clinical trials, EMA together with the European Commission and members of the Clinical Trials Facilitation Group established a working group to define and agree on the business requirements to be implemented in EVDAS for the safety assessing Member States to perform the tasks related to the SUSAR screening in EudraVigilance. The business requirements have been agreed and a new Clinical Trials Monitoring EVDAS Dashboard has been developed.
- The EudraVigilance Expert Working group met twice in 2021, on 18 March and 7 October. Moreover, the EMA-NCAs Pharmacovigilance Business team met regularly to discuss, agree and issue guidance on the different EudraVigilance operations.
- A EudraVigilance and Signal Management Information day took place on 24 November 2021 to inform users of EudraVigilance of technical and operational activities with anticipated timelines and highlight how the database and the users will be affected.

The key future activities to be undertaken in the database in relation to its operations are described below:

- EudraVigilance gateway software will be updated in 2022. The update will be done first in XCOMP then followed by production one month later to enable organisations to test. Although the update is not expected to have any impact on gateway connections to EudraVigilance, it is recommended that organisations test against XCOMP so if issues are found they can be resolved before the production system is updated. The relevant announcements will be made early 2022.
- Monthly publication of master cases with associated duplicates to facilitate case reconciliation by NCAs and MAHs is planned to start in 2022.
- Monthly provision of compliance reports for the purpose of the monitoring of ICSR submission time frames to all EudraVigilance registered organisations is expected to go live during 2022.
- Following a PRAC recommendation in October 2019 and the confirmation and announcement by EMA Management Board in December 2019, a key milestone will be the mandatory use, from 30 June 2022, of

  • the ISO Individual Case Safety Report standard as referred to in Article 26(2)(a) of the Commission Implementing Regulation (EU) No 520/2012 and the modalities on how to use this ISO ICSR standard defined in the ICH E2B(R3) documentation, and

  • the ISO terminology on pharmaceutical dose forms and routes of administration referred to in Article 25(1)(f) of Commission Implementing Regulation (EU) No 520/2012,

  in relation to reporting obligations to EudraVigilance.

Using this internationally agreed format and standard terminology will be a major step towards strengthening data quality and analytical capabilities in EudraVigilance.

EMA has published a change management plan and a guideline to import EDQM terms from EMA SPOR RMS. EMA will continue to support stakeholders in this important initiative to ensure their readiness.

- With the application of the new Clinical Trial regulation (Reg (EU) No 536/2014)), EudraVigilance will facilitate the forwarding of SUSARs from EVCTM to the Member States concerned. The SUSAR re-routing functionality has been tested with the Member States in order to be ready by 31st January 2022.
- The relevant training materials related to the new functionalities driven by the implementation of the new Clinical trials legislation have been updated including a new virtual live hands-on training course for clinical trial sponsors available on the EudraVigilance training page.
- In order to facilitate the SUSAR screening in EudraVigilance by the safety assessing Member States as define in the Commission Implementing regulation 2022/20, a new Clinical Trials Monitoring Dashboard has been launched in EVDAS to support the SUSAR screening as defined in the mentioned Commission Implementing Regulation. Before the dashboard was available, User Acceptance Test with Member States has been performed during January 2022. EMA has prepared a dedicated user manual and a webinar training was delivered on 27 January 2022.
- The Detailed guidance on ICSRs in the context of COVID-19 is expected to be updated during 2022 to incorporate guidance on the lack of prophylactic efficacy coding, the vaccine dose schedule data entry.
- The EMA is currently planning to undertake a review of the EudraVigilance data analytics platform and tools with the aim of enabling the Agency and the Network to more effectively and efficiently

deliver evidence from data-driven interrogation of adverse drug reaction reports. This will be done under the Signal and Safety Analytic Project approved by the EMA Portfolio Board. The relevant communications to the stakeholders will be issued in due course.

3. Data collection and data quality

Medicinal product information

In the database of all medicinal products authorised in the EU (the "Article 57 database"), the total number of medicinal products entries by MAHs in the XEVMPD as of 31 December 2021 was 951,169 (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 a better identification of medicines in reports of suspected adverse reactions, a 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.

2021 was characterised by a surge of safety reports related to COVID-19 vaccines and a slight decrease in the reporting of ADRs for other medicinal products. The high number of suspected adverse reactions reported after the use of COVID-19 vaccines is not unexpected considering that over 700 million doses of vaccines were administered in the EU in 2021. This represented the largest vaccination campaign ever conducted and also the fact that citizens and healthcare professionals were highly aware of the importance of reporting possible side effects. 2021 demonstrated EudraVigilance's ability to deal with increased submissions in such exceptional circumstances.

In 2021, 3,525,975 ICSRs were collected and managed in EudraVigilance. This figure represents a 93% increase compared to the numbers recorded in 2020, and it is characterised by a marked increase in EEA reports (+114%) and in non-serious (+156%) reporting. This increase is largely explained by the reports related to COVID-19 vaccines, which account for 48% (1,679,633) of all the ICSRs, and 67% (1,170,187) of the ICSRs originated in EEA.

The number of reports submitted directly by patients and consumers through the NCAs and MAHs (781,632) saw a 4-fold increase (+443%) compared to the previous year, largely driven by the reports for COVID-19 vaccines which accounted for 87% (680,272) 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.

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

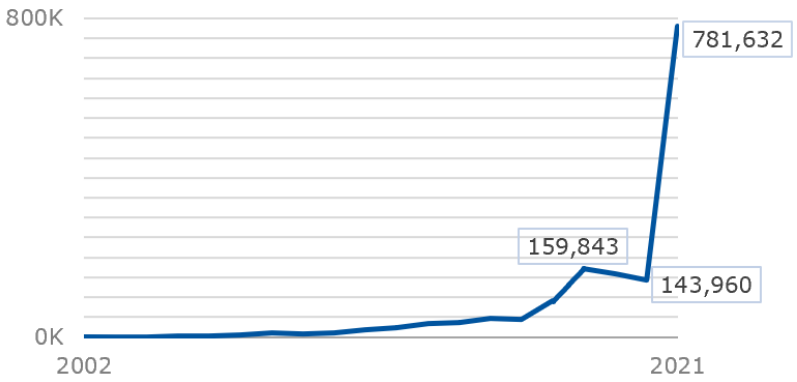


Figure 2. Trend of ADR reports from patients and consumers received in the EEA by NCAs and MAHs and reported to EudraVigilance.

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, business rules for data entry, ensuring the correct identification of medicinal products associated with reported adverse reactions, removal of duplicate reports, ensuring timely submission of serious and non-serious adverse reactions, adherence to coding practices and standards, and adequate case documentation.

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

4. Data analysis

EMA's pharmacovigilance system has been particularly efficient in detecting issues and dealing with them: for example, the EU was at the forefront in dealing with the TTS risk and Eudravigilance anlaysis was central to the assessment. The network identified and mitigated the risk for Vaxzevria and was proactive in dealing with the same potential risk for COVID-19 Vaccine Janssen – acting before the vaccine was even rolled out in the EU.

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 eRMRs. In 2021, over 27,000 individual eRMRs were generated for NCAs and the EMA's signal management team. These are produced every two weeks for medicinal products subject to additional monitoring and monthly, three-monthly or six-monthly for other products. Exceptionally, in 2021, eRMRs were produced weekly for

[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

the authorised COVID-19 vaccines to support the enhanced monitoring pandemic plan. Additional analyses are performed in EVDAS (the EudraVigilance data analysis system), including screening of line listings and disproportionality analyses and subgroup analyses.

Screening of these outputs is one of the principal sources of validated signals, i.e. information on observed adverse reactions potentially caused by a medicine and that warrant further investigation. For CAPs, EMA leads the monitoring; 2,477 potential signals were reviewed, including 992 relating to COVID-19 vaccines and 1,485 relating to other products (a 31% overall increase compared to 2020) by the Agency in 2021 (see Annex V for further breakdown)

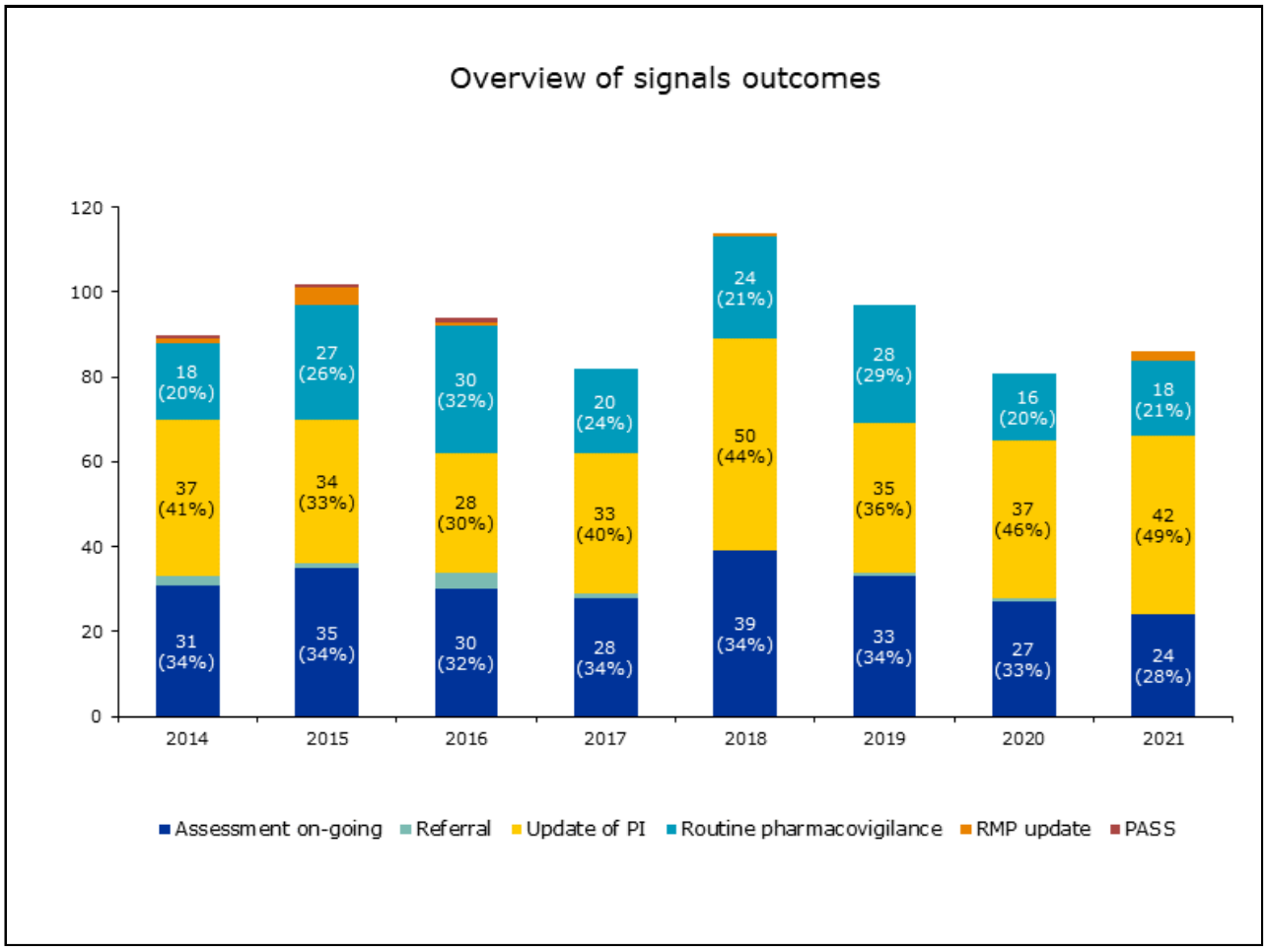
For active substances contained in NAPs, the monitoring of ADR reports in EudraVigilance and in national databases is shared between the NCAs in line with the 'List of substances and products subject to worksharing for signal management'[6], which defines a Lead Member State (LMS) for each active substance included. The list was updated in 2021 following changes in PSUSA leaderships and in marketing authorisation status. It currently includes 1,878 active substances. NCAs also monitor all medicines authorised nationally in their country for which no LMS has been appointed.

All detected and validated signals which are confirmed by the Rapporteur or LMS are brought to the attention of the PRAC for initial analysis, prioritisation and assessment. In 2021, the PRAC prioritised and assessed 86 confirmed signals (a 6% increase compared to 2020 and in line with the average for 2014-2020). Seven extraordinary PRAC meetings were convened for timely and focussed discussion on safety topics relating to COVID-19 vaccines.

Of the 86 signals assessed by the PRAC, 73 (85%) included data from EudraVigilance. Forty-two of the assessed signals (49%) 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 (see Figure 3). In 9 of these cases, the PRAC also recommended Direct Healthcare Professional Communications (DHPCs) to highlight new important safety information to prescribers. Eight signals also led to the update of the RMP. For 2 of these the RMP update was the only outcome, aiming to fully characterise and investigate the issue. For 18 signals (21%) continuing with routine safety monitoring of the medicine was considered sufficient. No PASS or safety referrals were initiated following signal reviews. The evaluation of 24 signals (28%) was still ongoing at the end of 2021, including 17 via a follow-up signal procedure and 7 in the upcoming PSURs/PSUSAs.

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

Figure 3. Overview of signals assessed by the PRAC.



Of the 86 signals assessed by PRAC in 2021, 21 (approx. 25%) related to COVID-19 vaccines; 15 of these signals were raised by EMA and 6 by MSs. This included signals of high public health importance such as thrombosis with thrombocytopenia syndrome (TTS) reported following use of adenoviral vaccines[7][8] (April 2021) and myocarditis and pericarditis reported following use of mRNA vaccines[9] (July 2021). 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, or the introduction of additional risk minimisation activities. Further details on all signals assessed by the PRAC in 2021 can be found in Annex V. The progress of process improvements and simplifications in signal management is detailed in Annex VI.

A pilot started in February 2018 whereby MAHs of selected active substances[10] must monitor them in EudraVigilance and inform EMA and NCAs of validated signals with their medicines[11]. It involved 288 active substances and combinations. These are mainly new active substances authorised centrally. Based on Article 57 data, more than 400 MAHs were impacted by the pilot. As of December 2021, the

[7] Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 6-9 April 2021 | European Medicines Agency (europa.eu)
[8] COVID-19 Vaccine Janssen: EMA finds possible link to very rare cases of unusual blood clots with low blood platelets | European Medicines Agency (europa.eu)
[9] Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 5-8 July 2021 | European Medicines Agency (europa.eu)
[10] 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
[11] https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:159:0005:0025:EN:PDF

Network had received 49 standalone signal notifications from MAHs. Of these, 11 signals were considered valid and processed accordingly, ultimately leading to 1 signal being confirmed for evaluation by the PRAC (none in 2021). All other MAHs also have access to cases for their medicinal products and therefore can integrate EudraVigilance data into their own signal management processes. In July 2021, the European Commission decided to further extend the pilot until the end of 2022, pending the update of the EU pharmacovigilance legislation based on the experience gained with the pilot.

5. Transparency, communication and training.

Safety updates for the COVID-19 vaccines were published on a monthly basis as were the full assessment reports for signals of public health interest. Regular stakeholder meetings for the public and press briefings were convened to keep the public informed on the latest COVID-19 developments and how the European regulatory system is working to protect public health. 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. This supports transparency and public trust in the work of the Agency and better and faster updates to product information.

Public access to aggregated EudraVigilance data has been available since 2012 via aggregated reports available in the European database of suspect adverse drug reactions reports (www.adrreports.eu) and was further improved in November 2017 by providing additional outputs such as line listings and individual case safety report forms. By the end of 2021, the website provided information on a total of 4,052 active substances, of which 796 were contained in CAPs and 3,256 in NAPs. During 2021, ADR data on the five COVID-19 vaccines was available to the general public via www.adrreport.eu

The Agency also continued to respond to requests for information from EudraVigilance or access to EudraVigilance documents in line with the current EudraVigilance Access Policy. In total, 39 requests were answered (+11 compared to 2020) within a median of 5 working days (versus 16 working days in 2020). Of these 39 requests, 9 (23%) were received from the EU regulatory network, supporting the scientific assessment of pharmacovigilance procedures and the remaining 30 (77%) were from external sources. Compared to 2020, an increased number of requests was received from journalists, in relation to the authorised COVID-19 vaccines. More details are provided in Annex VII.

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

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

- 12 training sessions on EudraVigilance ICSR submissions (11 virtual, 1 at Agency), with 206 users trained in total
- 1 EudraVigilance signal management info day, 124 attended.
- EVDAS training for NCAs was suspended during 2021 due to BCP. However, a recording of the last training which took place in November 2020 was made available to all NCAs via the EU Network Training Centre.

- PRAC assessors training took place in December 2021 and was focussed on the COVID-19 pandemic and the related safety monitoring tools, communications and processes. Over 300 assessors registered for the event.
- 6 XEVMPD courses for marketing authorisation holders and sponsors with total of 103 learners and 2 XEVMPD courses specifically for sponsors with 26 learners.

Some training and support activities organised by EMA were suspended during 2021 due to COVID-19 and BCP.

6. Conclusion

EudraVigilance is a central pillar for pharmacovigilance activities in the EEA, including during the public health crisis triggered by the COVID-19 pandemic. It played a crucial role in facilitating the early detection, management and mitigation of emerging risks related to authorised COVID-19 vaccines (including signals of high public health importance such as TTS and myocarditis).

ADR reporting to EudraVigilance in 2021 was the highest annual total ever recorded, driven by COVID-19 vaccine reporting. Over 3.5 million ICSRs were received in 2021, of which half originated from the EEA. Based on these reports, over 27,000 statistical outputs were produced and screened for the identification of signals which were subsequently assessed by the PRAC. Almost 25% of signals discussed at PRAC related to COVID-19 vaccines and several extraordinary PRAC meetings were convened, resulting in timely regulatory action, as needed.

EudraVigilance currently contains over 22.3 million ICSRs. It is being used by EMA, EU NCAs and MAHs, and plays a key role in global surveillance, with over 1.7 million reports forwarded to the WHO database in 2021.

Significant enhancements implemented in the database in previous years are now in routine operation and delivering improved functionalities for signal detection and monitoring of risks, performance of pharmacovigilance activities and identification of medicinal products for the EU network. Many further developments were initiated in 2021 in relation to the COVID-19 pandemic; this included the implementation of new tools to facilitate monitoring of ADR reports specifically related to COVID-19 vaccines.

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 EV monitoring. [*Legal basis:* Commission Implementing Regulation (EU) 520/212, Article 18 and 21]	Started 22 February 2018. Continued during 2021.
Data quality review and duplicate management of adverse reaction reports in EudraVigilance. [*Legal basis:* Regulation (EC) 726/2004, Article 24(3)]	Continued during 2021.
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 2021.
Providing all suspected adverse reaction reports occurring in the Union to the World Health Organization (WHO) Uppsala Monitoring Centre directly from EudraVigilance. [*Legal basis:* Regulation (EC) 726/2004 Article 28c(1), second subparagraph]	Continued during 2021.
Operation of the signal management processes based on EudraVigilance data, including the monthly provision of e-RMRs 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 the 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 2021.
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 2021.
Operation of the Medical Literature Monitoring service [*Legal basis:* Regulation (EC) 726/2004, Article 27]	Continued during 2021.

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

EudraVigilance data-processing network (EudraVigilance Gateway)

The EudraVigilance data-processing network as referred to in Article 24 of Regulation (EC) No. 726/2004 facilitates the electronic exchange of adverse drug reaction (ADR) reports between the Agency, national competent authorities (NCAs) and marketing authorisation holders (MAHs) for all medicines authorised in the European Economic Area (EEA). This network, known as the EudraVigilance gateway, has been in continuous operation since December 2001. On average the system was available 99.9% of the time throughout the year[12], exceeding the required 98% availability (see Fig. 4).

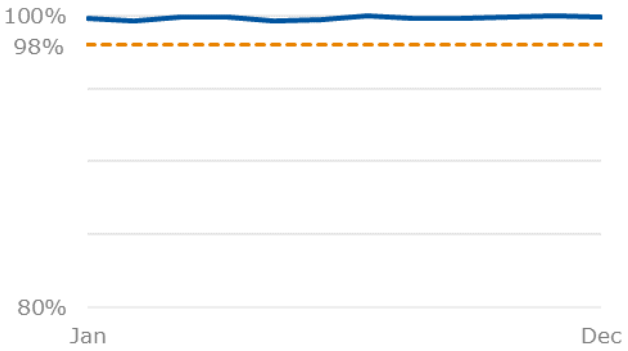


Figure 4. EudraVigilance gateway availability per month. The requirement is 98%. Please note that the scale starts at 80%. Planned downtime is excluded.

EudraVigilance database

For medicinal products authorised in the EEA, ADR reports are collected from both within and outside the EEA. By 31 December 2021, the EudraVigilance database held a total of 22,301,140 ADR reports (or ICSRs), referring to 12,961,576 individual cases (figure 4). The post-authorisation module (EVPM) contained 20,757,807 ICSRs (12,530,776 individual cases) and the clinical trial module (EVCTM) 1,543,333 ICSRs (430,800 individual cases).

[12] Only unplanned downtime is taken into consideration

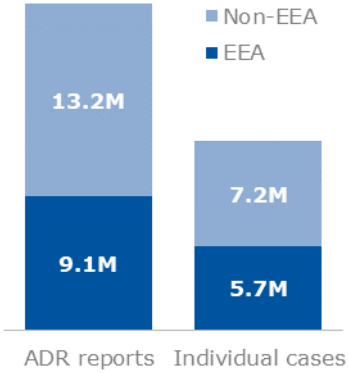


Figure 5. Number of ADR reports versus individual cases received in the EudraVigilance database from its inception in December 2001 until 31 December 2021 split by origin of the report in- or outside the EEA.

The numbers presented below in figures 5 and 6 refer to the ADR reports received in the post-authorisation module (EVPM). A total of 20,757,807 EVPM ADR reports have been processed over the years up to the end of 2021, of which 3,525,975 EVPM ADR reports were processed in 2021. This represents a 93% increase compared to the numbers recorded in 2020, and it is characterised by a marked increase in EEA (+114%) and non-serious (+156%) reporting. This increase is explained by the ADR reports related to COVID-19 vaccines (1,679,633 – 48%), of which 69% (1,170,187) were originated in EEA (Table 1). ADR reports are subsequently made available for signal detection and data analysis by the Agency and national competent authorities in the Member States.

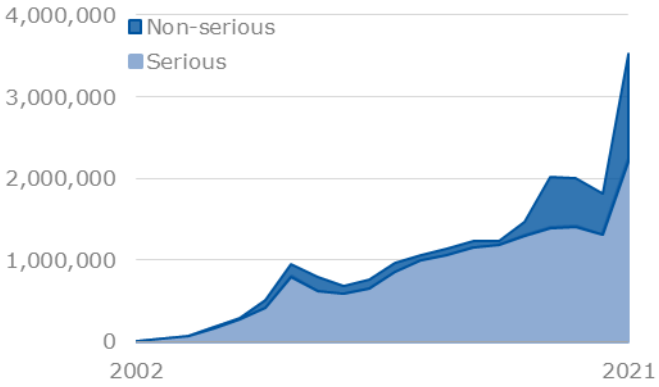


Figure 6. Number of ADR reports processed per year in EVPM.

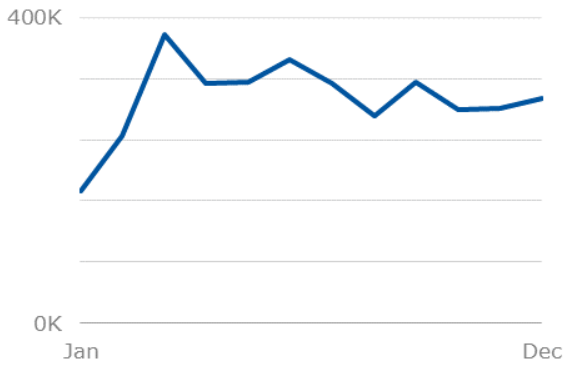


Figure 7. Number of ADR reports processed per month in EVPM in 2021.

Table 1. Number of ADR reports and unique cases transmitted in 2021 related to or excluding COVID-19 vaccines. Counts for 2020 are provided for comparison.

	2021			2020
	Total count	**Count related to COVID-19 vaccines**	**Count excluding COVID-19 vaccines**	**Total count**
EVPM ADR reports processed	3,525,975	1,697,633 (48%)	1,828,342 (52%)	1,821,211
EVPM ADR reports originated in EEA	1,743,238	1,170,187 (67%)	573,051 (33%)	812,784
Non-serious EVPM ADR reports	1,312,952	940,229 (72%)	372,723 (28%)	513,066
ADR reports submitted by European patients and consumers through the NCAs and MAHs	781,632	680,272 (87%)	101,360 (13%)	143,958
Individual cases submitted by European patients and consumers through the NCAs and MAHs	672,932	591,434 (88%)	81,498 (12%)	117,167

Figure 8 presents the total number of ADR reports received in EVPM for 2021 compared to the number of individual cases they are referring to. Each individual case in EudraVigilance refers to a single patient; an individual case is composed of at least one ICSR, 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.

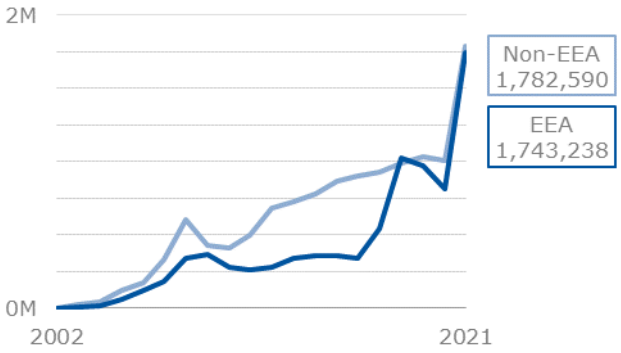


Figure 8. Number of ADR reports processed per year in EVPM split by cases occurred inside and outside the EEA.

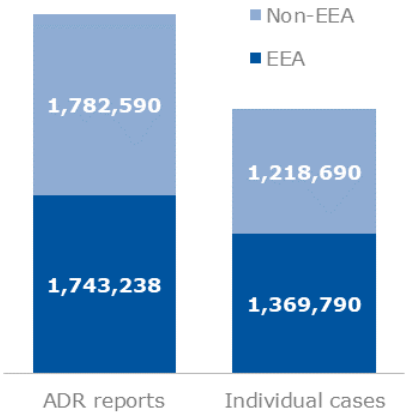


Figure 9. Number of ADR reports versus the number of individual cases in 2021 in EVPM.

In 2021, 781,632 ADR reports were submitted by European patients and consumers through the NCAs and MAHs, referring to 672,932 individual cases. This is an increase of 443% in such reports compared to the previous year (figure 9) and is dominated by reports related to COVID-19 vaccines, which account for 88% of the individual cases (Table 1). The mandatory reporting of non-serious EEA cases to EudraVigilance since November 2017 has been a key driver of the overall increased patient reporting in the past 3 years compared to previous period.

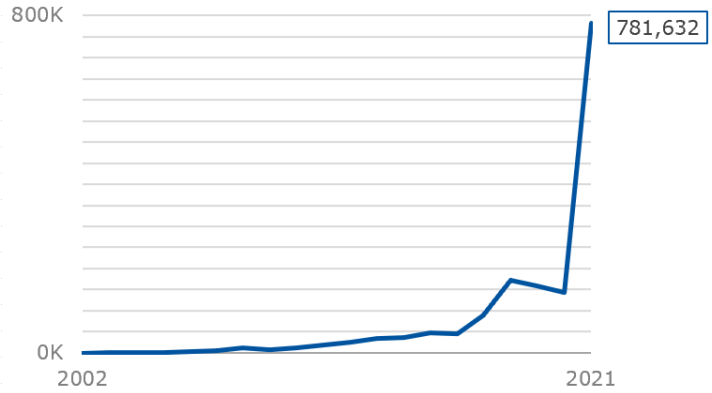


Figure 10. Number of ADR reports by European patients and consumers through the NCAs and MAHs.

E-reporting status for MAHs and sponsors of clinical trials

- 1,135 MAHs (at headquarter level) have sent reports to EVPM during 2021, a 2% increase compared to 2020.
- 609 sponsors of clinical trials (at headquarter level) have sent reports to the EudraVigilance Clinical Trials Module (EVCTM) during 2021, a 7% increase compared to 2020.
- A total of 18,891 individual MAH users 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 the Figure 10 shows the 15-day and 90-day reporting compliance of MAHs and sponsors of non-interventional studies when reporting to EVPM.

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

For the re-transmission of reports originally transmitted to MAHs by other organisations, the receipt date is the date the MAH received the most recent information from the other organisation, not the date that the other organisation received the most recent information from the original reporter. Nullification, amendment and error reports are excluded from the compliance calculations.

In 2021, 228,709 ICSRs were rerouted to NCAs following receipt of the reports from MAHs in EudraVigilance. 1,725,156 ICSRs were forwarded to WHO. A total of 190,102 download requests by MAHs were made, resulting in 7,090,053 ICSRs downloaded from the EudraVigilance database.

Table 2. Number of ADR reports and unique cases transmitted by MAHs and sponsors to EVPM and EVCTM in 2021

EV Module	Transmission type	Count
EVPM	ADR reports	2,091,618
	Individual cases	1,353,954
EVCTM	ADR reports	115,732
	Individual cases	36,354

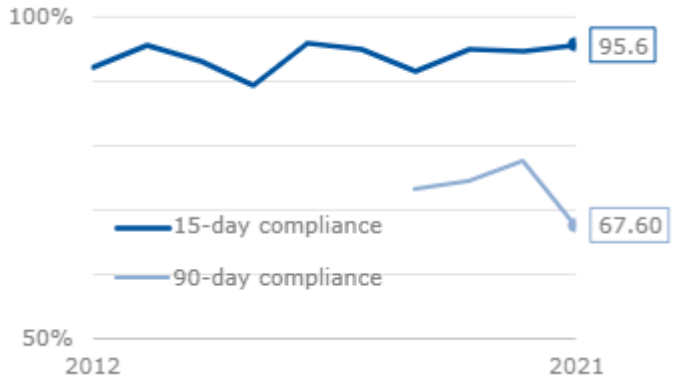


Figure 11. Compliance rate for serious (15-days) and non-serious (90-days) ADR reports to EVPM for all MAHs and sponsors by year. Please note that the scale starts at 50%. Non-serious ADR reports need to be submitted only since November 2017.

E-reporting status for NCAs

- All NCAs in the EEA are authorised to transmit safety reports to EudraVigilance.

- All NCAs reported ICSRs to EVPM, except for AFLUV (Liechtenstein): all ICSRs occurring in Liechtenstein are transmitted to EudraVigilance by MAHs. A total of 1,307 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 the 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 (Receipt Date – ICH E2B(R2) A.1.7/E2B(R3) C.1.5). The receipt date is treated as day 0, giving the NCA 15 days following that day to transmit the reports. Nullification, amendment and error reports are excluded from the compliance calculations.

Table 3. Number of ICSRs and unique cases transmitted by NCAs to EVPM and EVCTM during 2021

EV Module	Transmission type	Count
EVPM	ADR reports	1,434,357
	Individual cases	1,234,615
EVCTM	ADR reports	3,832
	Individual cases	2,105

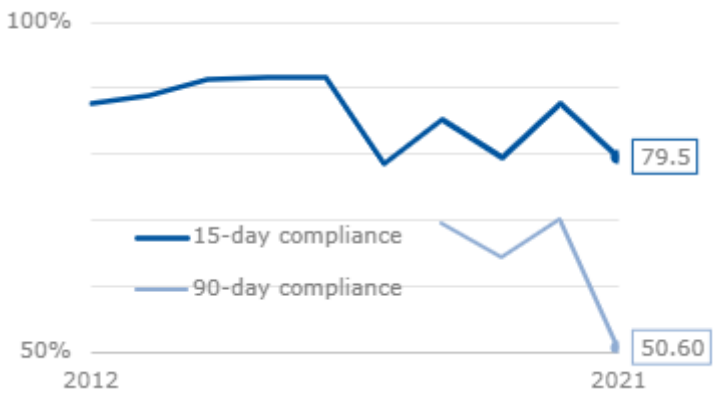


Figure 12. Compliance rate for serious (15-days) and non-serious (90-days) ADR reports to EVPM for all NCAs by year. Please note that the scale starts at 50%. Non-serious ADR reports need to be submitted only since November 2017.

During 2021, the following 8 NCAs transmitted SUSARs to EVCTM (SUSARs from other countries were received directly from sponsors of clinical trials):

- Belgium (Federal Agency for Medicines and Health Products)
- Denmark (Danish Health and Medicines Authority)
- Finland (Finnish Medicines Agency)
- Germany (Federal Institute for Drugs and Medical Devices)
- Germany (Paul-Ehrlich-Institut)

- Iceland (Icelandic Medicines Agency)
- Ireland (Health Products Regulatory Authority)
- Netherlands (Medicines Evaluation Board)

EudraVigilance database and support of signal management process

A total of 27,037 eRMRs were generated in 2021 to facilitate the continuous monitoring of the safety of medicines by the Agency and NCAs in the EEA. Of these,

- 10,681 were routine eRMRs, produced monthly
- 2,632 were 3-monthly eRMRs
- 1,388 were 6-monthly eRMRs
- 12,336 were additional eRMRs – produced fortnightly.

The steady increase in the number of additional eRMRs is related to the monitoring by the Agency of all new CAPs coming through the pipeline each year.

Annex III - Total number of medicinal product submissions by MAHs

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

- facilitating data analysis and signal detection to support better safety monitoring for patients;
- provision of access to EudraVigilance data:
  - reactively in accordance with the revised EudraVigilance Access Policy,
  - proactively:

    to MAHs to enable the performance of signal detection activities

    to healthcare professionals and the public via the www.adrreports.eu website,
- reliably identifying medicinal products that fall within the scope of the PSUR submissions and referral procedures;
- supporting literature monitoring activities;
- facilitating NCAs' inspections (e.g. sharing information on Pharmacovigilance Master File location);
- computing pharmacovigilance fees.

These data are validated by the Agency (see Annex IV for a summary of the validations performed in 2021). Table 4, below and Figures 12 and 13 provides a summary of the data submitted in as of 15 January 2021.

Table 4. Summary of medicinal product submissions to the XEVMPD

Total number of medicinal product submissions by MAHs by 31 December 2021 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).	951,169
Total number of MAHs (legal entities) established in the EU (corresponding to EudraVigilance codes).	5,883

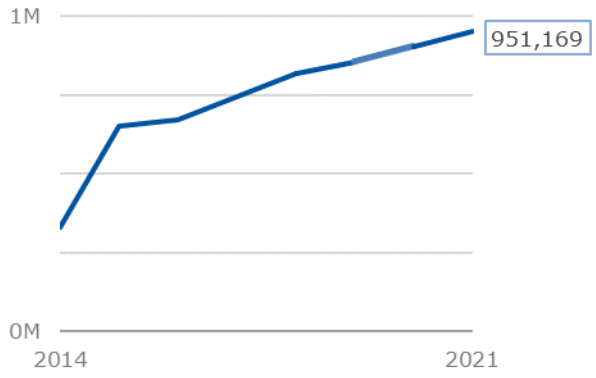


Figure 13. Total number of medicinal products (counted based on EudraVigilance codes) submitted (cumulative by year)

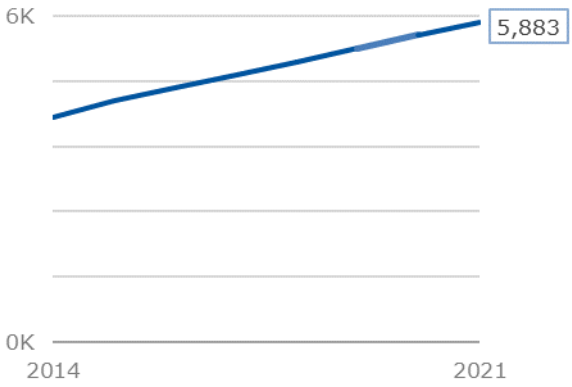


Figure 14. Total number of marketing authorisation holders (legal entities) established in the EU (corresponding to EudraVigilance codes) (cumulative by year)

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

It encompasses the following parameters:

- Name of the medicinal product;
- MAH;
- Authorising 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 2021 and provides 2020 and 2019 data for comparison.

Table 5. Summary of EudraVigilance data quality activities in 2021

Data quality area	Activities performed	2021	2020	2019
Identifying and managing duplicate individual cases	Duplicate couples assessed	144,883	160,047	176,736
	Master reports generated based on duplicated data	81,360	85,168	92,480
Coding of reported medicines and active substances	Reported medicinal products and active substance terms recoded	1,068,728	54,366	101,388
	ADR reports recoded (ICSRs)	959,665	76,990	79,552
Providing feedback on data quality	Organisations subject to ICSR data quality review	119	120	123
	Medicinal products in XEVMPD quality reviewed (and corrected if necessary)	139,053	145,320	136,848

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 2021, the EMA's signal management team reviewed in detail the information on 2,477 potential signals (i.e. drug-event pairs from screening of the EudraVigilance database, medical literature or information received from other regulatory authorities etc.). This figure includes 992 potential signals reviewed as part of the enhanced monitoring plan for COVID-19 vaccines, for which further details are provided below. This represents an approximately 31% increase compared to the previous year (see table 6). Excluding COVID-19 vaccines (new total, n=1485) would reveal a 21% drop in potential signals reviewed compared to 2020.

Table 6. Potential signals reviewed

Potential signals reviewed	2021*	2020	2019	2018	2017	2016	2015
Total	2477*	1888	1,806	2,204	2,062	2,076	2,372
Change from previous year	+589	+82	-398	+142	-14	-296	+342
% change from previous year	+31%	+4%	-18%	+7%	-1%	-12%	+17%

*1485 signals which are not related to Covid-19 vaccines and 992 signals for Covid-19 vaccines (tracked separately in 2 pilot files which may slightly overlap).

A specific monitoring strategy was created for COVID-19 vaccines. A dedicated vaccine eRMR was created for each of COVID-19 vaccines (weekly monitoring). 344 signals were reviewed specifically for COVID-19 vaccines: 220 from the eRMR, 64 from eVPR monitoring, 26 form literature monitoring, 10 from MS communications and 3 from other regulators. 11 signals were reviewed as part of ad-hoc searches and 10 as part of pregnancy monitoring. In addition to vaccine eRMRs, adverse events of special interest (AESIs) were under constant monitoring for each vaccine. A special monitoring tool (eVPR: excel Validation Perpetual Report) was created enabling in-stream review of every such new case report. Number of AESIs continuously reviewed for COVID-19 vaccines on an ongoing basis in 2021 was 648.

For other products, EudraVigilance screening also continues to be the major source of EMA's potential signals with 89% of reviewed potential signals in 2021 originating from EV screening (compared to 81% in 2020). Scientific literature screening gave rise to 9% of potential signals in 2021 (18% in 2020). Additionally, cooperation with other regulatory authorities worldwide accounted for 1% of potential signals (0.4% in 2020), including notifications from WHO/UMC, FDA, PMDA/MHLW, Health Canada and SwissMedic. Remaining 1% of signals were from other sources, including ESI notifications from MAHs and internal EMA meetings. The breakdown of action taken by potential signals opened by EMA has been relatively constant over time with 2-3% of signals reviewed being validated for further PRAC assessment (see Table 7).

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

Action taken	Number of potential signals - 2021	% of total	Number of potential signals - 2020	% of total	Number of potential signals - 2019	% of total
Not validated (closed)	1157	77.9%	1,530	81.0%	1,436	79.5%
Monitored	97	6.5%	138	7.3%	115	6.4%
Ongoing	193	13%	181	9.6%	205	11.4%
Prioritised and assessed by PRAC	40	2.7%	39	2.1%	50	2.8%
Total	1,485	100.0%	1,888	100.0%	1,806	100.0%

*excluding COVID-19 vaccines

Overview of signals prioritised and assessed by the PRAC

All detected validated signals which are confirmed by the Rapporteur or LMS are brought to the attention of the PRAC for initial analysis and prioritisation and assessment. The number of confirmed signals prioritised and assessed by the PRAC in 2021 was 86, compared with 81 in 2020, representing a 6% increase. 2021 was close to the average number of signals assessed annually between 2014-2020. Of these 86, 55 were validated by the Agency (15 COVID-19 vaccines and 40 for other products), 31 were validated by the MSs (6 COVID-19 vaccines and 25 for other products) in the course of ongoing safety monitoring through screening of reaction monitoring reports, ADR reports, medical literature and other safety data. Overall, 87% of the signals included data from EudraVigilance among their sources (85% in 2020).

Forty-two of the assessed signals (49%) 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. In nine of these cases, the PRAC also recommended Direct Healthcare Professional Communications (DHPCs) to highlight new important safety information to prescribers. Two signals also led to the update of the RMP to fully characterise and investigate the concern. In 18 signals (20%) continuing with routine safety monitoring of the medicine was considered sufficient. The evaluation of 24 signals (28%) is ongoing in 2021, including 17 via a follow-up signal procedure, 7 in the upcoming PSURs/PSUSAs. No signals resulted in referral procedures or PASS studies. See figure 15 for a summary.

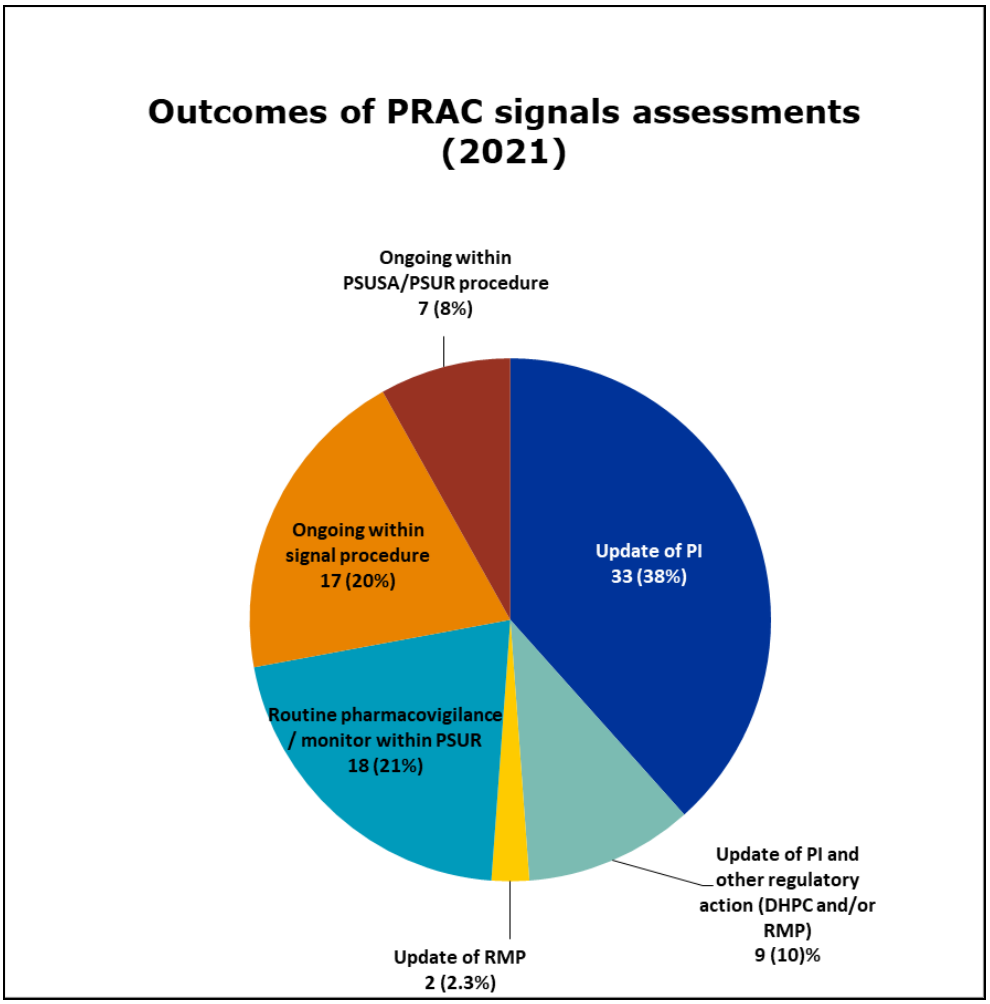


Figure 15. Outcomes of PRAC signal assessments (2021). PI: product information, DHPC: Direct Healthcare Professional Communication, RMP: Risk Management Plan, PSUR: Periodic Safety Update Report, PSUSA: PSUR Single Assessment.

Table 8. A list of all COVID-19 vaccine signals prioritised and assessed by the PRAC in 2021 is provided below, noting the latest status or outcome as of 31 December 2021, by chronological order of signal

COVID-19 vaccine	Issue/signal	Status or outcome
Vaxzevria (COVID-19 vaccine AZ)	Anaphylactic reaction	Update of PI and DHPC
Vaxzevria (COVID-19 vaccine AZ)	Capillary leak syndrome	Update of PI and DHPC
Comirnaty (BioNtech/Pfizer)	Localised swelling in persons with history of dermal filler injections	Update of PI
Vaxzevria (COVID-19 vaccine AZ)	Immune thrombocytopenia	Update of PI, DHPC and RMP
		ongoing (within

COVID-19 vaccine	Issue/signal	Status or outcome
Spikevax (Moderna)	Immune thrombocytopenia	PSUR/PSUSA)
Comirnaty (BioNtech/Pfizer)	Immune thrombocytopenia	routine pharmacovigilance / monitor within PSURs
Vaxzevria (COVID-19 vaccine AZ)	Embolic and thrombotic events	Update of PI, DHPC and RMP
COVID-19 vaccine Janssen	Embolic and thrombotic events	Update of PI, DHPC and RMP
Vaxzevria (COVID-19 vaccine AZ)	Acute macular outer retinopathy	Update of RMP
Comirnaty (BioNtech/Pfizer)	Myocarditis and pericarditis	Update of PI, DHPC and RMP
Spikevax (Moderna)	Myocarditis and pericarditis	Update of PI, DHPC and RMP
Comirnaty (BioNtech/Pfizer)	Erythema multiforme	Update of PI
Spikevax (Moderna)	Erythema multiforme	Update of PI
Comirnaty (BioNtech/Pfizer)	Glomerulonephritis and nephrotic syndrome	routine pharmacovigilance / monitor within PSURs
Spikevax (Moderna)	Glomerulonephritis and nephrotic syndrome	routine pharmacovigilance / monitor within PSURs
Comirnaty (BioNtech/Pfizer); Spikevax (Moderna); Vaxzevria (COVID-19 vaccine AZ); COVID-19 vaccine Janssen	Multisystem inflammatory syndrome	routine pharmacovigilance / monitor within PSURs
Spikevax (Moderna)	Capillary leak syndrome	Ongoing (signal)
Comirnaty (BioNtech/Pfizer)	Myocarditis and pericarditis	Update of PI
Spikevax (Moderna)	Myocarditis and pericarditis	Update of PI
Comirnaty (BioNtech/Pfizer)	Autoimmune hepatitis	Ongoing (signal)
Spikevax (Moderna)	Autoimmune hepatitis	Ongoing (signal)

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

Drug	Issue/signal	Status or outcome
atorvastatin; fluvastatin; lovastatin; pitavastatin; pravastatin; rosuvastatin; simvastatin	Bullous pemphigoid	routine pharmacovigilance / monitor within PSURs
Abatacept	Acute Respiratory Distress Syndrome (ARDS)	Ongoing (signal)
Adalimumab	Abnormal Weight Gain	Update of PI
Adalimumab	Acquired haemophilia	routine pharmacovigilance / monitor within PSURs
Alemtuzumab	Vitiligo	Ongoing (signal)
Alemtuzumab	Sarcoidosis	Update of PI
Alemtuzumab	Autoimmune encephalitis	Update of PI
Anakinra Canakinumab	Drug reaction with eosinophilia and systemic symptoms (DRESS)	update of PI
Anastrozole	Depressed mood disorders	update of PI
Atezolizumab	Optic neuritis	ongoing (Signal)
Atezolizumab	Cholangitis sclerosing	ongoing (within PSUR/PSUSA)
Azathioprine	Erythema nodosum	update of PI
Bupropion	Acute generalised exanthematous pustulosis (AGEP)	update of PI
Canakinumab	Interstitial lung disease (ILD) and alveolar proteinosis	ongoing (within PSUR/PSUSA)
Cannabidiol Calcineurin inhibitors: ciclosporin, tacrolimus Mammalian target of rapamycin (mTOR) inhibitors: everolimus, sirolimus; temsirolimus	Drug interaction between cannabidiol and mTOR inhibitors / calcineurin inhibitors	ongoing (Signal)
Ceftriaxone	Hepatitis	update of PI
Clindamycin	Acute renal failure	update of PI
Dabigatran	Autoimmune Haemolytic Anaemia	ongoing (within PSUR/PSUSA)
Donepezil	Cardiac conduction disorders including QT prolongation and Torsade de Pointes	update of PI
Durvalumab	Arthralgia	ongoing (Signal)

Drug	Issue/signal	Status or outcome
Efavirenz	Microcephaly	routine pharmacovigilance / monitor within PSURs
Eliglustat	Erectile dysfunction	routine pharmacovigilance / monitor within PSURs
Enzalutamide	Erythema multiforme	ongoing (Signal)
Ertapenem	Toxic Encephalopathy in patients with renal impairment	update of PI
Filgrastim	Immune Reconstitution Inflammatory Syndrome (IRIS)	routine pharmacovigilance / monitor within PSURs
Fluoroquinolones: ciprofloxacin; delafloxacin; levofloxacin; lomefloxacin; moxifloxacin; norfloxacin; ofloxacin; pefloxacin; prulifloxacin; rufloxacin	Acquired thrombotic thrombocytopenia purpura	routine pharmacovigilance / monitor within PSURs
Hydrocortisone	Adrenal crisis	update of PI and DHPC
Ibrutinib	Sudden death/cardiac death with ibrutinib and concomitant angiotensin-converting enzyme (ACE) inhibitors from a clinical trial	routine pharmacovigilance / monitor within PSURs
Ipilimumab	Transverse myelitis	update of PI
Labetalol	Nipple pain and suppressed lactation	update of PI
Lenvatinib	Colitis	update of PI
Liraglutide	Cutaneous amyloidosis	ongoing (within PSUR/PSUSA)
Lumacaftor/Ivacaftor	Drug reaction with eosinophilia and systemic symptoms (DRESS)	ongoing (Signal)
Methotrexate	Progressive multifocal leukoencephalopathy (PML)	update of PI
Obinutuzumab	Non-overt disseminated intravascular coagulation (DIC)	ongoing (Signal)
Octreotide	Pancreatic exocrine insufficiency	update of PI
Olanzapine	Cardiomyopathy	routine pharmacovigilance / monitor within PSURs

Drug	Issue/signal	Status or outcome
Olaparib	Pneumocystis Jirovecii Pneumonia	routine pharmacovigilance / monitor within PSURs
Olmesartan Pembrolizumab	Autoimmune hepatitis Paraneoplastic neurological syndrome	update of PI ongoing (within PSUR/PSUSA)
Pembrolizumab	Systemic scleroderma	routine pharmacovigilance / monitor within PSURs
Pembrolizumab nivolumab atezolizumab avelumab durvalumab cemiplimab ipilimumab	Immune-mediated cystitis	update of PI
Piperacillin piperacillin, tazobactam	Hemophagocytic lymphohistiocytosis (HLH)	update of PI
Ponatinib	Panniculitis	update of PI
Prednisolone	Bradycardia	update of PI
Pregabalin	Toxic epidermal necrolysis	ongoing (Signal)
Propylthiouracil	Drug reaction with eosinophilia and systemic symptoms (DRESS)	routine pharmacovigilance / monitor within PSURs
Remdesivir	Acute kidney injury	routine pharmacovigilance / monitor within PSURs
Remdesivir	Sinus bradycardia	update of PI
Rituximab	Sarcoidosis	routine pharmacovigilance / monitor within PSURs
Romosozumab	Cardiac arrhythmia	update of RMP
Romosozumab	Renal impairment	ongoing (within PSUR/PSUSA)
Sacubitril Valsartan	Vasoplegia Syndrome	ongoing (Signal)
Secukinumab	Henoch-Schoenlein purpura	update of PI
Secukinumab	Facial paralysis	routine pharmacovigilance / monitor within PSURs

Drug	Issue/signal	Status or outcome
Sorafenib	Tumour lysis syndrome	ongoing (Signal)
Sulfamethoxazole and trimethoprim (co-trimoxazole)	Acute respiratory distress syndrome	update of PI
Sulfametoxazole/trimethoprim	Haemophagocytic lymphohistiocytosis (HLH)	update of PI
Tocilizumab	Sarcoidosis	ongoing (Signal)
Tofacitinib	Major adverse cardiovascular events (MACE) and malignancies excluding non-melanoma skin cancer (NMSC) from a clinical trial	update of PI, RMP and DHPC
Tramadol	Serotonin syndrome	update of PI
Trastuzumab emtansine	Extravasation and epidermal necrosis	update of PI
Vildagliptin	Cutaneous Vasculitis	ongoing (Signal)
Warfarin	Anticoagulant-related nephropathy	update of PI

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 2021 is summarised below.

In line with the established role of SMART Processes to support the overall signal management process, the group has continued to provide guidance and clarifications as to what falls in the scope of signals, what are the best regulatory tools to support harmonisation of the product information, as well as possible efficiency gains.

SMART processes have also provided a platform to share information within the network on tools and best practices to support the close monitoring of medicinal products. Discussions focussed on those tools that were specifically introduced to intensively monitor the safety COVID-19 vaccines, e.g. the Vaccine Targeted Medical Events list, new EVDAS vaccines dashboards or the use of Observed to Expected analyses. The group also reiterated the importance of timely submission of ICSRs to EV to ensure prompt detection of possible safety issues arising from spontaneous reporting and provided criteria to guide the EU Network on the choice of the most appropriate regulatory procedure to review safety signals emerging with COVID-19 vaccines.

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

- Observed to expected (O/E) analysis could be used to either support signal detection or to refine previously detected signals for vaccines. The group performed preparatory work, both based on retrospective and prospective data, in anticipation of the COVID-19 vaccines being administered to refine the methodology on which O/E is based, understand the different input needed for the analysis and the corresponding assumptions, and prepare processes for calculations and presentation of the results. The method was successfully used to ascertain the signal of thrombosis with thrombocytopenia syndrome (TTS) associated with AstraZeneca's and Janssen's vaccines which led to a prompt regulatory action, early recognition of the risk and reduced mortality. The method was then used to ascertain all the main signals during the COVID-19 vaccination campaign (e.g. myocarditis).
- Testing machine learning model classifier to support the adjudication of cases of thrombosis with thrombocytopenia syndrome (TTS). The initial work aimed at determining whether a classifier of appropriate performance could be developed using cases submitted to EV that have been previously manually assessed. Multi-class classification tasks aimed to correctly categorise the different classes in which the cases were grouped (confirmed, probable, possible, criteria not met and unlikely) resulted in poor predictive performance. However, results significantly improved when the algorithm was used to classify group of classes (confirmed and probable vs all others). As a next step EMA will work on packaging the models and developing a suitable tool for users.
- Identification of adverse pregnancy outcomes in the context of COVID-19 vaccination. The existing pregnancy algorithm in EV was fine-tuned to support signal detection and risk communication.
- Pilot study conducted using social media data (Twitter and Google interest metric) aimed at understanding the usefulness of these sources of data in the monitoring of the vaccine safety and on signal refinement. The evidentiary value of Twitter posts collected prospectively was considered low. Contribution to better understanding of vaccine hesitancy could be explored further.

Annex VII - Requests for information and documents

In 2021, EMA responded to 39 requests for EudraVigilance (EV) data, where requests for information (involving aggregated data) and/or documents (line listings) were provided. This number of requests is an increase when compared to the previous two years (28 in 2020 and 32 in 2019, respectively). This increase was primarily driven by requests for COVID-19 related data, which accounted for 59% of total requests. Notwithstanding the elevated number of requests in 2021 as a result of the pandemic, EMA continues to receive significantly less EV data requests owing to the adverse reaction data proactively provided through the www.adrreports.eu website. The portal is publicly accessible and continues to fulfil most general public queries. In 2021, EMA received 175 COVID related queries, for which 23 involved EV data being provided. Consequently, the figure of 39 requests mentioned above, corresponds to internal requests from the EU regulatory network (9) in addition to external requests (30) 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, but are not limited to, disproportionality analyses, queries for data from the general public including patients, requests from academia, as well as a significantly higher number of queries from the press than in previous years.

Of the 39 requests for EV data, 31 (79.5%) were requests for information (involving aggregated data), whilst six (15.4%) involved requests for documents (line listings). The remaining 2 requests (5.1% of the total) concerned requests for both information and documents. Most requests were related to centrally authorised products (CAPs) alone, accounting for 66.7% of the total number of requests, whilst nationally authorised products (NAPs) alone accounted for 5.1%. Requests concerning both CAPs and NAPs accounted for the remaining 28.2%.

The median response time for the requests in 2021 was 5 days (range 0 – 85 days), notably faster when compared to previous years (16 days in 2019 and 12 days in 2018). Three requests (7.7%) were responded to past the deadline due to the complexity of the request or technical issues. All requesters were informed in advance of the delay.

COVID related queries

A high proportion of the requests for EV data in 2021 (23 out of 39) were relating to one or more of the centrally authorised COVID-19 vaccines. Of these COVID-19 related queries, requests for information accounted for 82.6% whilst the remaining requests were for access to documents. Just under half of these requests were from journalists (43.5%), followed by requests from patients (21.7%) and queries from academia (8.7%). The remaining requests were internal from the EU regulatory network.

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

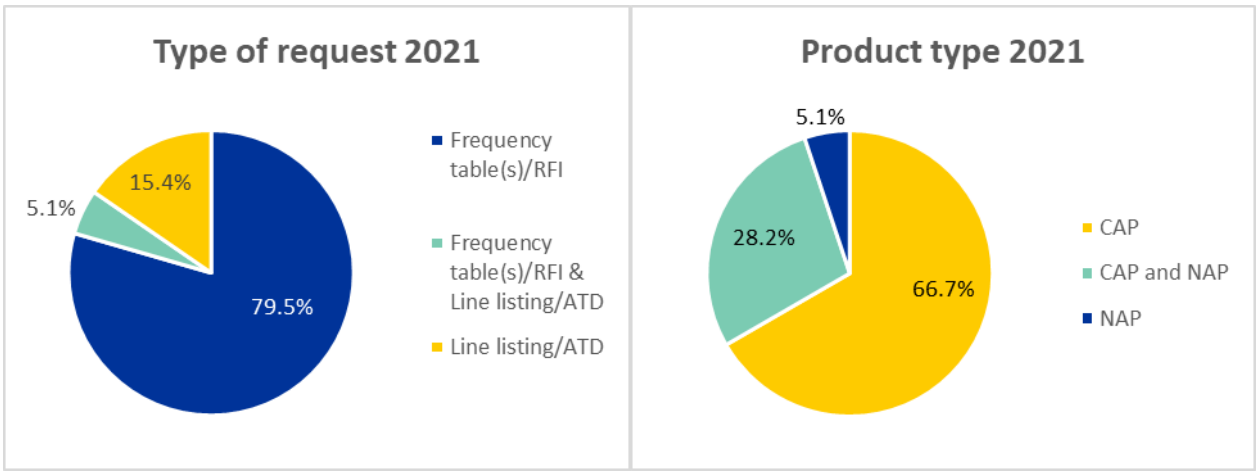


Figure 16 Overview of requests for EV data in 2021 by type of request (left) and product type (right).

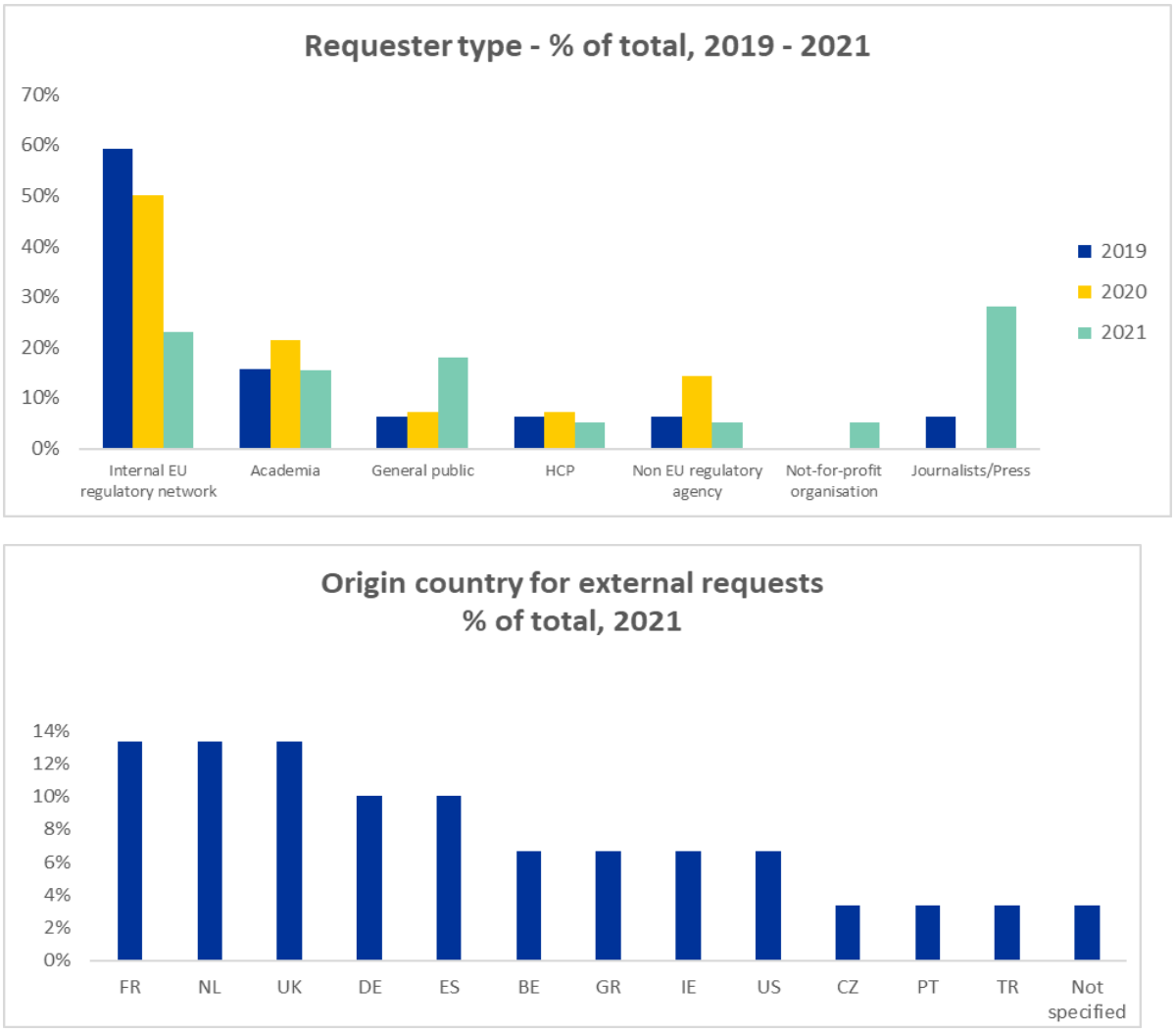


Figure 17 Overview of requests for EV data in 2021 by requester type (top) and country or region of origin for external requests (bottom).

Figure 18 Overview of requests responded to in 2021

Type of requester	Substance / product	Issue	Type of request
Academia	Biological products	ADRs of biological products for 25 EU countries	Line listing/ATD
Academia	Multiple	100 substances for which the highest number of serious and fatal cases were reported	Frequency table(s)/RFI
Healthcare professional	Multiple	Thrombotic thrombocytopenic purpura	Frequency table(s)/RFI
Healthcare professional	Pregabalin	Requested ADRs	Frequency table(s)/RFI
Press	Comirnaty	Fatal ADRs	Frequency table(s)/RFI
Academia	Multiple	ADRs related to prescribing errors	Frequency table(s)/RFI
EU regulatory network	Covid-19 vaccines	Fatal ADRs	Frequency table(s)/RFI
Press	Covid-19 vaccines	Fatal ADRs in EU	Frequency table(s)/RFI
Not-for-profit organisation	Cyclophosphamide	EV safety report ID for 19 specific case report numbers provided	Frequency table(s)/RFI
Not-for-profit organisation	Cyclophosphamide	EV safety report ID for two specific case report numbers provided	Frequency table(s)/RFI
Academia	Covid-19 vaccines	Cerebral venous thrombosis	Line listing/ATD
Academia	Multiple	ROR analysis of potentially inappropriate medicines for the elderly	Frequency table(s)/RFI
General public	Multiple	All ADRs in EEA	Frequency table(s)/RFI
Press	Multiple	All ADRs	Frequency table(s)/RFI

Type of requester	Substance / product	Issue	Type of request
EU regulatory network	Shingrix	Guillain-Barre syndrome	Frequency table(s)/RFI
Press	Covid-19 vaccines	Fatal ADRs	Frequency table(s)/RFI
Academia	Covid-19 vaccines	Cerebral venous thrombosis	Line listing/ATD
Press	Covid-19 vaccines	Fatal ADRs	Frequency table(s)/RFI
Press	Covid-19 vaccines	All ADRs	Frequency table(s)/RFI
Press	Covid-19 vaccines	All ADRs	Frequency table(s)/RFI
Press	Covid-19 vaccines	All ADRs	Frequency table(s)/RFI
Press	Covid-19 vaccines	All ADRs	Frequency table(s)/RFI
Press	Covid-19 vaccines	All ADRs	Frequency table(s)/RFI
Press	Covid-19 vaccines	All ADRs	Frequency table(s)/RFI
EU regulatory network	Fluoroquinolones	Acquired thrombotic thrombocytopenia purpura	Line listing/ATD
Non-EU regulatory agency	IV iron replacement therapies	Allergic reactions and hypersensitivity reactions in pregnant women	Frequency table(s)/RFI
EU regulatory network	Covid-19 vaccines	ADRs for the monthly vaccines safety updates	Frequency table(s)/RFI
Non-EU regulatory agency	IV iron replacement therapies	Allergic reactions and hypersensitivity reactions in pregnant women (follow up)	Frequency table(s)/RFI + Line listing/ATD
EU regulatory network	Covid-19 vaccines	ADRs for the monthly vaccines safety updates	Frequency table(s)/RFI

Type of requester	Substance / product	Issue	Type of request
EU regulatory network	Nomegestrol-containing products and chlormadinone-containing products	EV analysis for Art. 31 referral	Frequency table(s)/RFI + Line listing/ATD
EU regulatory network	Covid-19 vaccines	ADRs for the monthly vaccines safety updates	Frequency table(s)/RFI
General public	Clozapine	Myocarditis and pericarditis	Frequency table(s)/RFI
EU regulatory network	Covid-19 vaccines	ADRs for the monthly vaccines safety updates	Frequency table(s)/RFI
General public	Covid-19 vaccines	Fatal ADRs within 24 hours of vaccination	Frequency table(s)/RFI
General public	Covid-19 vaccines	All ADRs	Frequency table(s)/RFI
General public	Covid-19 vaccines	Country of origin for requested cases	Line listing/ATD
General public	Covid-19 vaccines	Country of origin for cases	Line listing/ATD
EU regulatory network	Covid-19 vaccines	ADRs for the monthly vaccines safety updates	Frequency table(s)/RFI
General public	Covid-19 vaccines	All ADRs reported by at least one healthcare professional	Frequency table(s)/RFI