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2020 Annual Report on EudraVigilance for the European Parliament, the Council and the Commission

Reporting period: 1 January to 31 December 2020

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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

EudraVigilance, the European database for 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 periodic safety update reports and the assessment of risk management plans (RMPs) by the Pharmacovigilance Risk Assessment Committee (PRAC). EudraVigilance is therefore one of the cornerstones of EU pharmacovigilance.

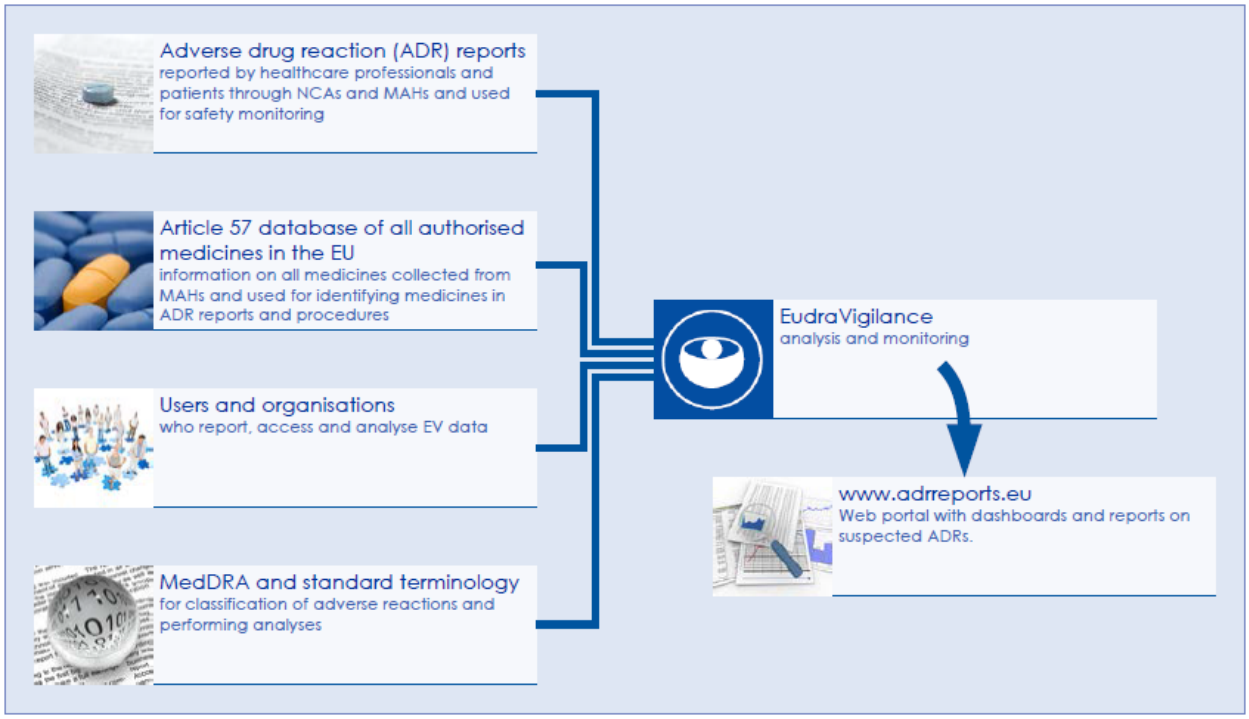


Figure 1. EudraVigilance users, data sources and data use.

The database currently holds **over 18.6 million individual case safety reports**[1] (ICSRs) referring to over 10.5 million individual cases 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 2020, notably:

- ***Operation of EudraVigilance including its new functionalities***. EudraVigilance continued to be maintained by the EMA on behalf of the EU medicines regulatory network, with further functional improvements in data analysis and signal detection delivered, including specific tools for the COVID-19 pandemic
- ***Collecting and processing of adverse drug reaction reports***. In 2020, 1.8 million ICSRs related to suspected adverse reactions occurring in the post-authorisation phase were collected and managed in EudraVigilance (1,821,211 – a 9% decrease compared to the previous year). Some 45% of these originated from the EEA (812,760). The number of reports submitted directly

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

by European patients and consumers through the NCAs and MAHs (143,958) has had a decrease of 10% compared to 2019. Annex II of the report provides more details.

- ***Maintaining and updating the database of information on all medicinal products authorised in the EU***. At the end of 2020, this database (the so-called "Article 57 database") contained information on more than 900,000 medicinal products (including different formulations and strengths as separate medicines). The availability of such a complete dataset allows the identification of medicines in ICSRs, supports the management of pharmacovigilance procedures (signals, Periodic Safety Update Reports (PSURs), referrals) and facilitates the administration of pharmacovigilance fees. It also allows marketing authorisation holders (MAHs) to update details of the qualified person responsible for pharmacovigilance (QPPV) and the pharmacovigilance system master file (PSMF) more easily without the need for submission of variations.
- ***Ongoing data quality activities***. The Agency has processes in place to ensure the quality and integrity of the information collected in EudraVigilance. In 2020, 160,000 duplicate reports were identified, more than 100,000 reported medicinal products and active substances were coded, and the quality of ADR reports was reviewed for 120 organisations.
- ***Creation and distribution of data analysis reports***. EudraVigilance allows for the monitoring of newly received ADR reports, for the identification of new risks or risks that have changed (e.g. in frequency or severity) and provides data analyses to support decision-making by PRAC in pharmacovigilance procedures. In 2020, more than 26,000 individual electronic reaction monitoring reports (eRMRs) were generated for the EU network.
- ***Screening for, and review of, potential signals***. In 2020, the EMA's signal management team reviewed in detail 1,888 potential signals[2] for centrally authorised products (CAPs) from screening of the EudraVigilance database (81%), medical literature (18%) or information received from regulatory authorities or other sources. For active substances of nationally authorised products (NAPs), the monitoring of ADR reports is shared between the NCAs. For 1,880 substances, a Lead Member State (LMS) is appointed for monitoring safety data and NCAs also monitor all medicines authorised nationally in their country for which no LMS has been appointed.
- ***Supporting the central role of the PRAC in assessing and monitoring the safety of human 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 2020, the PRAC prioritised and assessed 81 confirmed signals (representing a 16% decrease compared with 97 in 2019). Some 85% of them included data from EudraVigilance. Of the 81, 39 were validated by the Agency, 42 were validated by the MS; 22 were for NAPs, 41 for CAPs and 18 for both NAPs and CAPs.

  Thirty-seven of the assessed signals (46%) 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 two of these cases, the PRAC also recommended Direct Healthcare Professional Communications (DHPCs) to highlight new important safety information to prescribers. One signal led to the update of the RMP to fully characterise and investigate the concern. In 16 signals (20%) continuing with routine safety monitoring of the medicine was considered sufficient. The evaluation of 28 signals (35%) was ongoing at the end of 2020, including 14 via a follow-up signal procedure, 13 in the upcoming PSURs/PSUSAs and 1 via referral procedure. The first signal for an approved COVID-19 therapy was validated by the Agency and is being assessed by the PRAC (at the end of 2020 still ongoing within a signal assessment procedure).

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

- ***Access for MAHs for the monitoring of EudraVigilance data***. Since the launch of the new EudraVigilance functionalities in November 2017, MAHs have access to the individual cases submitted to EudraVigilance. A pilot is currently ongoing whereby MAHs of selected active substances perform safety monitoring in EudraVigilance and inform EMA and NCAs of validated signals with their medicines. In late 2019, based on the experience with the pilot, the European Commission services chose to extend the pilot for a further two-years in order to increase the experience upon which longer-term decisions on the utility of MAH monitoring can be judged.
- ***Direct provision of data to the World Health Organization (WHO)***. EudraVigilance is one of the sources of adverse event reports reported to WHO's Uppsala Monitoring Centre. During the 2020 reporting period, over a million (1,212,939) ICSRs were forwarded to WHO from EudraVigilance, making it one of the largest contributors to the WHO database.
- ***Public access to aggregated EudraVigilance data***. In November 2017, public access via www.adrreports.eu was further improved by providing additional outputs such as line listings and individual case report forms. By the end of 2020, the website provided information on a total of 4,052 active substances, of which 796 were contained in CAPs and 3,256 in NAPs.
- ***Training and support activities***. Extensive training offerings are available face-to-face or online as e-learning[3] for all stakeholders and training for the EU network is available through the EU Network Training Centre. Some of the training and support activities organised by the EMA were suspended or made on-line only during 2020 due to the COVID-19 pandemic.

2. Operation of EudraVigilance including its further development

EudraVigilance is a central pillar for pharmacovigilance activities in the EEA. The system permits 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 safety reporting of suspected unexpected serious adverse reactions (SUSARs) to investigational medicinal products that may occur during clinical trials.

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 system launch 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 23rd March 2020 to cover the period 2020-2022.

The key activities undertaken during 2020 are summarised here:

- During the public health crisis triggered by the COVID-19 pandemic, EudraVigilance is playing a crucial role facilitating the early detection of emerging risks related to medicines used to treat or prevent COVID-19 and its complications, both for authorised therapeutics and vaccines. The role of

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

EudraVigilance is described in the Pharmacovigilance Plan of the EU Regulatory Network for COVID-19 Vaccines[4]

- In the context of the COVID-19 pandemic, the EMA published the Detailed guidance on ICSRs in the context of COVID-19 and determined and elaborated the impact on reporting into EudraVigilance in the Notice to Stakeholders (Questions and Answers on regulatory expectations for medicinal products for human use during the Covid-19 pandemic[5]).
- The medical literature review (MLM) service increased in 2020 the number of substances to include medicines which are being investigated as potential treatments for COVID-19, and for which there are multiple MAHs. COVID-19-related search terms were also added to the regular literature searches.
- In April 2020, a dedicated dashboard was made available in EVDAS to NCA and EMA staff to support the monitoring of ADR reports related to COVID-19. In Q4 2020, new COVID-19 specific metrics were implemented in the electronic Reaction Monitoring Reports (eRMRs) for NCAs and EMA to facilitate the visualisation and screening of safety reports related to COVID-19.
- Integration of the EV Human XCOMP (external testing system) registration process with the Agency's identity and access management (IAM) components, together with improvements of the IAM Human components and the EudraVigilance Human registration process to include the self-management of virtual affiliates.
- Upgrade of the Human and Veterinary EudraVigilance business intelligence data warehouse platform component supporting the pharmacovigilance activities. The platform now uses the HTML5 technology, replacing Adobe Flash that is not supported beyond January 2021.
- Integration of the Human and Veterinary EudraVigilance system component; this is reflected in the update of the European Database of adverse reactions reports[6] to include information on veterinary medicines.
- Preparations related to the Brexit impact, 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[7]. The relevant changes include amongst others, the categorisation of UK cases as non-EEA cases from 01st 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 April 2020, an improved version of the electronic Reaction Monitoring Report (eRMR) was launched in the EVDAS MAHs' Dashboard to increase the quality of the data and minimise the number of technical issues. The new MAHs' Dashboard provides the possibility to retrieve eRMRs with reporting period from 15 days to one year.
- With the aim to enhance the quality of the data in the database and to describe the data management activities and the roles and responsibilities of the different stakeholders in the quality of the ICSRs, EMA developed and published a detailed guide regarding the EudraVigilance data management activities by the European Medicines Agency[8].

[4] https://www.ema.europa.eu/en/documents/other/pharmacovigilance-plan-eu-regulatory-network-covid-19-vaccines_en.pdf
[5] https://ec.europa.eu/health/sites/health/files/human-use/docs/guidance_regulatory_covid19_en.pdf
[6] https://www.adrreports.eu
[7] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/notice-stakeholders-withdrawal-united-kingdom-eu-rules-medicinal-products-human-use-veterinary_en.pdf
[8] https://www.ema.europa.eu/en/documents/other/detailed-guide-regarding-eudravigilance-data-management-activities-european-medicines-agency_en.pdf

- During 2020 the EudraVigilance training activities and stakeholder engagement have been adapted to virtual mode so the support to the operability of the system has been maintained. The EV training page reflects all the training, guidelines and stakeholders support activities[9].
- In the context of stakeholders' engagement, the EudraVigilance Expert Working Group with representatives from NCAs, MAHs and Clinical Trial Sponsors has finalised and published its work programme for 2021-2022[10].

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

- 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 will continue to support stakeholders in this important initiative to ensure their readiness and in this context, a revision of the EU ICSR Implementation Guide is currently ongoing and expected for publication by Q1 2021.

- 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.[11]

3. Data collection and data quality

Medicinal product information

The total number of medicinal products entries by MAHs in the XEVMPD as of 15 January 2021 is 904,559 (regardless of authorisation status e.g. valid, withdrawn). These entries provide a dataset of medicines in the EU, both those authorised through the centralised procedure and those authorised via national procedures. The 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), which was available for 99.9% of medicinal products. Full details on these items are presented in Annex III.

[9] https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance/eudravigilance-training-support
[10] https://www.ema.europa.eu/en/documents/work-programme/eudravigilance-expert-working-group-ev-ewg-work-programme-2021-2022_en.pdf
[11] https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trial-regulation

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[12] 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 underpins the operation of the EU pharmacovigilance system.

In the context of COVID-19, at the end of April EMA and NCAs have reminded patients with confirmed or suspected COVID-19 to report suspected side effects that they experience with any of the medicines they are taking. Visuals for social media were developed for both HCPs and patients[13].

In 2020, 1,821,211 ICSRs were collected and managed in EudraVigilance. This figure represents a 9% decrease compared to the numbers recorded in 2019, and it is characterised by a marked drop in EEA (-16%) and non-serious (-14%) reporting.

The number of reports submitted directly by patients and consumers through the NCAs and MAHs (143,958) has decreased (-10% compared to the previous year), confirming the downward trend started in 2019 after the surge in reporting observed in 2018.

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

EudraVigilance also continues to support the reporting of suspected unexpected serious adverse reactions (SUSARs) in accordance with EU clinical trial legislation[14] (see Annex II).

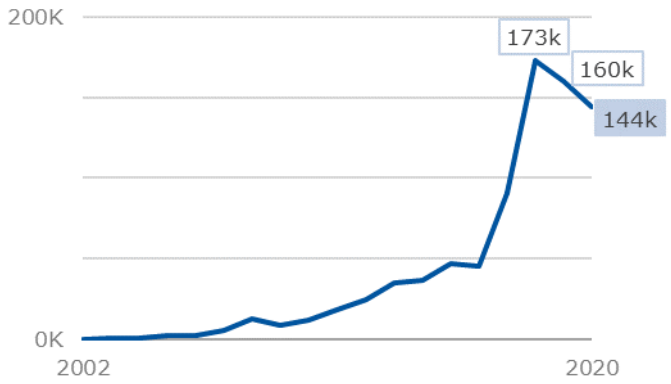


Figure 2. Trend of ADR reports from patients and consumers received in the EEA by NCAs and MAHs and reported to EudraVigilance.

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

[12] 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.
[13] https://www.ema.europa.eu/en/news/reporting-suspected-side-effects-medicines-patients-covid-19
[14] 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

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

EudraVigilance data monitoring is a collaborative effort between NCAs and the Agency and, since February 2018, MAHs (as part of the signal management pilot). The safety information contained in EudraVigilance is continuously screened using statistical reports called eRMRs. In 2020, over 26,000 individual eRMRs were generated for NCA 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. 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; of 1,888 potential signals which were reviewed by the Agency in 2020, approximately 81% originated from EudraVigilance, highlighting its central role for ADR data monitoring.

For active substances of 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'[15], which indicates a Lead Member State (LMS) for each included active substance. The list was updated in 2020 following changes in PSUSA leaderships and in marketing authorisation status. It currently includes 1,880 active substances. NCAs also monitor all medicines authorised nationally in their country for which no LMS has been appointed.

A pilot started in February 2018 whereby MAHs of selected active substances[16] have to monitor them in EudraVigilance and inform EMA and NCAs of validated signals with their medicines[17]. 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 2020, the Network had received 45 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 2020, the confirmed signal is from 2019). All other MAHs also have access to cases for their medicinal products and therefore can integrate EV data into their own signal management processes. In late 2019, based on the experience with the pilot, the European Commission services chose to extend the pilot for a further two-years in order to increase the experience upon which longer-term decisions on the utility of MAH monitoring can be judged.

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 2020, the PRAC prioritised and assessed 81 confirmed signals (a 16% decrease compared to 2019); 85% included data from EudraVigilance. Thirty-seven of the assessed signals (46%) resulted in a recommendation for an

[15] http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500226389
[16]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
[17] https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:159:0005:0025:EN:PDF

update of the product information for patients and healthcare professionals, thus providing updated guidance on the safe and effective use of the medicines. In two of these cases, the PRAC also recommended Direct Healthcare Professional Communications (DHPCs) to highlight new important safety information to prescribers. One signal led to the update of the RMP to fully characterise and investigate the concern and 1 signal resulted in referral procedure. In 16 signals (20%) continuing with routine safety monitoring of the medicine was considered sufficient. The evaluation of 27 signals (33%) is ongoing in 2021, including 14 via a follow-up signal procedure and 13 in the upcoming PSURs/PSUSAs.

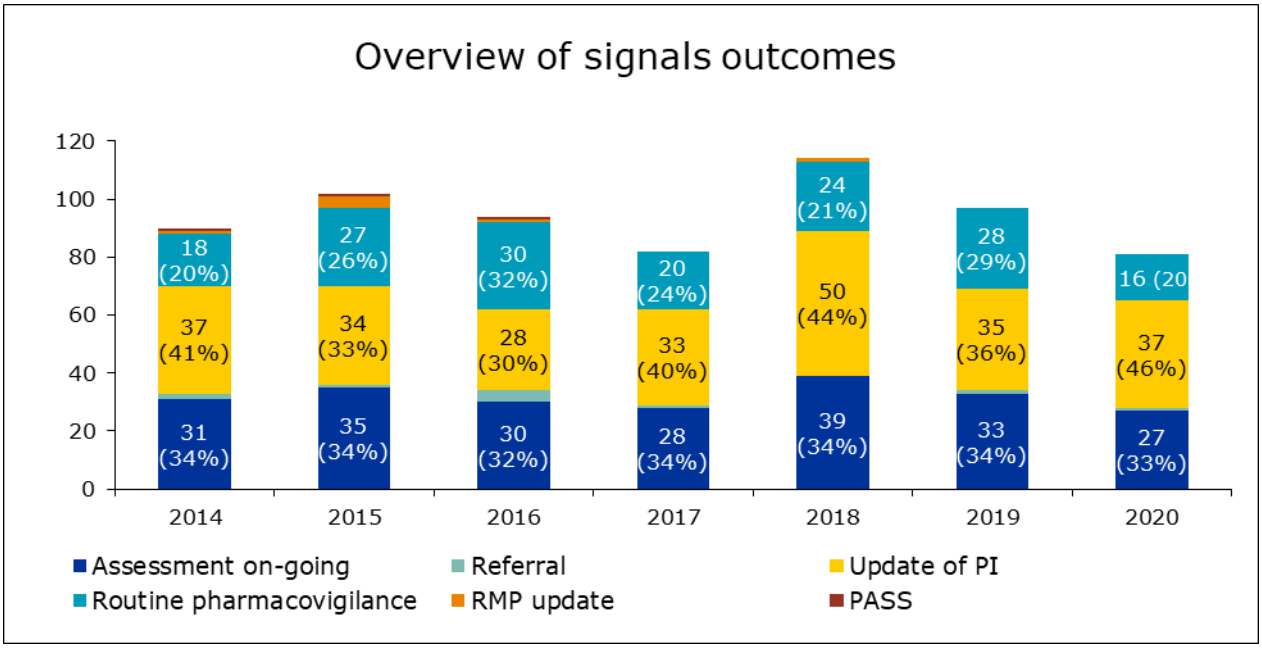


Figure 3. Overview of signals assessed by the PRAC.

In July 2020 the first signal for an approved COVID-19 therapy, involving Veklury (remdesivir), was validated by the Agency and is being assessed by the PRAC (ongoing as a signal at the end of 2020)[18]

EudraVigilance monitoring thus facilitates 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 results 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 2020 can be found in Annex V. The progress of process improvements and simplifications in signal management is detailed in Annex VI.

5. Transparency, communication and training

Public access to aggregated EudraVigilance data has been available since 2012 via aggregated reports available at 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 2020, the website provided information on a total of 4,052 active substances, of which 796 contained in CAPs and 3,256 in NAPs. There were over 2.5 million visits to the website in 2020 (an increase of nearly 50% compared to 2019). At the end of 2020, ADR data related to the first Covid-19 vaccine authorised via

[18] https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-28-september-1-october-2020

the centralised procedure (Comirnaty) was made available at the European Database of Suspected Adverse Drug reactions reports (www.adrreport.eu).

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.

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, 28 requests were answered within a median of 16 working days. Approx. 50% of all requests were received from the EU regulatory network, supporting the scientific assessment of pharmacovigilance procedures. An increase was noted in requests received from academia. More details are provided in Annex VII.

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

- Total of 12 training sessions on EudraVigilance ICSR submissions (11 virtual, 1 at Agency), with 192 users trained in total,
- 1 EudraVigilance Information Day, 198 attendees (no Information Day in 2019),
- 6 training sessions on XEVMPD have taken place virtually in 2020 and 90 users were trained.
- EVDAS training session for NCAs took place in November 2020 and 40 pharmacovigilance assessors were trained.
- 156 participants registered for online XEVMPD assessment/followed training on XEVMPD via its e-learning platform in 2020.

Some training and support activities organised by the EMA were suspended during 2020 due Covid-19 and BCP.

6. Conclusion

ADR reporting to EudraVigilance continues at high levels. Over 1.8 million ICSRs were received in 2020, of which 812,760 originated from the EEA, and based on these reports, over 26,000 statistical outputs were produced and screened for the identification of signals which are subsequently assessed by the PRAC.

EudraVigilance currently contains over 18.6 million ICSRs. It is being used by EMA, EU NCAs and MAHs, and plays a role in global surveillance, with over 1.2 million reports forwarded to the WHO database in 2020.

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 2020 in relation to the COVID-19 pandemic; this included the creation of new tools to facilitate monitoring of ADR reports specifically related to COVID-19.

EudraVigilance is a central pillar for pharmacovigilance activities in the EEA, including during the public health crisis triggered by the COVID-19 pandemic. It will play a crucial role in facilitating the early detection and management of any emerging risks related to authorised COVID-19 therapeutics and 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.

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 2020.
Data quality review and duplicate management of adverse reaction reports in EudraVigilance. [*Legal basis:* Regulation (EC) 726/2004, Article 24(3)]	Continued during 2020.
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 2020.
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 2020.
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 2020.
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 2020.
Operation of the Medical Literature Monitoring service [*Legal basis:* Regulation (EC) 726/2004, Article 27]	Continued during 2020.

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[19], exceeding the required 98% availability (see Fig. 3).

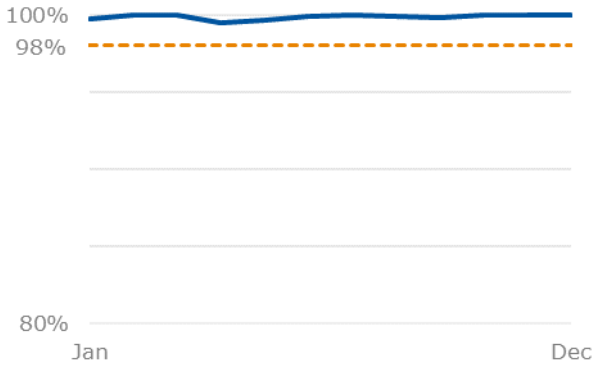


Figure 3. EudraVigilance gateway availability per month. The requirement is 98%. Please note that the scale starts at 80%. Planned downtime is excluded.

EudraVigilance database

For medicinal products authorised in the EEA, ADR reports are collected from both within and outside the EEA. By 31 December 2020, the EudraVigilance database held a total of 18,655,237 ADR reports (or ICSRs), referring to 10,511,158 individual cases (figure 4). The post-authorisation module (EVPM) contained 17,231,805 ICSRs (10,108,494 individual cases) and the clinical trial module (EVCTM) 1,423,432 ICSRs (402,664 individual cases).

[19] Only unplanned downtime is taken into consideration

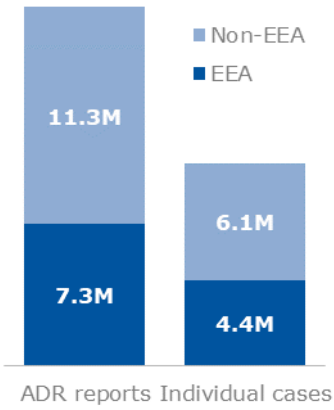


Figure 4. Number of ADR reports versus individual cases received in the EudraVigilance database from its inception in December 2001 until 31 December 2020 split by origin of the report in- or outside the EEA.

The numbers presented below in figures 5 and 6 refer to the ADR reports received in the post-authorisation module (EVPM). A total of 17,231,805 EVPM ADR reports have been processed over the years up to the end of 2020, of which 1,821,211 EVPM ADR reports were processed in 2020. This represents a 9% decrease compared to the numbers recorded in 2019, and it is characterised by a marked drop in EEA (-16%) and non-serious (-14%) reporting. ADR reports are subsequently made available for signal detection and data analysis by the Agency and national competent authorities in the Member States.

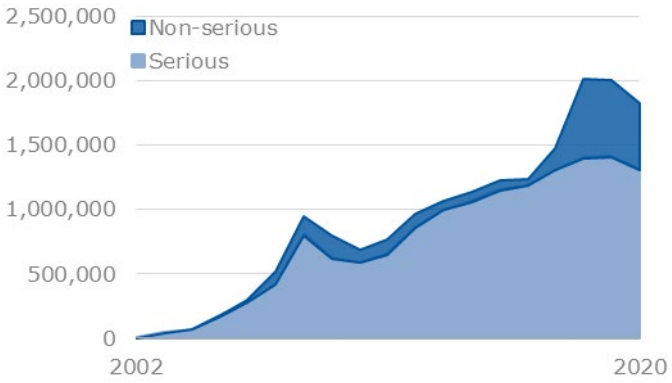


Figure 5. Number of ADR reports processed per year in EVPM.

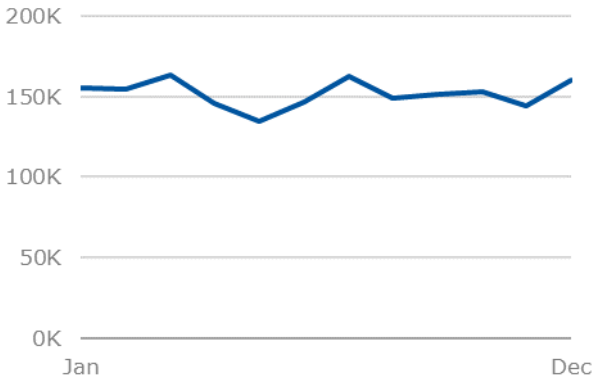


Figure 6. Number of ADR reports processed per month in EVPM in 2020.

Figure 8 presents the total number of ADR reports received in EVPM for 2020 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.

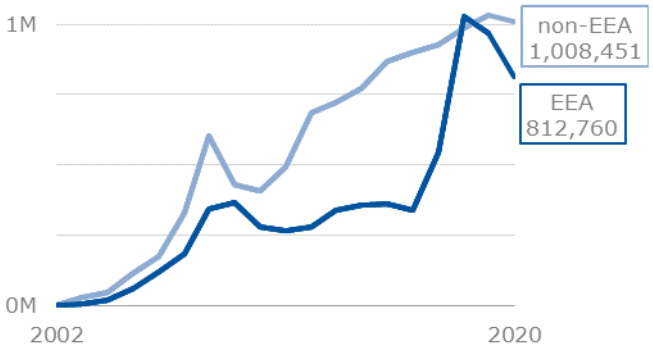


Figure 7. Number of ADR reports processed per year in EVPM split by cases occurred inside and outside the EEA.

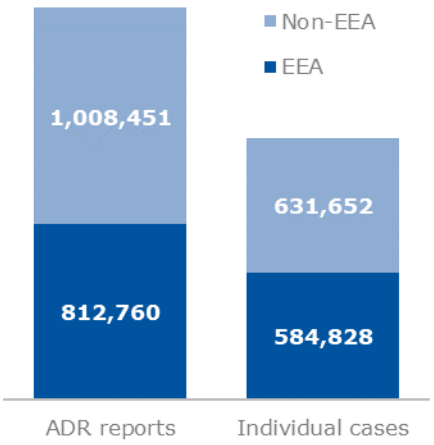


Figure 8. Number of ADR reports versus the number of individual cases in 2020 in EVPM.

In 2020, 143,958 ADR reports were submitted by European patients and consumers through the NCAs and MAHs, referring to 117,167 individual cases. This is a decrease of 10% in such reports compared to the previous year (figure 9), which in line with the overall downward trend. 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.

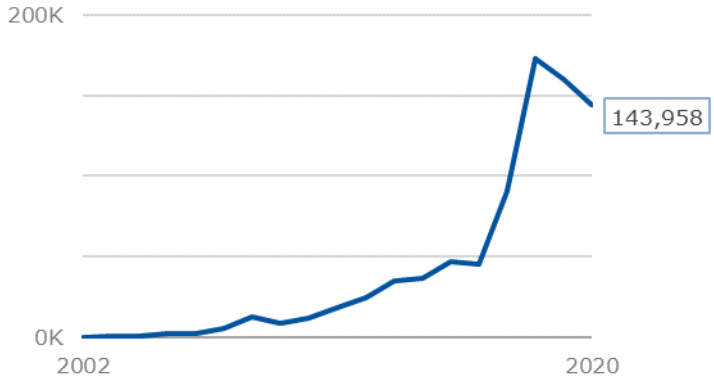


Figure 9. Number of ADR reports by European patients and consumers through the NCAs and MAHs.

E-reporting status for MAHs and sponsors of clinical trials

- 1,119 MAHs (at headquarter level) have sent reports to EVPM during 2020, a 3% increase compared to 2019.
- 573 sponsors of clinical trials (at headquarter level) have sent reports to the EudraVigilance Clinical Trials Module (EVCTM) during 2020, a 1% increase compared to 2019.
- A total of 44,909 individual MAH users are registered in EudraVigilance.

Table 1 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 2020, 251,558 ICSRs were rerouted to NCAs following receipt of the reports from MAHs in EudraVigilance. 1,212,939 ICSRs were forwarded to WHO. A total of 219,652 download requests by MAHs were made, resulting in 8,073,849 ICSRs downloaded from the EudraVigilance database.

Table 1. Number of ADR reports and unique cases transmitted by MAHs and sponsors to EVPM and EVCTM in 2020

EV Module	Transmission type	Count
EVPM	ADR reports	1,568,920
	Individual cases	973,779
EVCTM	ADR reports	106,649
	Individual cases	32,609

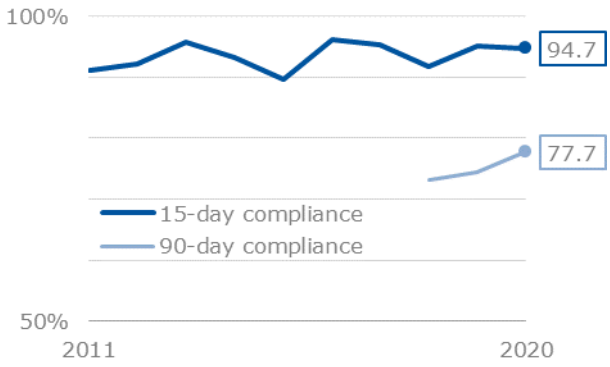


Figure 10. Compliance rate for serious (15-days) and non-serious (90-days) ADR reports to EVPM for all MAHs and sponsors by year. Please note that the scale starts at 50%. Non-serious ADR reports need to be submitted only since November 2017.

E-reporting status for NCAs

- All 32 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 1,107 individual NCA users are registered in EudraVigilance.

Table 2 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 2. Number of ICSRs and unique cases transmitted by NCAs to EVPM and EVCTM during 2020

EV Module	Transmission type	Count
EVPM	ADR reports	252,291
	Individual cases	242,701
EVCTM	ADR reports	7,529
	Individual cases	4,665

Figure 11. 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 2020, the following 10 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)
- Czech Republic (State Institute for Drug Control)
- Denmark (Danish Health and Medicines Authority)
- 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)
- Sweden (Medical Products Agency)
- United Kingdom (Medicines & Healthcare Products Regulatory Agency).

EudraVigilance database and support of signal management process

A total of 26,040 eRMRs were generated in 2020 to facilitate the continuous monitoring of the safety of medicines by the Agency and NCAs in the EEA. Of these,

- 11,436 were routine eRMRs, produced monthly
- 2,724 were 3-monthly eRMRs
- 1,300 were 6-monthly eRMRs
- 10,580 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 2020). Table 3, below and Figures 12 and 13 provides a summary of the data submitted in as of 15 January 2021.

Marketing authorisation holders (MAHs) with medicinal product records referencing 'United Kingdom (GB)' as the 'Authorisation Country Code' had the obligation to review their product data in the Article 57 database and, for products that continue to be authorised by UK with respect to Northern Ireland after 31 December 2020, change the country of authorisation to 'United Kingdom (Northern Ireland)' with the assigned country code 'XI'. MAHs were able to amend their authorised medicinal products to change the country of authorisation to 'United Kingdom (Northern Ireland)' from 15 December 2020. The review and update of records had to be preferably completed before 31 December 2020 and in any case no later than by 31 January 2021.

Table 3. Summary of medicinal product submissions to the XEVMPD

Total number of medicinal product submissions by MAHs by 15 January 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).	904,559
Total number of MAHs (legal entities) established in the EU (corresponding to EudraVigilance codes).	5,660

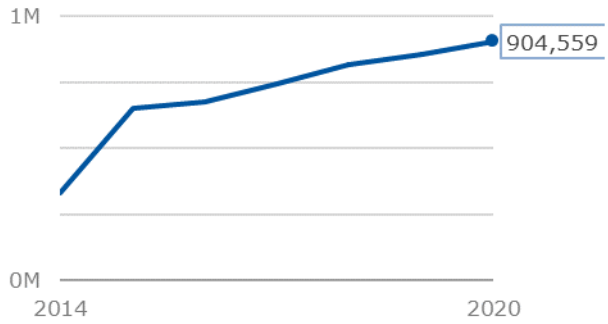


Figure 12. Total number of medicinal products (counted based on EudraVigilance codes) submitted (cumulative by year)

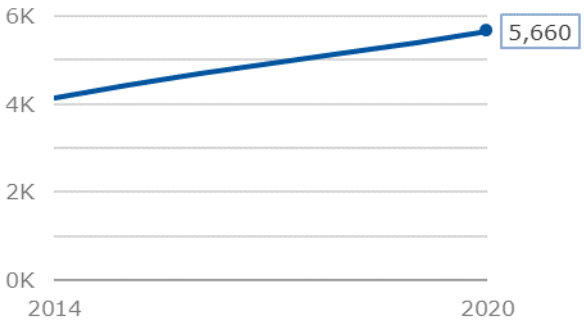


Figure 13. Total number of marketing authorisation holders (legal entities) established in the EU (corresponding to EudraVigilance codes) (cumulative by year)

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

It encompasses the following parameters:

- Name of the medicinal product;
- MAH;
- Authorising 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 4 below refers to the data quality activities performed by the Agency in 2020 and provides 2019 and 2018 data for comparison.

Table 4. Summary of EudraVigilance data quality activities in 2020

Data quality area	Activities performed	2020	2019	2018
Identifying and managing duplicate individual cases	Duplicate couples assessed	160,047	176,736	177,811
	Master reports generated based on duplicated data	85,168	92,480	121,929
Coding of reported medicines and active substances	Reported medicinal products and active substance terms recoded	54,366	101,388	61,202
	ADR reports recoded (ICSRs)	76,990	79,552	56,756
Providing feedback on data quality	Organisations subject to ICSR data quality review	120	123	237
	Medicinal products in XEVMPD quality reviewed (and corrected if necessary)	145,320	136,848	292,367

Annex V – Signal detection

A signal refers to information on one or more observed suspected adverse reactions potentially caused by a medicine and that warrant further investigation. In 2020, the EMA's signal management team reviewed in detail the information on 1,888 potential signals (i.e. drug-event pairs from screening of the EudraVigilance database, medical literature or information received from other regulatory authorities etc.). This represents an approximately 4% increase compared to the previous year, see table 5 for more details.

Table 5. Potential signals reviewed

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

EudraVigilance screening continues to be the major source of EMA's potential signals with 81% of reviewed potential signals in 2020 originating from EV screening (compared to 78% in 2019). Scientific literature screening gave rise to 18% of potential signals in 2020 (20% in 2019). Additionally, cooperation with other regulatory authorities worldwide accounted for 0.4% of potential signals (1% in 2019), namely 3 from PMDA/MHLW, 2 from WHO/UMC and 2 from Health Canada. 0.4% of potential signals originated from other sources.

In response to the COVID-19 pandemic, a specific dashboard was created in EudraVigilance in April 2020. The aim of this tool was to help with the monitoring and detection of safety signals related to COVID-19 therapies. One hundred and nine signals were opened in 2020 in the context of COVID-19 (mostly for medicines used off label to treat and prevent complications related to COVID-19) using this new dashboard among all other sources (EV screening, literature) resulting in 1 signal validated by the Agency and assessed by the PRAC (remdesivir/Veklury and acute kidney injury, ongoing as a signal at the end of 2020).

Table 6. The overview of all potential signals by action taken is shown below

Action taken	Number of potential signals 2020	% of total	Number of potential signals 2019	% of total	Number of potential signals 2018	% of total
Not validated (closed)	1,530	81.0%	1,436	79.5%	1,800	81.7%
Monitored	138	7.3%	115	6.4%	152	6.9%
Ongoing	181	9.6%	205	11.4%	178	8.1%
Prioritised and assessed by PRAC	39	2.1%	50	2.8%	74	3.4%
Total	1,888	100.0%	1,806	100.0%	2,204	100.00%

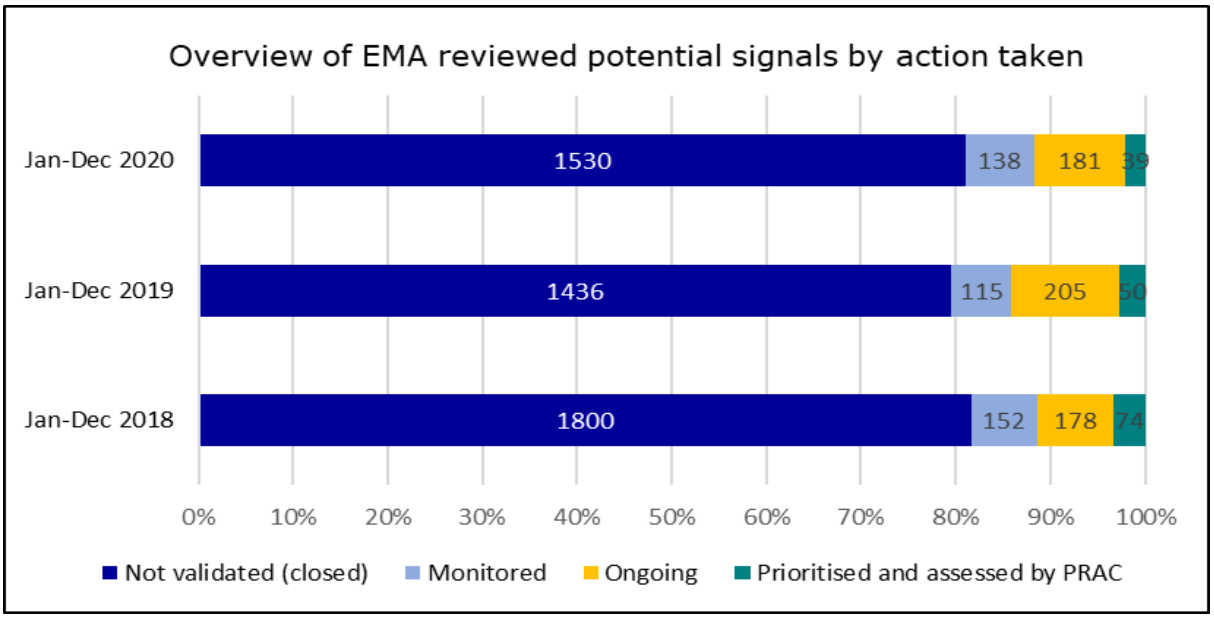


Figure 14. Overview of EMA reviewed potential signals by action taken.

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 2020 was 81, compared with 97 in 2019, representing a 16% decrease. 2020 was below the average number of signals assessed annually between 2014-2020. Of these 81, 39 were validated by the Agency, 42 were validated by the MSs in the course of ongoing safety monitoring through screening of reaction monitoring reports, ADR reports, medical literature and other safety data. No signals were validated by MAHs. Overall 85% of the signals included data from EudraVigilance among their sources (80% in 2019).

Thirty-seven of the assessed signals (46%) 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 two of these cases, the PRAC also recommended Direct Healthcare Professional Communications (DHPCs) to highlight new important safety information to prescribers. One signal led to the update of the RMP to fully characterise and investigate the concern. In 16 signals (20%) continuing with routine safety monitoring of the medicine was considered sufficient. The evaluation of 27 signals (33%) is ongoing in 2021, including 14 via a follow-up signal procedure, 13 in the upcoming PSURs/PSUSAs. One signal resulted in a referral procedure. See figure 15 for more details.

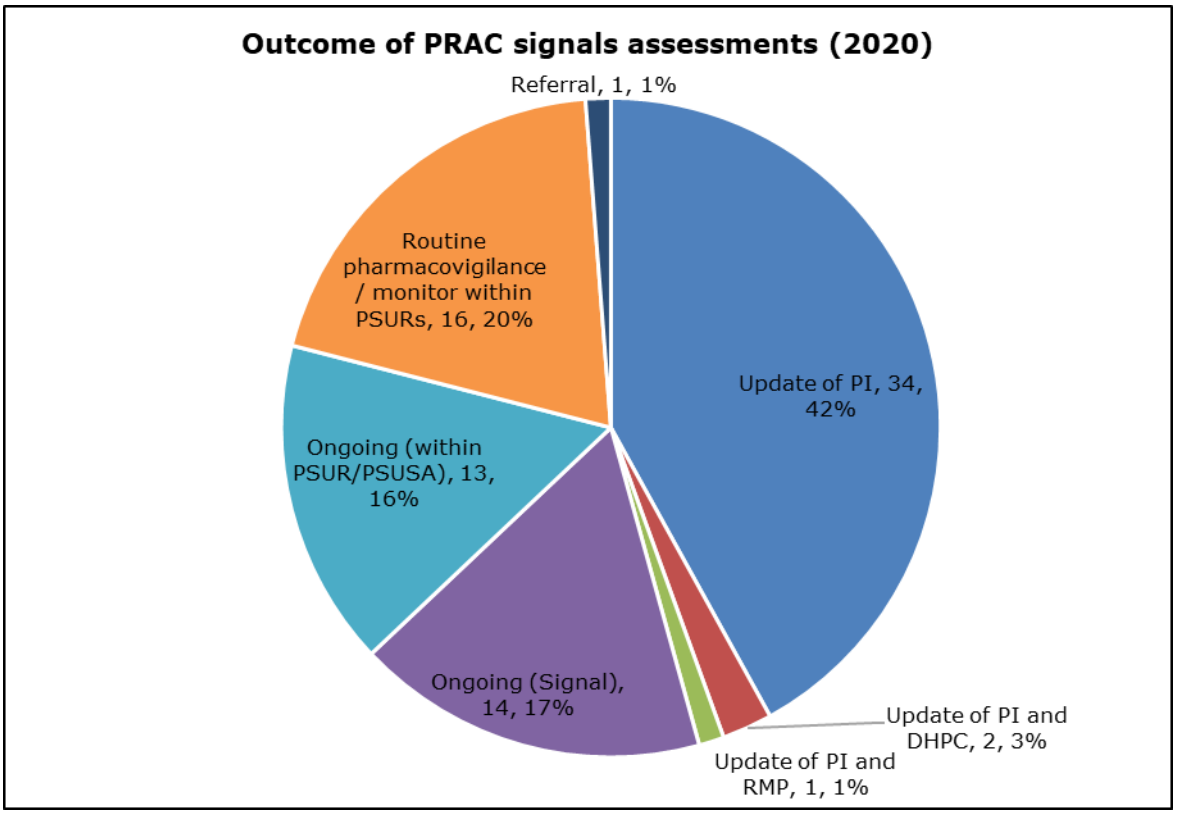


Figure 15. Outcomes of PRAC signal assessments (2020). PI: product information, DHPC: Direct Healthcare Professional Communication, RMP: Risk Management Plan, PSUR: Periodic Safety Update Report, PSUSA: PSUR Single Assessment.

Table 7. A list of all signals prioritised and assessed by the PRAC in 2020 is provided below, noting the latest status or outcome as of 31 December 2020.

Drug	Issue/signal	Status or outcome
Pembrolizumab; nivolumab; atezolizumab; avelumab; durvalumab; cemiplimab; ipilimumab	Immune-mediated cystitis	ongoing (Signal)
Cannabidiol; Tacrolimus	Drug interaction with cannabidiol leading to tacrolimus serum level increased and toxicity	update of PI
Trastuzumab emtansine	Extravasation and epidermal necrosis	ongoing (Signal)
Anakinra; Canakinumab	Drug reaction with eosinophilia and systemic symptoms (DRESS)	ongoing (Signal)
Cefepime	Drug reaction with eosinophilia and systemic symptoms (DRESS)	ongoing (within PSUR/PSUSA)
Ceftriaxone	Encephalopathy	update of PI
Dabrafenib; Trametinib	Sarcoidosis	update of PI

Drug	Issue/signal	Status or outcome
Ibrutinib	Hepatitis E	update of PI and monitor within PSURs
Immune checkpoint inhibitors	Eosinophilic fasciitis	routine pharmacovigilance / monitor within PSURs
Lamotrigine	Photosensitivity	update of PI
Anastrozole	Depressed mood disorders	ongoing (Signal)
Apixaban	Erythema multiforme	ongoing (within PSUR/PSUSA)
Bisoprolol	Angioedema	update of PI
Dabigatran	Gastro-oesophagitis	routine pharmacovigilance / monitor within PSURs
Filgrastim	Immune reconstitution inflammatory syndrome (IRIS)	ongoing (Signal)
Mirtazapine	Drug reaction with eosinophilia and systemic symptoms (DRESS)	update of PI
Azathioprine	Erythema nodosum	ongoing (Signal)
Dupilumab	Corneal disorders	update of PI and RMP
Olaparib	Angioedema	update of PI
Isatuximab	Anaphylactic reaction	ongoing (within PSUR/PSUSA)
Nivolumab	Lichen sclerosus	ongoing (within PSUR/PSUSA)
Andexanet alfa	Erroneous assay results for levels of anti-factor Xa activity with use of andexanet alfa	update of PI and DHPC
Baricitinib	Diverticulitis	update of PI
3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins): atorvastatin; fluvastatin; lovastatin; pitavastatin; pravastatin; rosuvastatin; simvastatin	Bullous pemphigoid	ongoing (Signal)
Methotrexate	Progressive multifocal leukoencephalopathy	ongoing (Signal)
Adalimumab	Autoimmune encephalitis	routine pharmacovigilance /

Drug	Issue/signal	Status or outcome
		monitor within PSURs
Abiraterone	Interaction with sulphonylureas leading to hypoglycaemia	update of PI
5 alfa-reductase inhibitors (5ARIs): finasteride; dutasteride	Risk of type 2 diabetes mellitus	ongoing (within PSUR/PSUSA)
Adalimumab	Pericarditis	routine pharmacovigilance / monitor within PSURs
Buprenorphine; buprenorphine, naloxone; Selective serotonin reuptake inhibitors (SSRIs); Serotonin norepinephrine reuptake inhibitors (SNRIs); Tricyclic antidepressants (TCAs); Monoamine oxidase inhibitors (MAOIs); Other psychiatric medicines; Serotonin receptor agonists; Antiemetics; Other serotonergic drugs	Drug-drug interaction with serotonergic drugs leading to serotonin syndrome	update of PI
Pembrolizumab	Systemic scleroderma	ongoing (Signal)
Anastrozole	Hallucinations	routine pharmacovigilance / monitor within PSURs
Dabrafenib Trametinib	Disseminated Intravascular Coagulation (DIC)	routine pharmacovigilance / monitor within PSURs
Golimumab	Inflammatory myopathy	update of PI
Palbociclib	Cutaneous lupus erythematosus	ongoing (within PSUR/PSUSA)
Tofacitinib	Psychiatric disorders	ongoing (within PSUR/PSUSA)
Tramadol	Hiccups	ongoing (within PSUR/PSUSA)
Prasugrel	Severe cutaneous adverse reactions	routine pharmacovigilance / monitor within PSURs
Sevoflurane	Diabetes insipidus	ongoing (within PSUR/PSUSA)
Azithromycin	Increased cancer risk among patients with bronchiolitis obliterans after hematopoietic cell transplantation, treated with	ongoing (within PSUR/PSUSA)

Drug	Issue/signal	Status or outcome
	azithromycin	
Lorlatinib	Nephrotic syndrome	ongoing (within PSUR/PSUSA)
Sacubitril/valsartan	Ventricular arrhythmia	routine pharmacovigilance / monitor within PSURs
Dipeptidyl peptidase-4 (DPP-4) inhibitors: alogliptin; linagliptin; saxagliptin; sitagliptin; vildagliptin	Rhabdomyolysis	routine pharmacovigilance / monitor within PSURs
Bevacizumab	Guillain-Barré syndrome (GBS)	routine pharmacovigilance / monitor within PSURs
Ifosfamide (solution for infusion)	Increased risk of encephalopathy	referral
Ceftriaxone	Hepatitis	ongoing (Signal)
Nivolumab	Haemophagocytic lymphohistiocytosis	update of PI
Immune checkpoint inhibitors: atezolizumab; avelumab; cemiplimab; durvalumab; ipilimumab; nivolumab; pembrolizumab	Tuberculosis	update of PI
Vismodegib	Pancreatitis	routine pharmacovigilance / monitor within PSURs
Mycophenolate mofetil; Mycophenolic acid; Myfortic	Posterior reversible encephalopathy syndrome	routine pharmacovigilance / monitor within PSURs
Ibuprofen; Ketoprofen and fixed-dose combinations	Serious exacerbation of infections	update of PI
Idelalisib	DRESS (Drug reaction with eosinophilia and systemic symptoms)	update of PI
Insulins: human insulin; insulin isophane; insulin degludec; insulin degludec/liraglutide; insulin glargine; insulin aspart; insulin lispro; insulin detemir; insulin glulisine; insulin bovine; insulin porcine	Cutaneous amyloidosis	update of PI
Paroxetine	Microscopic colitis	update of PI
Thiazide and thiazide-like diuretics and	Choroidal effusion	update of PI

Drug	Issue/signal	Status or outcome
combinations		
Adalimumab	Abnormal weight gain	ongoing (Signal)
Hormone replacement therapy (HRT)	New information on the known risk of breast cancer	update of PI
Cladribine	Seizure	ongoing (within PSUR/PSUSA)
Mirtazapine	Amnesia	update of PI
Sertraline	Risk of microscopic colitis	update of PI
Lisdexamfetamine (LDX)	Risk for QT prolongation and cardiac arrhythmia	update of PI
Lopinavir; Ritonavir	Adrenal dysfunction in infants	routine pharmacovigilance / monitor within PSURs
Prednisolone; Prednisone	Risk of bradycardia	ongoing (Signal)
Desogestrel	Suppressed lactation	update of PI
Macrogol 3350- 4000 with and without electrolytes	Colitis ischaemic	update of PI
Capecitabine	Anaphylactic reaction	update of PI
Tumour necrosis factor (TNF) inhibitors: adalimumab; certolizumab pegol; etanercept; golimumab; infliximab	Kaposi´s sarcoma	update of PI
Sacubitril Valsartan	Psychosis and psychotic disorders	ongoing (within PSUR/PSUSA)
Abiraterone	Anaphylactic reaction	update of PI
Chloroquine; hydroxychloroquine	Psychiatric disorders	update of PI
Fluoroquinolones: Ciprofloxacin; Levofloxacin; Lomefloxacin; Moxifloxacin; Norfloxacin; Ofloxacin; Pefloxacin; Prulifloxacin; Rufloxacin, Delafloxacin , Levofloxacin	Heart valve regurgitation, cervical artery dissection, and aortic aneurysm and dissection	update of PI and DHPC and monitor within PSURs
Interferon alfa-2a; Interferon alfa-2b; peginterferon alfa-2a; peginterferon alfa-2b	Neuromyelitis optica spectrum disorder	update of PI
Paclitaxel	Progressive multifocal leukoencephalopathy	routine pharmacovigilance / monitor within PSURs
Remdesivir	Acute kidney injury	ongoing (Signal)

Drug	Issue/signal	Status or outcome
Pomalidomide	Progressive multifocal leukoencephalopathy	update of PI and monitor within PSURs
Efavirenz	Microcephaly	ongoing (Signal)
Vedolizumab	Evans syndrome, autoimmune haemolytic anaemia, immune thrombocytopenic purpura	routine pharmacovigilance / monitor within PSURs
Paroxetine; sertraline; fluoxetine; escitalopram; citalopram; amitriptyline; venlafaxine; trazodone; bupropion; mirtazapine; duloxetine; vortioxetine (antidepressants)	Post-partum haemorrhage	update of PI and monitor within PSURs
Pembrolizumab	Sjögren's Syndrome	update of PI
Pembrolizumab	Vasculitis	update of PI
Teriparatide	Myeloma	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 2020 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 in the context of the current pandemic. This includes consideration of more expedited timelines to confirm signals raised in the context of COVID-19, input to the list of potential COVID-19 therapeutics or to the vaccines monitoring preparedness plan, identification of contact points within the national competent authorities to collect data on vaccines exposure, among others.

The group has also continued to oversee the monitoring of EudraVigilance (EV) by MAHs during the current pilot phase, which was extended until the end of 2021.

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

- Identification of adverse pregnancy outcomes in EudraVigilance: the existing algorithm designed to improve adverse pregnancy outcome in EV was fine-tuned by adjusting for indications. The results showed a better performance of the algorithm in terms of both sensitivity and specificity. The algorithm will be made available in EVDAS and shared with the network to facilitate data retrieval
- Estimation of the impact of mandatory reporting of non-serious reports in EudraVigilance introduced by the updated European Union pharmacovigilance legislation: since introduction of the legislation the proportion of non-serious spontaneous reports occurring in EEA in EudraVigilance has risen from 22.6% to slightly more than 60%. Applying the routine signal detection algorithms to both serious and non-serious reports, as opposed to only serious reports, resulted in a small overall increase in signals of disproportionate reporting. The sensitivity of the signal detection system was slightly increased and the proportion of signals that correspond to known adverse drug reactions (a measure of efficiency) was unchanged. This result was also confirmed by numerous sensitivity analyses.
- Approaches to enhance safety monitoring during mass COVID-19 vaccination campaign:
  - Adverse Events of Special Interest (AESI): the ACCESS project ('vACcine Covid-19 monitoring readinESS'), has defined the AESI. Work has been done to map them to MedDRA PTs and to identify vaccine targeted medical events for intensive monitoring in EV
  - Tools have been amended or created to enhance the monitoring and the screening for adverse drug reaction: examples include system to assess and track causality at case level for each AESIs submitted to EV; a dedicated eRMR for vaccine as well as a dedicated EVDAS queries and dashboards
  - Additional methods tailored to vaccine safety monitoring have been identified and are being tested retrospectively on a historical vaccination data (H1N1). The methods selected are the imbalance analysis between competing vaccines, the time to onset and the observed to

expected analysis. The current disproportionality method (reporting odds ratio) is used as a benchmark. The aim of the test is to investigate complementarities and gain provisional experience.

Annex VII - Requests for information and documents

In 2020, 28 EV data requests were responded to, a similar number compared to two previous years (32 in 2019 and 28 in 2018, respectively) but a lower compared to 2017 (63 requests).
The declining number of queries is due to the information proactively provided at the www.adrreports.eu portal, which satisfies the majority of general public queries, together with the access provided to Marketing Authorisation Holders (MAHs). Since 2017, the portal contains details of the individual case reports redacted in line with the EV access policy in addition to a range of data displayed in the aggregated reports. Hence in the statistics above in addition to the EU regulatory network requests only those external requests are counted which could not be satisfied with the publicly/MAH- accessible data and a tailored EV search had to be performed. This includes for instance disproportionality reports, queries from academia (6), request from non-EU regulatory agencies (4), or detailed queries from patients. Of note: a significant number of questions from the public received via the askEMA channel were also answered by referring to www.adrreports.eu.

Requests for information (RFI) and requests for access to documents (ATD) accounted for 64% and 32% of all queries, respectively, while one request referred to both. Requests related to nationally authorised products (NAPs) alone accounted for 50% of the total, whilst 36% of requests were related to centrally authorised products (CAPs), the rest of queries were for both types of products. Half of the requests were received from the EU regulatory network. The highest number of external requests, as in previous years, were received from the US and Germany. The median response time was 16 working days.

An overview is provided below in figures 18 and 19 by type of request, authorization procedure of concerned product(s), requester type, and query origin.

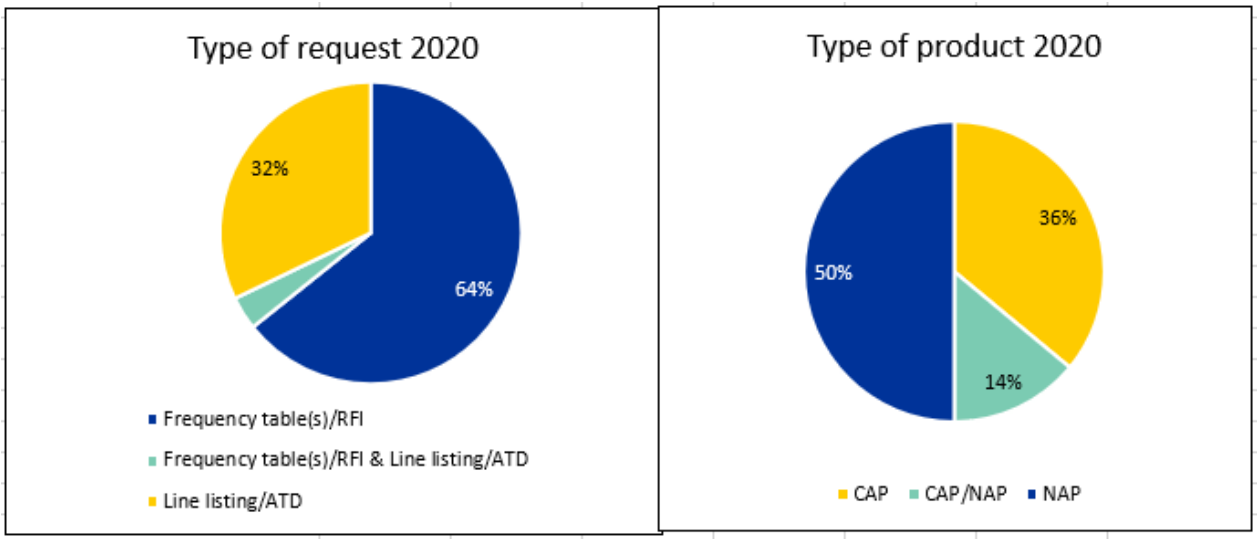
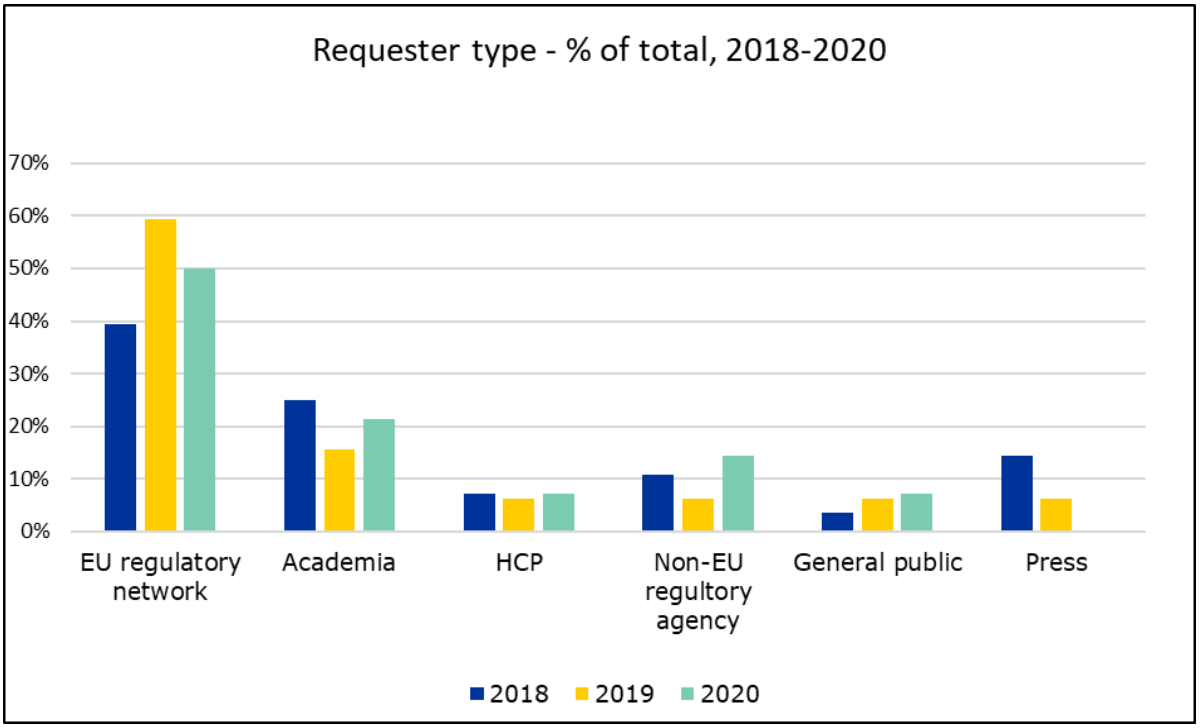


Figure 18. Overview of requests for EV data by type of request (left) and product type (right).



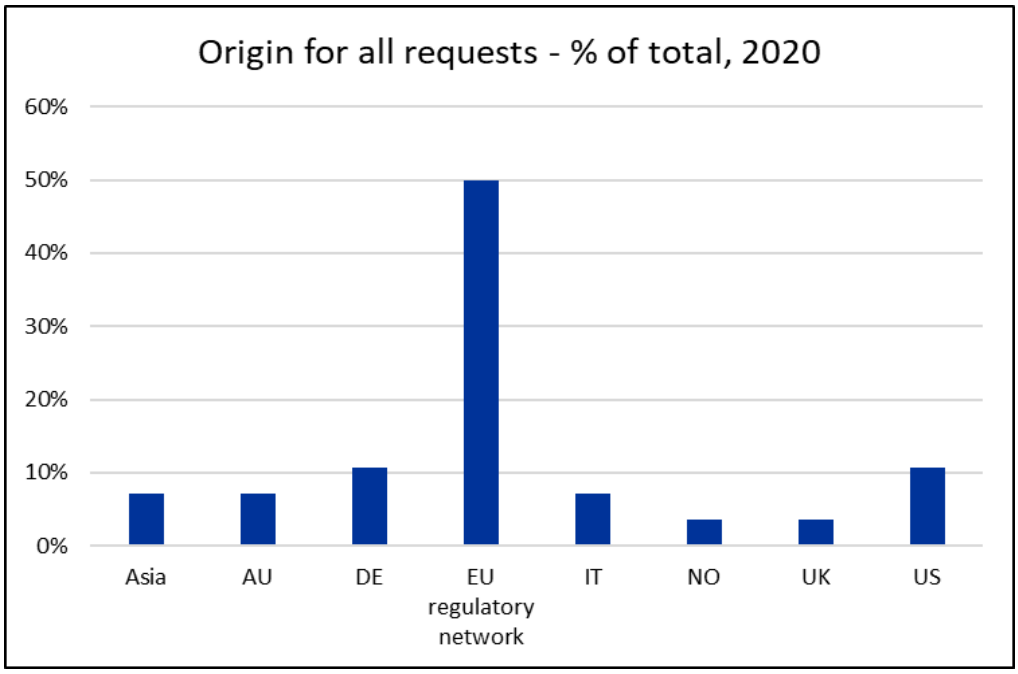


Figure 19. Overview of requests for EV data by requester type (top) and country or region of origin for all requests (bottom), countries/region shown for external requests.

Table 8. Overview of requests responded to in 2020

Type of requester	Substance/ product	Issue	Type of request
Academia	Glucagon-like peptide-1 (GLP-1) analogues	Proportional reporting ratio (PRR) of specific events	Frequency table(s)/RFI
EU regulatory network	Ifosfamide	Encephalopathy - overview of case reports	Frequency table(s)/RFI
EU regulatory network	Tumour necrosis factor alpha (TNF-alpha) inhibitors	Kaposi's sarcoma - overview of case reports	Frequency table(s)/RFI & Line listing/ATD
General public	Gardasil/Gardasil9	Immune thrombocytopenic purpura	Frequency table(s)/RFI
General public	Fluoroquinolones	Tendon injury	Frequency table(s)/RFI
EU regulatory network	Fluoroquinolones	Heart valve regurgitation	Frequency table(s)/RFI
Non-EU regulatory agency	Olanzapine	Delirium sedation syndrome (reports from an EEA country)	Line listing/ATD
Academia	Selected stimulants, e.gg amphetamine, atomoxetine, guanfacine, methylphenidate	Suspected drug abuse	Line listing/ATD
EU regulatory network	Methoxyflurane	Paediatric cases	Frequency table(s)/RFI
Academia	Clozapine	Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome)	Line listing/ATD
EU regulatory network	Tuberculosis products	Overview of case reports for Baltic countries	Frequency table(s)/RFI
EU regulatory network	Nifuroxazide	Possible genotoxicity and carcinogenicity - overview of case reports	Frequency table(s)/RFI

Type of requester	Substance/ product	Issue	Type of request
Academia	Antipsychotic medications	Lactation disorders	Line listing/ATD
EU regulatory network	Ifosfamide	Support of referral: encephalopathy	Frequency table(s)/RFI
EU regulatory network	Ibuprofen	Use in COVID-19	Frequency table(s)/RFI
EU regulatory network	Chloroquine	Chloroquine poisoning in COVID-19	Frequency table(s)/RFI
Non-EU regulatory agency	Hydroxychloroquine	Fatal outcome in COVID-19 (3 EEA reports)	Line listing/ATD
Non-EU regulatory agency	Zostavax vaccine	Disseminated disease (in immunosuppressed patients)	Frequency table(s)/RFI
EU regulatory network	Chloroquine (CQ), hydroxychloroquine (HCQ) and azithromycin (AZT)	Data for the use of CQ/HCQ +/- AZT in COVID-19	Frequency table(s)/RFI
Non-EU regulatory agency	Chloroquine	Methemoglobinaemia in COVID-19	Line listing/ATD
Academia	Tramadol, pentazocine, codeine, oxycodone	Abuse/misuse/dependence	Line listing/ATD
HCP	Vaccines (various)	Parsonage-Turner Syndrome	Frequency table(s)/RFI
HCP	Echinacea	Possible autoimmune reactions	Frequency table(s)/RFI
EU regulatory network	Ulipristal (Esmya) - follow up	Update on severe liver injury leading to liver transplantation	Line listing/ATD

Type of requester	Substance/ product	Issue	Type of request
Academia	Sitagliptin and glimepiride	Proportional reporting ratio (PRR) of specific events	Frequency table(s)/RFI
EU regulatory network	Glucagon-like peptide-1 (GLP-1) analogues	Delayed gastric emptying	Frequency table(s)/RFI
EU regulatory network	Icatibant (Firazyr)	Medication errors related to strength	Line listing/ATD
EU regulatory network	Pravastatin/fenofibrate (Pravafenix)	Gynaecomastia	Frequency table(s)/RFI