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2019 Annual Report on EudraVigilance for the European Parliament, the Council and the Commission

Reporting period: 1 January to 31 December 2019

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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)
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
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labor and Welfare (Japan)
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 the monitoring of 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 reviews 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.

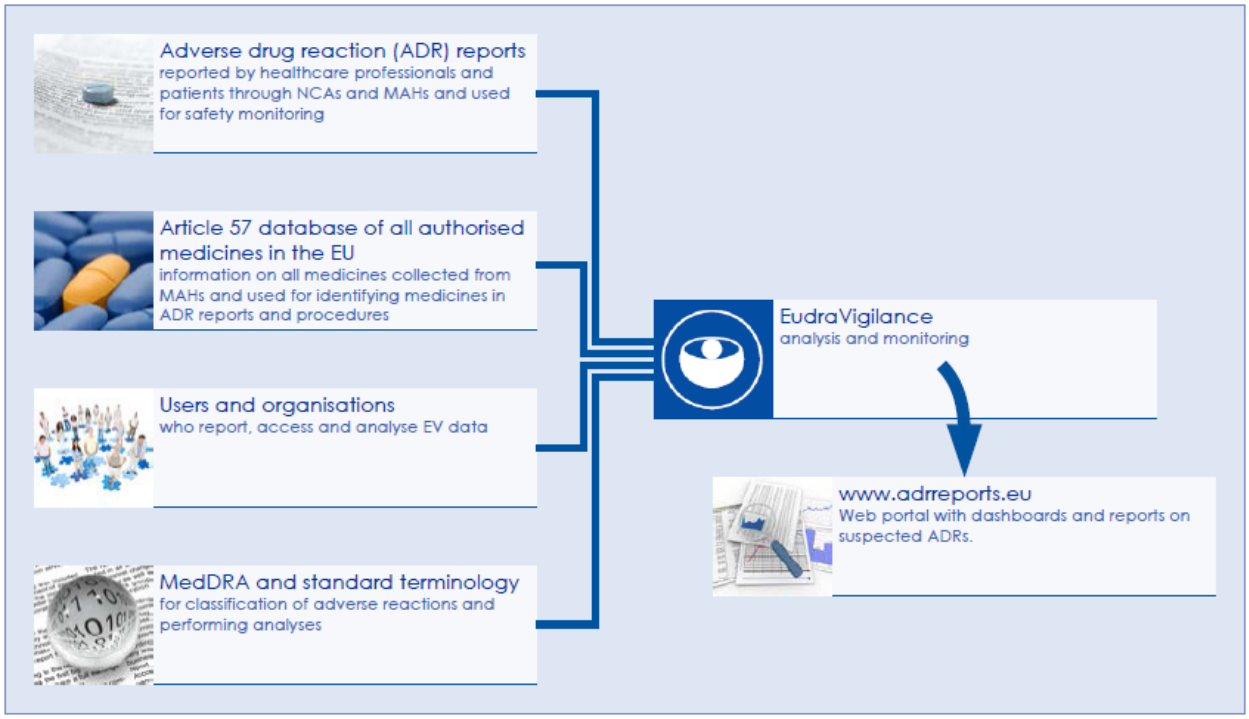

Figure 1. EudraVigilance users, data sources and data use.

The database currently holds **over 16.7 million individual case safety reports** (ICSRs) referring to over 9.4 million cases and is one of the largest pharmacovigilance databases in the world. It has undergone significant development in recent years. 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 2019, 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.
- ***Collecting and processing of adverse drug reaction reports***. In 2019, just over 2 million reports related to suspected adverse reactions occurring in the post-authorisation phase were collected and managed in EudraVigilance (2,002,814 – a similar number to the previous year). Some 48% of these originated from the EEA (968,738). The number of reports submitted directly by European patients and consumers through the NCAs and MAHs (159,860) decreased slightly in 2019 (-7% compared to 2018). 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 2019, this database (the so-called "Article 57 database") contained information on more than 850,000 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 2019, 176,000 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 123 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 2019, a total of 24,464 electronic reaction monitoring reports (eRMRs) were generated for the EU network.
- ***Screening for, and review of, potential signals***. In 2019, the EMA's signal management team reviewed in detail 1,806 potential signals[1] for centrally authorised products (CAPs) from screening of the EudraVigilance database (78%), medical literature (20%) 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 1,882 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 2019, the PRAC prioritised and assessed 97 confirmed signals (in line with the average number of signals assessed annually between 2013-2018). Out of these, 50 were validated by the Agency, 46 were validated by the MS and 1 by the MAH; 27 were for NAPs, 56 for CAPs and 14 for both NAPs and CAPs. 80% of all 97 signals included data from EudraVigilance. Thirty-five of the assessed signals (36%) 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 four of these cases, the PRAC also recommended a Direct Healthcare Professional Communication (DHPC) to highlight new important safety information to prescribers. Three signals led to the update of the risk management plan (RMP) to fully characterise and investigate the concern. In 28 cases (29%) continuing with routine safety monitoring of the medicine was considered sufficient. The evaluation of 34 signals (35%) was ongoing at the end of 2019, including 26 via a follow-up signal procedure and 8 in an upcoming PSUR/PSUSA.
- ***Access for MAHs for the monitoring of EudraVigilance data.*** Since the launch of the new EudraVigilance functionalities in November 2017, MAHs have access to ICSRs 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. As of June 2019, the Network had received 31 standalone signal notifications from

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

MAHs. Of these, 8 signals were considered valid and processed accordingly, ultimately leading to one signal being confirmed for evaluation by the PRAC. All other MAHs also have access to ICSRs 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.

- ***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 2019 reporting period, nearly a million (989,167) 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 2019, the website provided information on a total of 3,724 active substances, of which 753 contained in CAPs and 2,971 in NAPs.
- ***Training and support activities***. Extensive training offerings are available face-to-face or online as e-learning[2] 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 during 2019 due to Brexit and Business Continuity plan (BCP).

2. Operation of EudraVigilance including its further development

EudraVigilance is maintained by EMA on behalf of the EU medicines regulatory network. As noted in previous reports, an improved EudraVigilance (human) system was launched on 22 November 2017, which allowed for enhanced signal detection and data analysis, and the benefits of this have continued in 2019. The key improvements are detailed in table 1 below.

New feature	Benefit
Enhanced signal-detection and data-analysis tools to support safety monitoring directly by NCAs and MAHs.	Better detection of new or changing safety issues, enabling rapid action to protect public health.
Improved quality and completeness of ICSR data.	Better searchability and more efficient data analysis.
Enhanced scalability of the EudraVigilance system.	Ability to support a large increase of ICSRs including the new requirement to submit non-serious cases to EudraVigilance.
Simplified reporting of ICSRs to EudraVigilance and the rerouting of ICSRs to Member States.	Reduced duplication of efforts. MAHs need only to submit ICSRs to EudraVigilance and no longer need to provide them separately to NCAs.
Direct provision of data to the World Health	Enhanced collaboration between EMA and WHO

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

New feature	Benefit
Organization (WHO) Uppsala Monitoring Centre from EudraVigilance.	without the need for NCAs to separately submit ICSRs to WHO UMC.

Figure 2. Summary of new features and benefits of the new EudraVigilance system

EudraVigilance is the central pillar for pharmacovigilance activities in the EEA: by allowing effective monitoring of suspected adverse reactions and detection of risks related to medicines safety, it is a major contributor to the protection and promotion of public health. Furthermore, EudraVigilance facilitates the safety reporting of suspected unexpected serious adverse reactions (SUSARs) to investigational medicinal products occurring during clinical trials.

A 4-year EudraVigilance Operational Plan was prepared in June 2017 at the request of the PRAC, which oversees the operation of EudraVigilance. The operational plan describes key activities and developments that impact on or relate to EudraVigilance and its stakeholders over a period of four years. An update of the plan covering the period 2020 to 2022 is currently ongoing and expected for publication by Q2 2020.

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.

This is a major step towards strengthening data quality and analytical capabilities in EudraVigilance based on the use of the internationally agreed format and standard terminology.

EMA will continue to support stakeholders in this important initiative to ensure their readiness by providing hands-on and online training as well as webinars as a platform to address technical and operational questions and by updating the EU ICSR Implementation Guide.

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 2020 is 855,564 (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 over 99.8% of medicinal products. 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[3] 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 2019, 2,002,814 ICSRs were collected and managed in EudraVigilance, 968,738 of which originate from the EEA. This is in line with the numbers recorded the previous year (-0.7% overall compared to 2018), with a slight decrease in EEA reporting (-6%) and a small increase in non-EEA reporting (+5%).

The number of reports submitted directly by patients and consumers through the NCAs and MAHs (159,860) slightly decreased (-7%) in 2019 compared to the previous year.

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[4] (see Annex II).

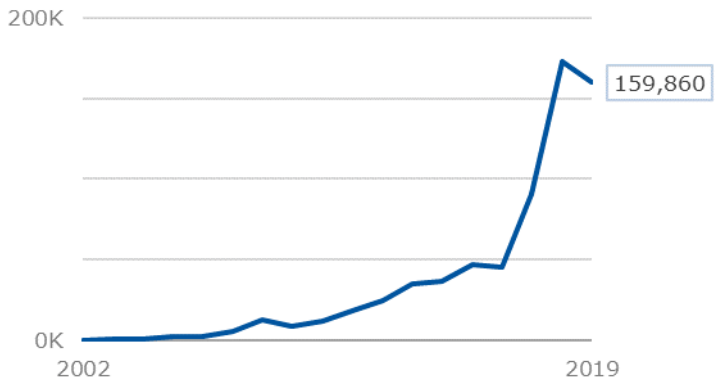

Figure 2. Trend of ADR reports from patients and consumers received in the EEA by NCAs and MAHs and reported to EudraVigilance.

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

[3] 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.
[4] 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

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 2019, a total of 24,464 eRMRs were generated for NCA and EMA staff. 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 1,806 potential signals which were reviewed by the Agency in 2019, approximately 78% originated from EudraVigilance, highlighting its central role for ADR data monitoring.

For active substances of NAPs, the monitoring of ADR reports is shared between the NCAs in line with the 'List of substances and products subject to worksharing for signal management'[5], which indicates a Lead Member State (LMS) for each included active substance. The list was updated in 2019 following the reallocation of 108 active substances previously monitored by the UK as well as the appointment of an LMS for 219 previously unallocated substances and it currently includes 1,882 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[6] have to monitor them in EudraVigilance and inform EMA and NCAs of validated signals with their medicines. 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. Thirty-one standalone signal notifications from MAHs were received as of June 2019. Eight signals out of these 31 were considered valid and processed accordingly, ultimately leading to one signal being confirmed for evaluation by the PRAC. After considering the experience gained through the first year of the pilot, EMA and the European Commission have agreed to further prolong the exercise until end of 2021 with a view to generate more robust data. This means that until then, only MAHs with an active substance on the pilot list will have to continue performing signal detection in EV. All other MAHs also have access to EV data and can integrate the data into their own signal management processes. However, during the pilot period they will have no obligation to continuously monitor EV and/or inform the regulatory authorities of validated signals from EV.

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 2019, the PRAC prioritised and assessed 97 confirmed signals (a 15% decrease compared to 2018 and compared with 82 in 2017, representing a 18% increase); 80% included data from EudraVigilance. Thirty-five of the assessed signals (36%) 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 four of these cases, the PRAC also recommended Direct Healthcare Professional

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

Communications (DHPCs) to highlight new important safety information to HCPs. Three signals led to the update of the RMP to fully characterise and investigate the concern. In 28 cases (29%) continuing with routine safety monitoring of the medicine was considered sufficient. The evaluation of 34 signals (35%) is ongoing in 2020, including 26 via a follow-up signal procedure and 8 in the upcoming PSUR/PSUSA.

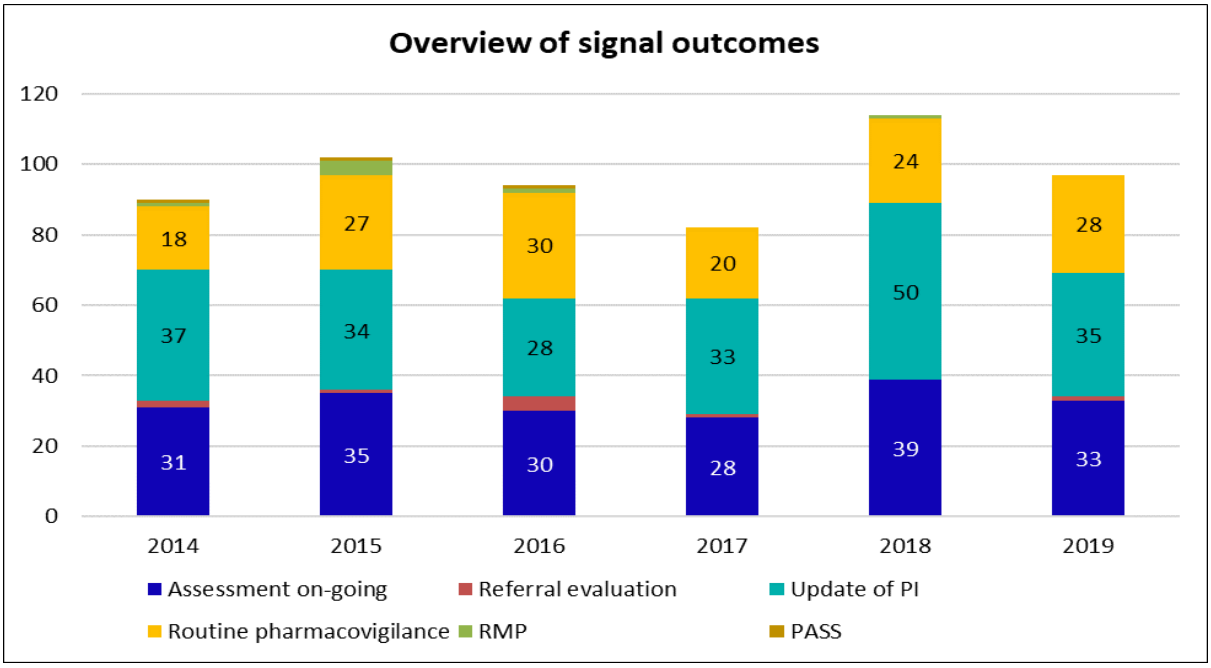

Figure 3. Overview of signals assessed by the PRAC.

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 2019 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 report forms. By the end of 2019, the website provided information on a total of 3,724 active substances, including 753 contained in 1,167 CAPs and 2,971 in NAPs. There were over 1.7 million visits to the website in 2019.

At EU level EMA keeps MAHs informed on EudraVigilance developments via its website. In addition, a newsletter 'What's new in Pharmacovigilance - QPPV update' was published on the Agency's website[8] to provide EU QPPVs with information on recent developments in EU pharmacovigilance activities including relevant projects.

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, 32 requests were answered within a median of 12 working days. Approx. 60% 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 22 training sessions on EudraVigilance ICSR submissions, with 276 participants,
- 7 training sessions on the XEVMPD, with 59 participants,
- 175 XEVMPD users followed training via the dedicated e-learning platform.

Some training and support activities organised by the EMA were suspended during 2019 due to Brexit and BCP. No courses took place at the EMA premises. No EudraVigilance and Signal Management information days were organised in 2019.

6. Conclusion

ADR reporting to EudraVigilance continues at high levels since the release of the enhanced version of EudraVigilance in November 2017. More than 2 million ADR reports were received in 2019, of which almost 1 million originated from the EEA, and based on these reports, over 24,464 statistical outputs were produced and screened for the identification of signals which are subsequently assessed by the PRAC.

EudraVigilance currently contains over 16.7 million ADR reports. It is being used by EMA, EU NCAs and MAHs, and plays a role in global surveillance, with nearly 1 million reports forwarded to the WHO database in 2019.

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. 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 2019.
Data quality review and duplicate management of adverse reaction reports in EudraVigilance. [*Legal basis:* Regulation (EC) 726/2004, Article 24(3)]	Continued during 2019.
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 2019.
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 2019.
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 2019.
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 2019.
Operation of the Medical Literature Monitoring service [*Legal basis:* Regulation (EC) 726/2004, Article 27]	Continued during 2019.

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[7], exceeding the required 98% availability.

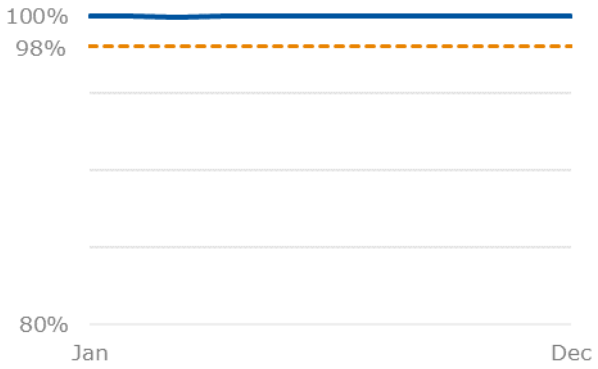

Figure 4. EudraVigilance gateway availability per month. The requirement is 98%. Please note that the scale starts at 80%. Planned downtime is excluded.

EudraVigilance database

For medicinal products authorised in the EEA, ADR reports are collected from both within and outside the EEA. By 31 December 2019, the EudraVigilance database held a total of 16,719,909 ADR reports (or ICSRs), referring to 9,470,288 individual cases (figure 4). The post-authorisation module (EVPM) contained 15,410,623 ADR reports (9,092,117 cases) and the clinical trial module (EVCTM) 1,309,286 reports (378,171 cases).

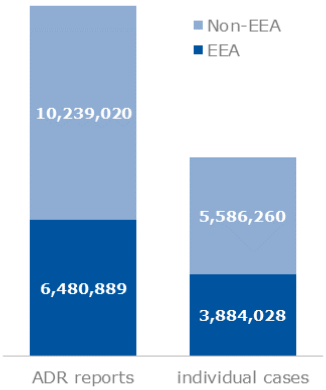

Figure 5. Number of ADR reports versus individual cases received in the EudraVigilance database from its inception in December 2001 until 31 December 2019 split by origin of the report in- or outside the EEA.

[7] Only unplanned downtime is taken into consideration

The numbers presented below refer to the ADR reports received in the post-authorisation module (EVPM). A total of 15,410,623 EVPM ADR reports have been processed over the 18 years up to the end of 2019. A total of 2,002,814 EVPM ADR reports were processed in 2019. This is similar to the numbers recorded in the previous year (-0.7% compared to 2018) following the transfer to the new EV system in November 2017 which made it mandatory to submit non-serious ADR reports from within the EEA. ADR reports are subsequently made available for signal detection and data analysis by the Agency and national competent authorities in the Member States.

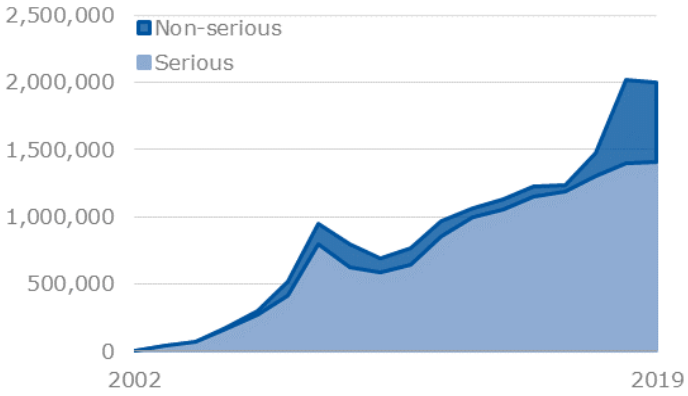

Figure 6. Number of ADR reports processed per year in EVPM.

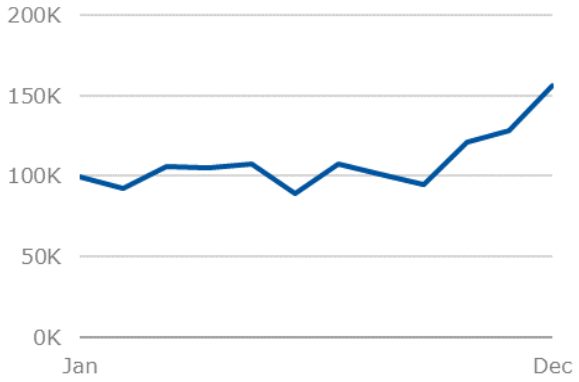

Figure 7. Number of ADR reports processed per month in EVPM in 2019.

Figure 8 presents the total number of ADR reports received in EVPM for 2019 compared to the number of cases they are referring to. Each individual case in EudraVigilance refers to a single patient; an individual case is composed of at least one report, called the initial report, which might be complemented by follow-up reports with updated additional information on the case. These reports, both initial and follow-up, are known as ADR reports or individual case safety reports (ICSRs).

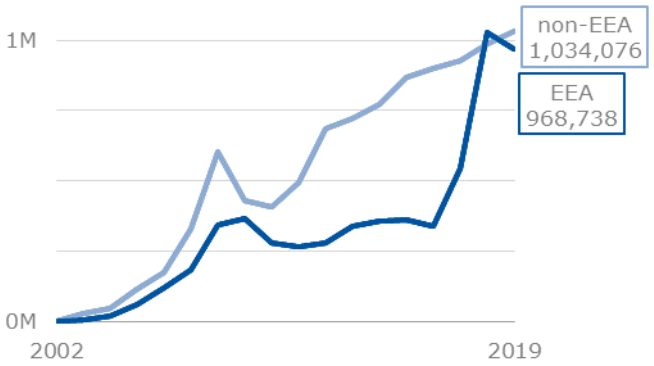

Figure 8. Number of ADR reports processed per year in EVPM split by cases occurred inside and outside the EEA.

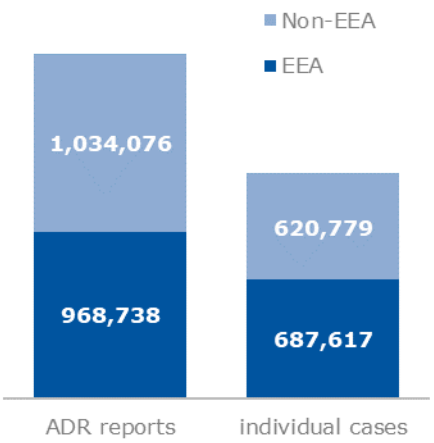

Figure 9. Number of ADR reports versus the number of individual cases in 2019 in EVPM.

In 2019, 159,860 ADR reports were submitted by European patients and consumers through the NCAs and MAHs, referring to 122,073 individual cases. This is a decrease of 7% in such reports compared to

the previous year (figure 9). Again, the mandatory reporting of non-serious cases to EudraVigilance since November 2017 is a key driver of the increased patient reporting in 2018 and 2019.

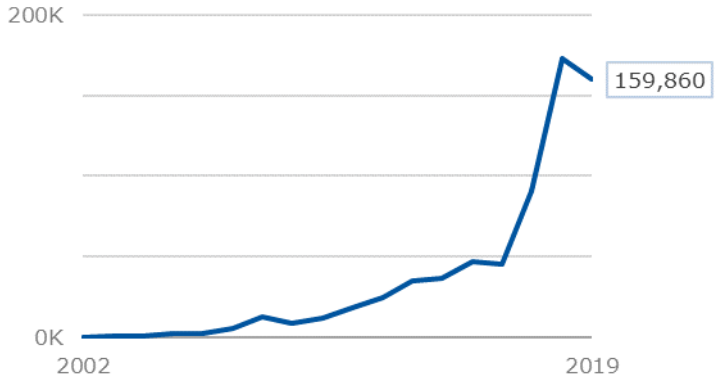

Figure 10. Number of ADR reports by European patients and consumers through the NCAs and MAHs.

E-reporting status for MAHs and sponsors of clinical trials

- A total of 1,564 MAHs (at headquarter level) have sent reports to EVPM in the period between 1 January 2002 and 31 December 2018, an approx. 10% increase compared to 2018.
- A total of 1,145 sponsors of clinical trials (at headquarter level) have sent reports to the EudraVigilance Clinical Trials Module (EVCTM) in the period between 1 May 2004 and 31 December 2019, an approx. 8% increase compared to 2018.
- A total of 18,893 individual MAH users are registered for EudraVigilance.

Table 1 below shows the total number of unique cases and ICSRs transmitted by MAHs and sponsors to EVPM and EVCTM and the associated figure shows the 15-day and 90-day reporting compliance of MAHs and sponsors of clinical trials 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 2019, 278,709 ICSRs were rerouted to NCAs following receipt of the reports from MAHs in EudraVigilance. 989,167 ICSRs were forwarded to WHO. A total of 209,960 download requests by MAHs were made resulting in 10,922,912 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 2019

EV Module	Transmission type	Count
EVPM	ADR reports	1,674,923
	Individual cases	1,014,615
EVCTM	ADR reports	116,867

EV Module	Transmission type	Count
	Individual cases	35,934

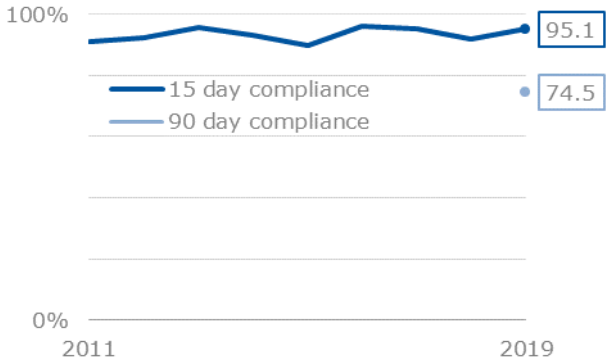

Figure 11. Compliance rate for serious (15-days) and non-serious (90-days) ADR reports to EVPM for all MAHs and sponsors by year.

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) and the Division de la Pharmacie et des Médicaments (Luxembourg), for which special arrangements are currently in place:
  - all ICSRs occurring in Liechtenstein are transmitted to EudraVigilance by MAHs,
  - the NCA for Luxembourg has their reports transmitted by the French national agency.
- A total of 1,237 individual NCA users are registered for EudraVigilance.

Table 2 below shows the total number of unique cases and ICSRs transmitted by NCAs to EVPM and EVCTM and the associated figures 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 2019

EV Module	Transmission type	Count
EVPM	ADR reports	327,889
	Individual cases	293,781
EVCTM	ADR reports	8,341
	Individual cases	5,154

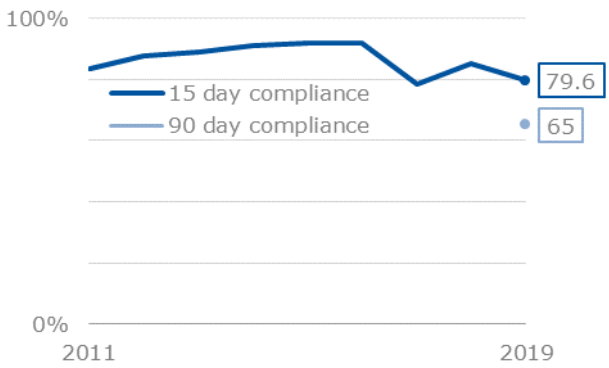

Figure 12. Compliance rate for serious (15-days) and non-serious (90-days) ADR reports to EVPM for all NCAs by year.

During 2019, the following 9 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)
- Germany (Federal Institute for Drugs and Medical Devices)
- Germany (Paul-Ehrlich-Institut)
- Greece (National Organisation for Medicines)
- 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 24,464 eRMRs were generated in 2019 to facilitate the continuous monitoring of the safety of medicines by the Agency and NCAs in the EEA. Of these,

- 11,556 were routine eRMRs, produced monthly
- 2,724 were 3-monthly eRMRs
- 1,274 were 6-monthly eRMRs
- 8,910 were additional eRMRs – produced fortnightly.

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 in accordance with Article 28a of Regulation (EC) No 726/2004

    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.

MAHs were required to resubmit their medicinal product information in accordance with the new format between July and December 2014. These data are validated by the Agency (see Annex IV for a summary of the validations performed in 2019). Table 3, below and its associated figures, provides a summary of the data resubmitted in the new format as of 15 January 2020.

Table 3. Summary of medicinal product submissions to the XEVMPD

Total number of medicinal product submissions in new format by MAHs by 15 January 2020 in accordance with Article 57(2), second subparagraph of Regulation (EC) 726/2004	
Total number of medicinal products (counted on the basis of EudraVigilance codes) submitted in the new format.	855,564
Total number of MAHs (legal entities) established in the EU (corresponding to EudraVigilance codes).	5,406

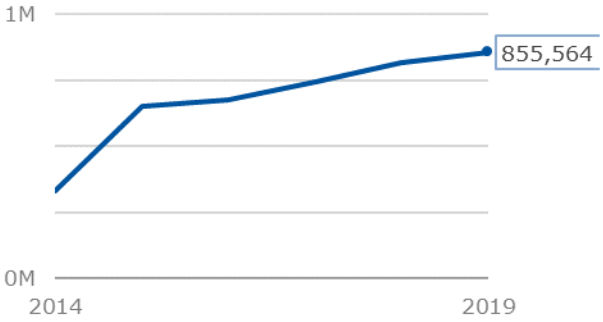

Figure 13. Total number of medicinal products (counted based on EudraVigilance codes) submitted in the new format (cumulative by year)

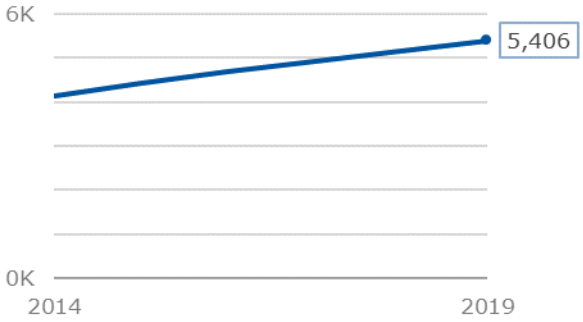

Figure 14. Total number of marketing authorisation holders (legal entities) established in the EU (corresponding to EudraVigilance codes) (cumulative by year)

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 reports, performing the coding of the reported medicines and reported active substances, and providing feedback on the quality of both ADR reports and medicinal product information sent by NCAs, MAHs and sponsors. The table below refers to the data quality activities performed by the Agency in 2019 and provides 2018 and 2017 data for comparison.

Table 4. Summary of EudraVigilance data quality activities in 2019

Data quality area	Activities performed	2019	2018	2017
Identifying and managing duplicates	Duplicate couples assessed	176,736	177,811	275,020
	Master reports generated based on duplicated data	92,480	121,929	133,635
Coding of reported medicines and active substances	Reported medicinal products and active substance terms recoded	101,388	61,202	35,727
	ADR reports recoded (ICSRs)	79,552	56,756	41,124
Providing feedback on data quality	Organisations subject to ICSR data quality review	123	237	125
	Medicinal products in XEVMPD quality reviewed (and corrected if necessary)	136,848	292,367	369,073

Annex V – Signal detection

A signal refers to information on one or more observed adverse reactions potentially caused by a medicine and that warrant further investigation. In 2019, the EMA's signal management team reviewed in detail the information on 1,806 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 18% decrease compared to the previous year.

Potential signals reviewed	2019	2018	2017	2016	2015
Total	1,806	2,204	2,062	2,076	2,372
difference	-398	142	-14	-296	342
% compared to previous	-18%	7%	-1%	-12%	17%

EudraVigilance screening continues to be the major source of EMA's potential signals with 78% of reviewed potential signals in 2019 originating from EV screening (compared to 78.7% in 2018). Scientific literature screening gave rise to 20% of potential signals in 2019 (17.8% in 2018). Additionally, cooperation with other regulatory authorities worldwide accounted for 1% of potential signals (1.8% in 2018), namely 6 from the FDA, 12 from PMDA/MHLW and 3 from Health Canada. 1% of potential signals originated from other sources. The overview by action taken is shown below:

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

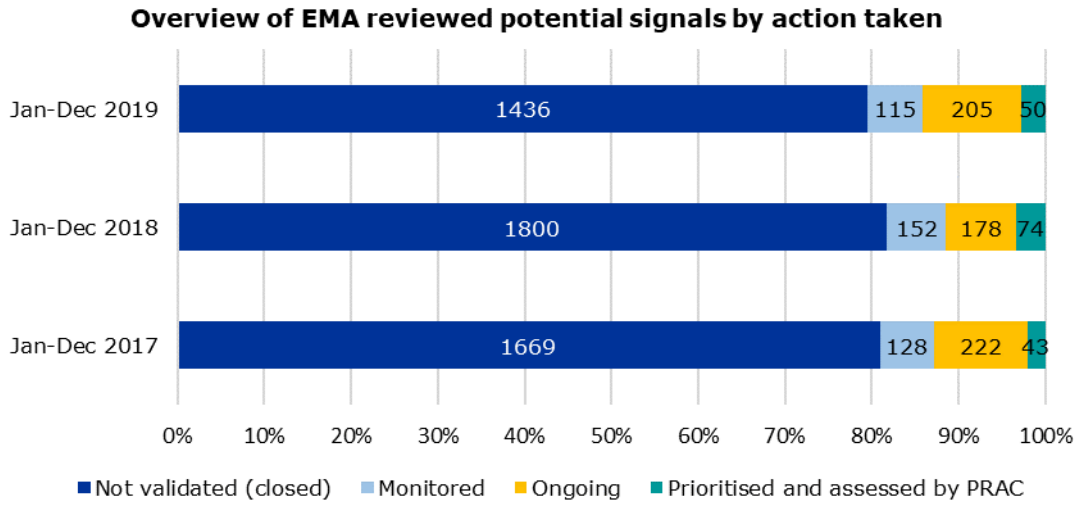

Figure 15. Overview of EMA reviewed potential signals by action taken.

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 2019 was 97, compared with 114 in 2018, representing a 15% decrease (compared with 82 in 2017 a 18% increase). 2019 was in line with the average number of signals assessed annually between 2013-2018. Of these, 50 were validated by the Agency, 46 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. One signal was validated by the MAH. Overall 80% of the signals included data from EudraVigilance among their sources (79% in 2018).

Thirty-five of the assessed signals (36%) 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 four of these cases, the PRAC also recommended Direct Healthcare Professional Communications (DHPCs) to highlight new important safety information to prescribers. Three signals led to the update of the RMP to fully characterise and investigate the concern. In 28 cases (29%) continuing with routine safety monitoring of the medicine was considered sufficient. The evaluation of 34 signals (35%) is ongoing in 2020, including 26 via a follow-up signal procedure and 8 in the upcoming PSUR/PSUSA.

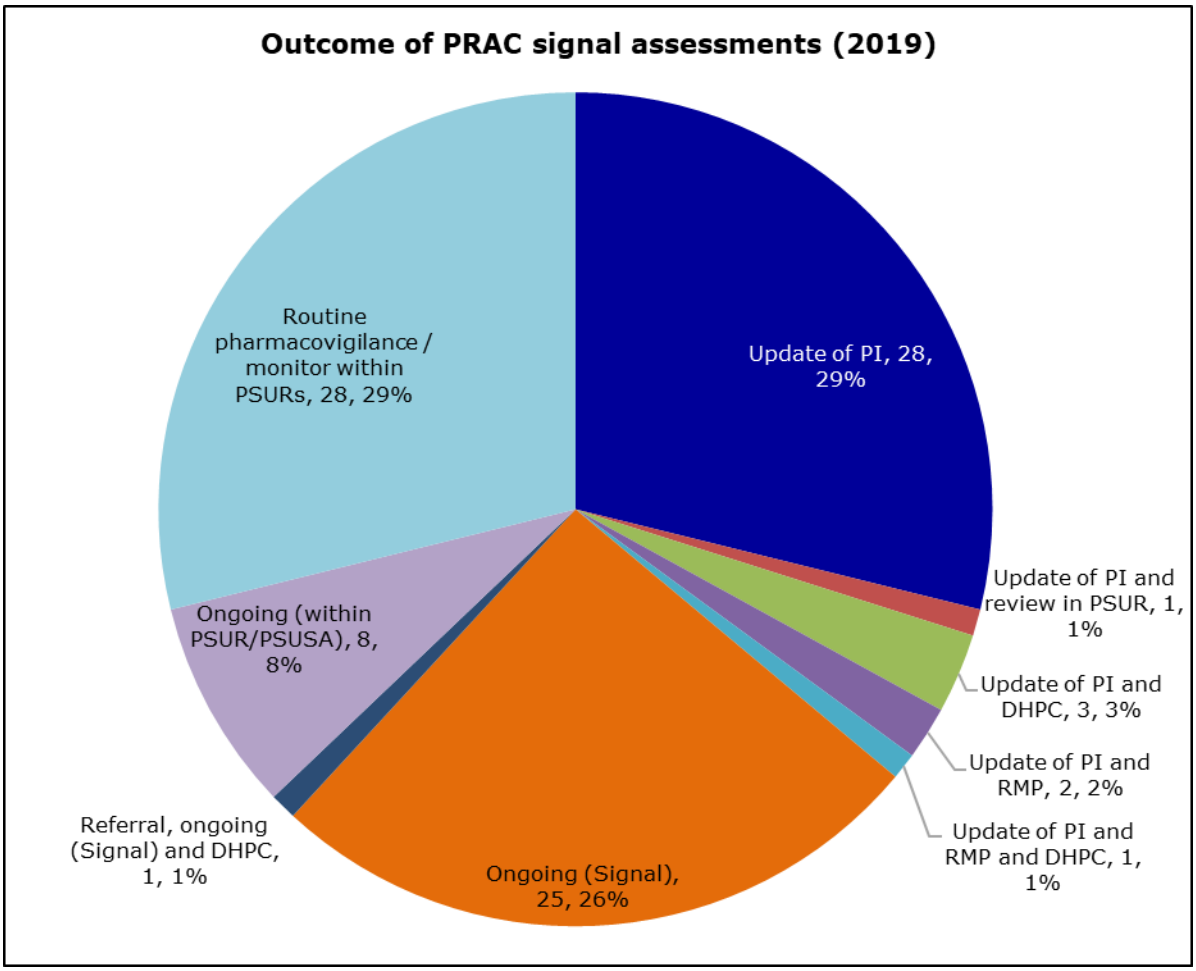

Figure 16. Outcomes of PRAC signal assessments (2019). PI: product information, DHPC: Direct Healthcare Professional Communication, RMP: Risk Management Plan, PSUR: Periodic Safety Update Report, PSUSA: PSUR Single Assessment.

A list of all signals prioritised and assessed by the PRAC in 2019 is provided below, noting the latest status or outcome as of 31 December 2019.

Drug	Issue/signal	Status or outcome
Abiraterone	Interaction with sulphonylureas leading to hypoglycaemia	ongoing (Signal)
5 alfa-reductase inhibitors (5ARIs): finasteride; dutasteride	Risk of type 2 diabetes mellitus	ongoing (Signal)
Acetylsalicylic acid	Evaluation of data on cancer-related mortality from a single study in elderly adults	routine pharmacovigilance / monitor within PSURs
Adalimumab	Autoimmune encephalitis	ongoing (Signal)
Adalimumab	Pericarditis	ongoing (Signal)
Amino acid and lipid solutions mixed with vitamins/ trace elements for parenteral nutrition of neonates	Signal of adverse outcomes in neonates treated with solutions not protected from light	update of PI and DHPC
Anastrozole	Hallucinations	ongoing (Signal)
Andexanet alfa	Signal of erroneous assay results for levels of anti-factor Xa activity with use of andexanet alfa	ongoing (Signal)
Angiotensin converting enzyme inhibitors: benazepril; captopril; enalapril; imidapril; moexipril; perindopril; quinapril; ramipril; zofenopril	Evaluation of data on risk of lung cancer from a population-based cohort study	routine pharmacovigilance / monitor within PSURs
Apixaban	Pancreatitis	routine pharmacovigilance / monitor within PSURs
Atezolizumab	Anaphylactic reaction	update of PI
Azacitidine	Progressive multifocal leukoencelopathy	routine pharmacovigilance / monitor within PSURs
Belimumab	Lupus nephritis	routine pharmacovigilance / monitor within PSURs
Benralizumab	Pneumonia	update of PI
Bevacizumab	Splenic infarction	routine pharmacovigilance /

Drug	Issue/signal	Status or outcome
		monitor within PSURs
Bevacizumab	Guillain-Barré syndrome (GBS)	ongoing (Signal)
Biotin	Interference with clinical laboratory tests	update of PI
Buprenorphine, naloxone	Drug-drug interaction with serotonergic drugs leading to serotonin syndrome	ongoing (Signal)
Ceftriaxone	Encephalopathy	ongoing (Signal)
Clopidogrel; clopidogrel, acetylsalicylic acid	Interaction with boosted antiviral human immunodeficiency virus (HIV) therapy leading to insufficient inhibition of platelet aggregation	update of PI
Dabigatran	Alopecia	update of PI
Dasabuvir /elbasvir; grazoprevir / glecaprevir; pibrentasvir / ledipasvir; sofosbuvir / ombitasvir; paritaprevir; ritonavir / sofosbuvir; sofosbuvir; velpatasvir / sofosbuvir; velpatasvir; voxilaprevir	Autoimmune hepatitis	routine pharmacovigilance / monitor within PSURs
Dimethyl fumarate	Arthritis and arthralgia	routine pharmacovigilance / monitor within PSURs
Dipeptidyl peptidase-4 (DPP-4) inhibitors: alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin	Rhabdomyolysis	ongoing (Signal)
Dipeptidyl peptidase-4 (DPP-4) inhibitors: alogliptin; linagliptin; saxagliptin; sitagliptin; vildagliptin; glucagon-like peptide-1 (GLP-1) receptor agonists: albiglutide; dulaglutide; exenatide; liraglutide; lixisenatide; semaglutide	Increased risk of cholangiocarcinoma in adults with type 2 diabetes	routine pharmacovigilance / monitor within PSURs
DOACs: Rivaroxaban; apixaban; dabigatran; edoxaban	Recurrent thrombosis in patients with antiphospholipid syndrome	update of PI and DHPC
Dolutegravir; abacavir sulfate, dolutegravir sodium, lamivudine; dolutegravir, rilpivirine	Evaluation of preliminary data from an observational study on birth outcomes in human immunodeficiency virus (HIV)-infected women	update of PI and RMP and DHPC

Drug	Issue/signal	Status or outcome
Durvalumab	Pemphigoid	update of PI
Durvalumab	Myasthenia gravis	update of PI and RMP
Febuxostat	Gynaecomastia	routine pharmacovigilance / monitor within PSURs
Ferric carboxymaltose; iron; iron dextran; iron (III) isomaltoside; iron sucrose; sodium ferric gluconate	Coronary arteriospasm	update of PI
Gabapentin	Dysphagia	update of PI
Golimumab	Inflammatory myopathy	ongoing (Signal)
Hormone replacement therapy (HRT)	New information on the known risk of breast cancer	ongoing (Signal)
Ibrutinib	Ischaemic stroke	update of PI
Ibrutinib	Neutrophilic dermatoses	ongoing (within PSUR/PSUSA)
Ibuprofen	Acute generalised exanthematous pustulosis (AGEP)	update of PI
Ibuprofen Ketoprofen and fixed-dose combinations	Serious exacerbation of infections	ongoing (Signal)
Idelalisib	Arthritis and arthralgia	routine pharmacovigilance / monitor within PSURs
Idelalisib	DRESS (Drug reaction with eosinophilia and systemic symptoms)	ongoing (Signal)
Ifosfamide (solution for infusion)	Increased risk of encephalopathy	ongoing (Signal)
Imiquimod	Pemphigus	routine pharmacovigilance / monitor within PSURs
Immune checkpoint inhibitors: atezolizumab; avelumab; cemiplimab; durvalumab; ipilimumab; nivolumab; pembrolizumab	Tuberculosis	ongoing (Signal)
Inactivated poliomyelitis vaccine, including combination vaccines	Case reports from outside the EU of immune thrombocytopenic purpura	routine pharmacovigilance / monitor within PSURs
Infliximab	Kaposi´s sarcoma	ongoing (Signal)

Drug	Issue/signal	Status or outcome
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	ongoing (Signal)
Ivacaftor; ivacaftor, tezacaftor	Increased blood creatine phosphokinase (CPK)	ongoing (within PSUR/PSUSA)
Lithium	Risk of drug induced lichenoid reaction	update of PI
Loperamide	Brugada syndrome in the context of loperamide abuse	update of PI
Mesalazine	Nephrolithiasis	update of PI
Methadone, Levomethadone	Opioid toxicity in infants exposed to levomethadone and/or methadone via breast milk	ongoing (within PSUR/PSUSA)
Modafinil Armodafinil	Evaluation of data on fetal outcomes including congenital anomalies from a single observational study in the US	update of PI and RMP
Mycophenolate mofetil; Mycophenolic acid; Myfortic	Posterior reversible encephalopathy syndrome	ongoing (Signal)
Natalizumab	Psoriasis	routine pharmacovigilance / monitor within PSURs
Nilotinib	Anaphylactic reaction	ongoing (within PSUR/PSUSA)
Nivolumab	Scleroderma	routine pharmacovigilance / monitor within PSURs
Nivolumab	Hypoparathyroidism	update of PI
Nivolumab	Haemophagocytic lymphohistiocytosis	ongoing (Signal)
Olanzapine	Salivary hypersecretion	update of PI
Olanzapine	Gestational diabetes	routine pharmacovigilance / monitor within PSURs
Omalizumab	Acquired haemophilia	routine pharmacovigilance /

Drug	Issue/signal	Status or outcome
		monitor within PSURs
Ondansetron	Signal of birth defects following in-utero exposure during the first trimester of pregnancy arising from recent publications	update of PI and CR in PSUR
Pantoprazole	Microscopic colitis	update of PI
Paracetamol	Paracetamol use in pregnancy and child neurodevelopment and effects on the urogenital apparatus	update of PI
Paracetamol	Maternal paracetamol use during pregnancy and premature ductus arteriosus closure in offspring	routine pharmacovigilance / monitor within PSURs
Paroxetine	Microscopic colitis	ongoing (Signal)
Pazopanib	Tumour lysis syndrome (TLS)	ongoing (within PSUR/PSUSA)
Pembrolizumab	Gastrointestinal ulcer	ongoing (within PSUR/PSUSA)
Pembrolizumab	Optic neuritis	routine pharmacovigilance / monitor within PSURs
Perampanel	Hepatotoxicity	ongoing (within PSUR/PSUSA)
Pirfenidone	Hyponatraemia	ongoing (within PSUR/PSUSA)
Pirfenidone	Herpes viral infections (MedDRA High Level Terms)	routine pharmacovigilance / monitor within PSURs
Prasugrel	Severe cutaneous adverse reactions	ongoing (Signal)
Pregabalin	Respiratory depression (with and without concomitant opioid use)	routine pharmacovigilance / monitor within PSURs
Propylthiouracil	Risk of congenital anomalies	update of PI
Rivaroxaban	Premature ending of the GALILEO study in patients who have received an artificial heart valve through a transcatheter aortic valve replacement (TAVR)	update of PI and DHPC

Drug	Issue/signal	Status or outcome
Sacubitril / valsartan	Ventricular arrhythmia	ongoing (Signal)
Sebelipase Alfa	Nephrotic syndrome	routine pharmacovigilance / monitor within PSURs
Secukinumab	Generalised exfoliative dermatitis	update of PI
Selective serotonin reuptake inhibitors (SSRI): citalopram; escitalopram	Drug interaction with fluconazole	update of PI
Serotonin and noradrenaline reuptake inhibitors (SNRI): desvenlafaxine; duloxetine; milnacipran; venlafaxine; Selective serotonin reuptake inhibitors (SSRI): citalopram; escitalopram; fluoxetine; fluvoxamine; paroxetine; sertraline; Vortioxetine	Persistent sexual dysfunction after drug withdrawal	update of PI
Sertraline	Maculopathy	update of PI
Sodium-glucose co-transporter 2 (SGLT2) inhibitors: canagliflozin; canagliflozin, metformin; dapagliflozin; dapagliflozin, metformin; empagliflozin; empagliflozin, metformin; empagliflozin, linagliptin; ertugliflozin, metformin; ertugliflozin, sitagliptin; saxagliptin, dapagliflozin	New information on the known association between sodium-glucose co-transporter 2 (SGLT2) inhibitors and diabetic ketoacidosis (DKA) in surgical patients	update of PI
Sorafenib	Acute generalised exanthematous pustulosis (AGEP)	routine pharmacovigilance / monitor within PSURs
Sulfasalazine	Interference with dihydronicotinamide-adenine dinucleotide / dihydronicotinamide-adenine dinucleotide phosphate (NADH/NADP) reaction assays	update of PI
Temozolomide	Drug reaction with eosinophilia and systemic symptoms (DRESS)	update of PI
Teriflunomide	Psoriasis	update of PI
Thiazide and thiazide-like diuretics	Choroidal effusion	ongoing (Signal)
Ticagrelor	Severe cutaneous adverse reactions (SCARs)	routine pharmacovigilance / monitor within PSURs
Tigecycline	Bradycardia	routine

Drug	Issue/signal	Status or outcome
		pharmacovigilance / monitor within PSURs
Tocilizumab	Psoriasis	routine pharmacovigilance / monitor within PSURs
Tocilizumab	Facial paralysis	routine pharmacovigilance / monitor within PSURs
Tocilizumab	Drug reaction with eosinophilia and systemic symptoms (DRESS)	routine pharmacovigilance / monitor within PSURs
Tofacitinib	Increased risk of pulmonary embolism and overall mortality arising from a post-authorisation safety study in patients with cardiovascular risk factors treated for rheumatoid arthritis with tofacitinib 10 mg twice daily	referral and DHPC
Topiramate	Uveitis	update of PI
Vascular endothelial growth factor (VEGF) inhibitors: aflibercept; axitinib; bevacizumab; cabozantinib; lenvatinib; nintedanib; pazopanib; pegaptanib; ponatinib; ramucirumab; ranibizumab; sorafenib; sunitinib; tivozanib; vandetanib, bevacizumab	Artery dissections and aneurysms	update of PI
Vismodegib	Pancreatitis	ongoing (Signal)

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 2019 is summarised below.

In line with the established role of SMART Processes to support the overall signal management process, the group has provided guidance and clarifications as to what falls in the scope of signals and how best to liaise and share information with other relevant EU bodies when signals concern e.g. interference of a medicine with laboratory test results.

The group also discussed the outcome of the EMA Signal Management audit performed by the EC Internal Audit Service in 2018. The audit concluded with positive remarks for the efficient implementation of the Signal Management process with special emphasis to the stakeholder engagement and transparency aspects.

The group has also continued to oversee the monitoring of EudraVigilance (EV) by MAHs during the current pilot phase. In this context, input has been provided as concerns the implementation plan and the evaluation of the pilot. Based on the preliminary evaluation, the pilot has been further extended for a duration of 24 months.

SMART processes discussed the further strengthening of the signal management work-sharing as regards EV data monitoring for active substances contained in medicinal products authorised nationally in more than one Member State. A higher number of substances have been allocated: this includes also substances previously monitored by the UK, but proactively reallocated to a new Lead member State, in preparation of Brexit.

Further guidance has been provided on scenarios when communication may be needed in relation to a signal, including EU DHPCs and national communications. Additionally, ways to optimise the sharing of knowledge (within the network) on signals that have been reviewed but not validated by a Member State have been considered, in order to limit the potential for duplication.

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

- Identification of adverse pregnancy outcomes in EudraVigilance: a new algorithm to facilitate the retrieval of adverse pregnancy outcomes in EudraVigilance was created and tested. The results showed a better performance of the algorithm - in terms of both sensitivity and specificity – compared to the currently available methods in EudraVigilance to identify pregnancy cases.
- Characterisation of signals received for geriatric patients with the aim to observe the type of reactions as well as the medicinal products more typically reported in the elderly population. In addition, the study aims at identifying differences from signals received from the general population.
- Estimation of the impact of non-serious reports in EudraVigilance further to the changes introduced by the updated European Union pharmacovigilance legislation that made mandatory the inclusion of non-serious reports from the European Economic Area (EEA). A descriptive analysis of the non-serious reports showed that they now represent around 60% of the total reports submitted in the EEA. In terms of signal detection, removing the non-serious reports resulted in fewer true and false positives compared to current processes; this resulted in a lower sensitivity but the same positive predictive value.

- Monitor of abuse of prescribed opioids. The group scoped possible methods: robust regression, auto-regression and change-points analysis. The most promising method seems the auto-regression model with relative frequency of reports; however, new research is needed in this area and potential validation is recommended.
- Creation of a tool meant to semi-automate the process of updating the PROTECT ADR database. Considering current limitations (in terms of false positives and false negatives), the next step includes benchmarking and improving the performance of the tool.

Annex VII - Requests for information and documents

In 2019, 32 EV data requests were responded to, two of which had follow-up requests. This is a similar number compared to 2018 (with 28 requests) but a lower compared to previous years e.g. 63 requests responded to in 2017. The declining number of queries can be linked to the information proactively provided at the www.adrreports.eu, which in the vast majority of general public queries seems sufficient to satisfy the questions asked. With the 2017 enhancement of EVDAS, the public portal has been updated to contain the documents of individual case reports redacted in line with the EV access policy. Hence the figure of 32 requests above includes, in addition to internal requests from the EU regulatory network (the great majority), only those external requests which could not be satisfied with the information provided via www.adrreports.eu. This includes for instance public queries across MedDRA dictionary (www.adrreports.eu uses preferred term only), queries from academia (5 in total), requests for data from non-EU regulatory agencies, or from the press.

Requests for information (RFI) and requests for access to documents (ATD) accounted for 62.5% and 26.1% of all queries, respectively, while the remaining 9.4% of requests covered both. Requests related to centrally authorised products (CAPs) alone accounted for 46.9% of the total whilst 37.5% of requests were related to nationally authorised products (NAPs). An increase, to almost 60% of the total, was observed in requests from within the EU regulatory network. The highest number of external requests, comparable to previous years, was received from the US and Germany.

The median response time for the requests was 12 days (range 1-66 days). Only one (academic) request was responded to past the deadline due to a technical issue relating to a MedDRA upgrade in EV, whilst most of the requests (56%) were answered within 14 days.

An overview is provided below by type of request, authorisation procedure of concerned product(s), requester type, and origin country (external requests only).

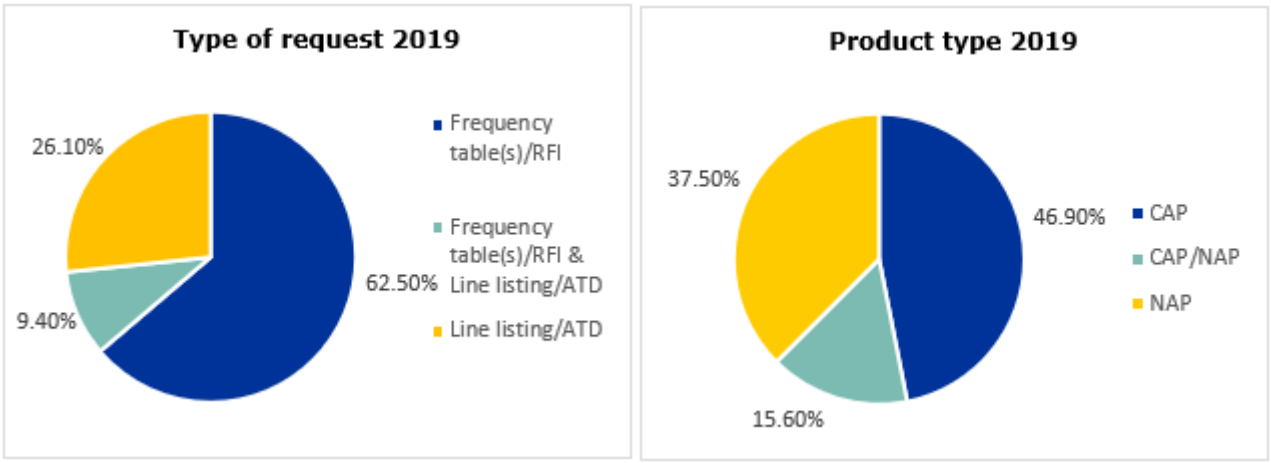

Figure 18. Overview of requests for EV data by type of request (left) and product type (right).

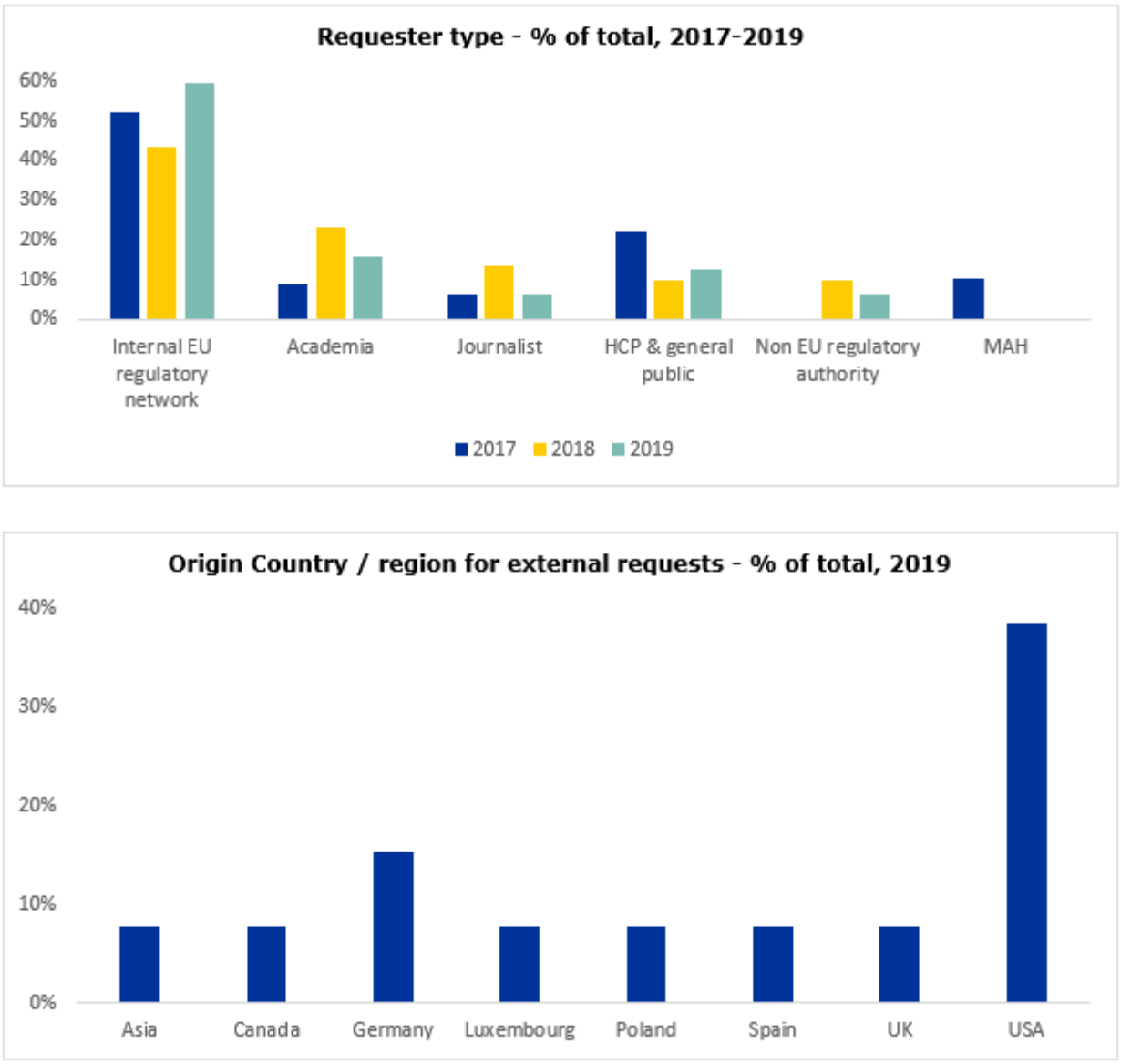

Figure 19. Overview of requests for EV data by requester type (top) and country or region of origin for external requests (bottom).

Overview of requests responded to in 2019

Type of requester	Substance/ product	Issue	Type of request
HCP	N/A	The total number of spontaneous cases to date in EV post marketing module data	Frequency table(s)/RFI
Internal EU regulatory	Serotonin-norepinephrine reuptake Inhibitor (SNRI) and Selective serotonin reuptake	Persistent sexual dysfunction	Frequency table(s)/RFI

Type of requester	Substance/ product	Issue	Type of request
network	inhibitors		
Internal EU regulatory network	Vascular Endothelial Growth Factor inhibitors	Artery dissections and aneurysm	Frequency table(s)/RFI
Journalist	HPV vaccines	Fatal event(s)	Frequency table(s)/RFI
Internal EU regulatory network	Fentanyl (PecFent)	Overdose and related events (respiratory depression, circulatory depression, hypotension and shock)	Line listing(s)/ATD
Non-EU regulatory agency	Mifepristone	Ultrasound imaging for confirmation of gestational age	Line listing(s)/ATD
Internal EU regulatory network	Fenspiride	Broad SMQs QT prolongation and cardiac arrhythmias	Line listing(s)/ATD
Internal EU regulatory network	Onasemnogene abeparvovec (Zolgensma)	Fatal event	Line listing(s)/ATD
Academia	Benzydamine	Drug abuse	Line listing(s)/ATD
Academia	Promethazine	Drug abuse	Line listing(s)/ATD
Internal EU regulatory network	Doxorubicin; Amphotericin B; Morphine; Cytarabine; Cytarabine, Daunorubicin; Vincristine; Irinotecan; Daunoribicin	Medication errors with liposomal vs. non-liposomal formulations	Line listing(s)/ATD
General public	Pneumococcal polysaccharide conjugate vaccine (adsorbed) (Synflorix)	Patient query	Frequency table(s)/RFI
Academia	Opioids	Request of extended subset of ICSR data elements (level 2a)	Line listing/ATD
HCP	Top ten substances in EV	Medication errors	Frequency table(s)/RFI
Internal EU regulatory network	Tofacitinib (Xeljanz)	Pediatric data	Frequency table(s)/RFI & Line listing/ATD
Internal EU regulatory network	Mecasermin (Increlex)	Malignancies	Frequency table(s)/RFI &

Type of requester	Substance/ product	Issue	Type of request
			Line listing/ATD
Internal EU regulatory network	Heparins	Monitoring of PV signals for heparin derived products	Frequency table(s)/RFI
Non-EU regulatory agency	Nicotine (Nicorette QuickMist Mouth Spray)	Drug abuse	Line listing/ATD
Internal EU regulatory network	Yescarta-Kymriah EBMT	ADRs	Frequency table(s)/RFI
Internal EU regulatory network	Biosimilar products	Identification and granularity	Frequency table(s)/RFI
Internal EU regulatory network	Ranitidine	Potential risk of NDMA formation in-vivo	Frequency table(s)/RFI
Internal EU regulatory network	Dipeptidyl peptidase 4 (DPP-4) inhibitors	Rhabdomyolysis	Frequency table(s)/RFI
Internal EU regulatory network	Leuprorelin	Medication errors and lack of efficacy	Frequency table(s)/RFI
Internal EU regulatory network	Cyproterone	Meningiomas	Frequency table(s)/RFI
Internal EU regulatory network	Ingenol	Skin neoplasms malignant and unspecified	Frequency table(s)/RFI
Internal EU regulatory network	Ondansetron	Pediatric data	Frequency table(s)/RFI
Internal EU regulatory network	Dipeptidyl peptidase 4 (DPP-4) inhibitors	Severe cutaneous adverse reactions (SCAR)	Frequency table(s)/RFI
Academia	Ayurvedic medications	Hepatic events	Frequency table(s)/RFI & Line listing/ATD
Academia	Glucagon-like peptide-1 (GLP-1) analogues	Proportional reporting ratio (PRR) for thyroid cancer	Frequency table(s)/RFI

Type of requester	Substance/ product	Issue	Type of request
General public	Pregabalin	Blindness and fatalities in the EU	Frequency table(s)/RFI
Journalist	Denosumab (Prolia)	Seizures and hypocalcemia at the same time	Frequency table(s)/RFI D
Internal EU regulatory network	HPV vaccines	Ovarian failure	Frequency table(s)/RFI D