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2018 Annual Report on EudraVigilance for the European Parliament, the Council and the Commission

Reporting period: 1 January to 31 December 2018

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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Abbreviations used in the document

ADR	Adverse Drug Reaction
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.

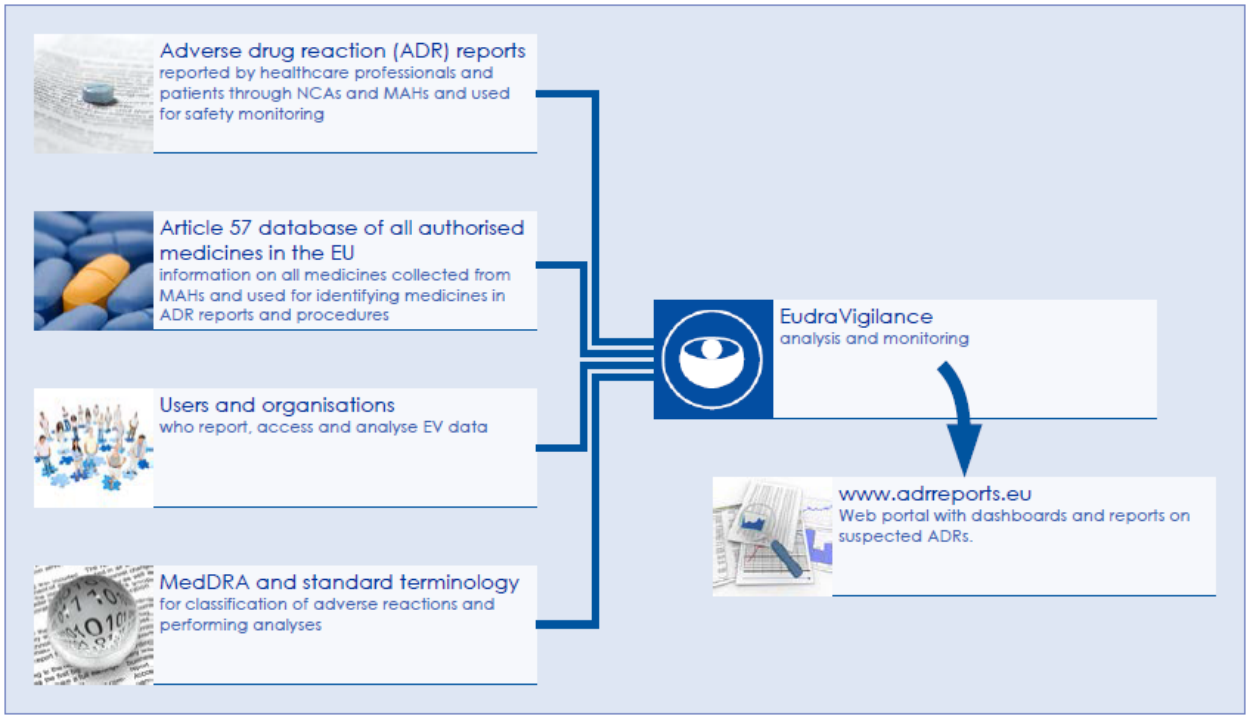


Figure 1. EudraVigilance users, data sources and data uses.

The database currently holds over 14.5 million individual case safety reports (ICSRs) referring to over 8.3 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 2018, notably:

- *Operation of EudraVigilance including its new functionalities.* EudraVigilance is maintained by the EMA on behalf of the EU medicines regulatory network with further enhanced functional improvements in data analysis and signal detection delivered.
- *Collecting and processing of adverse drug reaction reports.* In 2018, 2,015,881 reports related to suspected adverse reactions occurring in the post-authorisation phase were collected and managed in EudraVigilance (a 37% increase compared to 2017). 1,028,386 of these reports originated from the EEA (an 89% increase compared to 2017). The number of reports submitted directly by European patients and consumers through the NCAs and MAHs (172,762) increased 91% in 2018. Please see Annex II for more details.

- *Maintaining and updating the database of information on all medicinal products authorised in the EU.* The database (the so-called "Article 57 database") now contains information on 816,765 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.* This includes developing standards and guidance, detecting and managing duplicate reports, review and feedback to reporters on the quality of ICSRs they submitted, and quality review and updates of information on authorised medicinal products.
- *Creation and distribution of 23,292 data analysis reports on the safety of medicines to the EU network (electronic reaction monitoring reports - eRMRs) and support of data analyses as part of assessments carried out in pharmacovigilance procedures.* 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 supports decision making by PRAC.
- *Screening for and review of potential signals for centrally authorised products (CAPs) as well as nationally authorised products (NAPs)*. In 2018, the EMA's signal management team reviewed in detail 2,204 potential signals, i.e. drug-event pairs from screening of the EudraVigilance database (78.7%), medical literature (17.8%) or information received from regulatory authorities or other sources. For active substances of NAPs the monitoring of ADR reports is shared between the NCAs. For 1,703 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 validated signals which are confirmed by the Rapporteur or lead Member State (MS) are brought to the attention of the PRAC for initial analysis, prioritisation and assessment. In 2018, the PRAC prioritised and assessed 114 confirmed signals (a 39% increase compared to 2017); 79% included data from EudraVigilance. Fifty of the assessed signals (44%) 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 six of these cases, the PRAC also recommended Direct Healthcare Professional Communications (DHPCs) to highlight new important safety information to prescribers. One additional signal led to the update of the RMP to fully characterise and investigate the concern. In 24 cases (21%) continuing with routine safety monitoring of the medicine was considered sufficient. The evaluation of 39 signals (34%) is ongoing in 2019, including 22 via a follow-up signal procedure and 17 in the 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. In the context of the pilot, six validated signals have been notified by MAHs by the end of 2018. All other MAHs also have access to ICRs for their medicinal products and therefore can integrate the data into their own signal management processes.

- *Direct provision of data to the World Health Organization (WHO) Uppsala Monitoring Centre* from EudraVigilance. 1,010,544 ICSRs were forwarded to WHO from EudraVigilance in 2018, making it one of the major 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 2018, the website provided information on a total of 2,982 active substances including 707 contained in 1,114 CAPs and 2,275 in NAPs.
- *Training and support activities.* A large training offering is available online as e-learning[1] for all stakeholders and training for the EU network is available through the EU Network Training Centre. Many of training and support activities organised by the EMA were open to all stakeholders, including two EudraVigilance and Signal Management information days (with combined attendance of 244 delegates), 2 training sessions on the EudraVigilance Data Analysis System, EVDAS (36 NCA experts), 27 training sessions on EudraVigilance ICSR submissions (469 users) and 5 training sessions on the XEVMPD (64 users), with additional 153 users trained on the XEVMPD e-learning platform. Furthermore, 11 and 14 webinars were organised for NCAs and MAHs, respectively, to aid with the resolution of operational and technical questions and 5 additional signal management webinars were organised for MAHs.

2. Operation of EudraVigilance including its new functionalities

EudraVigilance is maintained by EMA on behalf of the EU medicines regulatory network. Further development culminated in the launch of the new EudraVigilance (human) system on 22 November 2017. This allowed for enhanced signal detection and data analysis. The key features 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 Organization (WHO) Uppsala Monitoring Centre from EudraVigilance.	Enhanced collaboration between EMA and WHO without the need for NCAs to separately submit ICSRs to WHO UMC.

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

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

In 2018, the PRAC, which is overseeing the operation of EudraVigilance, adopted the "EudraVigilance Operational Plan 2018 to 2020[2]". The operational plan describes key activities and developments that will impact on or relate to EudraVigilance and its stakeholders during the next three years. These include system maintenance, integration with the Agency's identity and access management, aspects resulting from the UK's withdrawal from the EU as well as the impact of EMA relocation on the Agency's business continuity planning, and the use of ICH E2B(R3) and ISO IDMP standards in EEA and other considerations. For more information, see EudraVigilance change management on EMA website[3].

3. Data collection and data quality

Medicinal product information

The total number of medicinal products entries by MAHs in the XEVMPD as of 28 January 2019 is 816,765 (regardless of authorisation status e.g. valid, withdrawn). These entries provide a dataset of authorised 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 99.5% of medicinal products. Full details on these items are presented in Annex III.

Reporting of ADR reports and patient involvement

Every report of a suspected ADR by a patient or healthcare professional contributes to safety monitoring and thus to the safe and effective use of medicines. Additionally, robust research[4] has demonstrated that collating reports into big datasets and using statistical analyses of the data allows safety issues to be detected, and therefore dealt with, more rapidly. In this context, the reporting of suspected ADRs underpins the operation of a EU pharmacovigilance system.

In 2018, 2,015,881 ICSRs were collected and managed in EudraVigilance, 1,028,386 of which originate from the EEA. This is an overall 37% increase and a 89% increase in EEA reporting compared to 2017. This major increase is mainly due to the mandatory reporting of non-serious ICSRs after the go-live of the new system on 22 November 2017. The number of reports submitted directly by patients and consumers through the NCAs and MAHs (172,762) in the EU also increased (91%) in 2018 for the same reasons.

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[5] (see Annex II).

[2] https://www.ema.europa.eu/documents/other/eudravigilance-operational-plan-milestones-2018-2020_en.pdf
[3] https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance
[4] Alvarez Y et al. Validation of statistical signal detection procedures in EudraVigilance post-authorization data: a retrospective evaluation of the potential for earlier signalling. Drug Saf. 2010; 33(6):475-487.
[5] 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

Figure 3. Trend of ADR reports from patients and consumers received in the EEA by NCAs and MAHs and reported to EudraViglance.

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 such as training, detecting and merging duplicate reports, 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 2018, a total of 23,292 eRMRs were generated for NCA and EMA staff. These are produced every two weeks for medicinal products subject to additional monitoring and monthly for most 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 principle sources of validated signals, i.e. potential new associations or new aspects of known associations between medicines and ADRs which may be caused by the medicine. For CAPs, EMA leads the monitoring; of 2,204 potential signals which were reviewed by the Agency in 2018, approximately 78.7% 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'[6], which indicates a Lead Member State for each included active substance. The list currently includes 1,703 active

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

substances. NCAs also monitor all medicines authorised nationally in their country for which no Lead Member State has been appointed.

A pilot started in February 2018 whereby MAHs of selected active substances[7] have to monitor them in EudraVigilance and inform EMA and national competent authorities of validated signals with their medicines. All other MAHs also have access to EudraVigilance data and can integrate the data into their own signal management processes. In the context of the pilot, six validated signals were notified by MAHs by the end of 2018.

All detected and validated signals which are confirmed by the Rapporteur or lead MS are brought to the attention of the PRAC for initial analysis, prioritisation and assessment. In 2018, the PRAC prioritised and assessed 114 confirmed signals (a 39% increase compared to 2017); 79% included data from EudraVigilance. Fifty of the assessed signals (44%) 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 six of these cases, the PRAC also recommended a DHPC to highlight new important safety information to prescribers and in two, also to update the RMP. One additional signal led to the update of the RMP to fully characterise and investigate the concern, in the absence of a product information update. In 24 cases (21%) continuing with routine safety monitoring of the medicine was considered sufficient. The evaluation of 39 signals (34%) is currently ongoing, including 22 via a follow up signal procedure and 17 in the next PSUR/PSUSA.

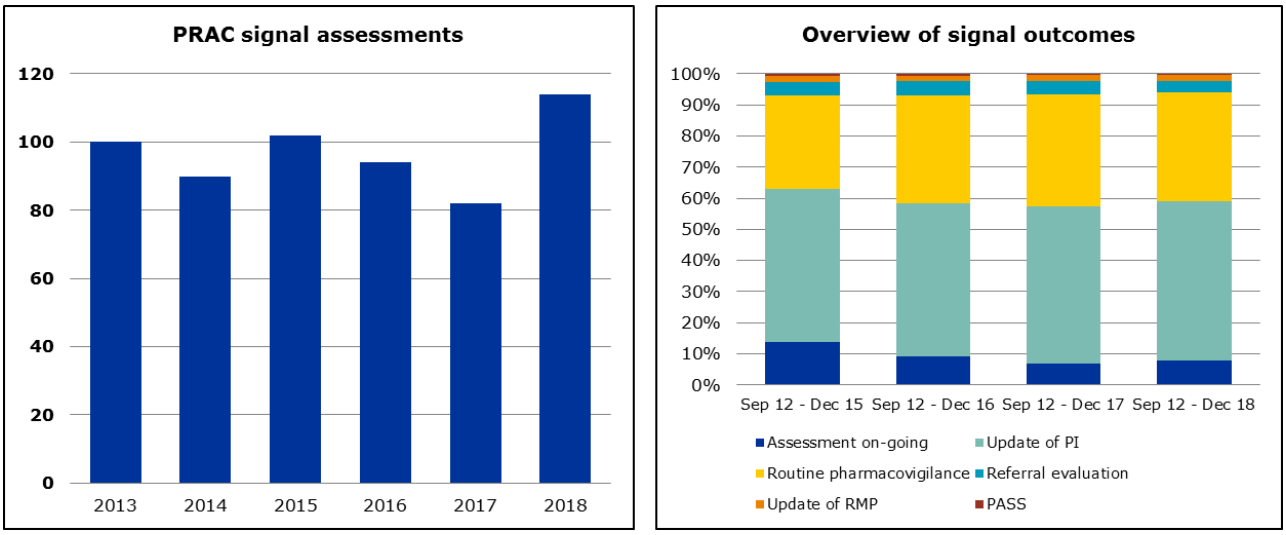


Figure 4. Overview of signals assessed by the PRAC.

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 2018 can be found in Annex V. The progress of process improvements and simplifications in signal management is detailed in Annex VI.

[7]Based on all active substances and combinations that were included in the list of medicinal products subject to additional monitoring as of 25 October 2017 (Rev. 49). https://www.ema.europa.eu/documents/other/list-active-substances-involved-pilot-signal-detection-eudravigilance-marketing-authorisation_en.xls

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 enhanced in 2017 and 2018, to include further outputs such as case line listings and case report forms. By the end of 2018, the website provided information on a total of 2,982 active substances (including 707 substances in 1,114 CAPs and 2,275 in NAPs). There were over 2.45 million visits to the website in 2018.

At EU level EMA keeps MAHs informed on EudraVigilance developments via its website. Furthermore two meetings were held with industry representatives to discuss challenges and opportunities with the new functionalities. In addition, two newsletters 'What's new in Pharmacovigilance - QPPV updates' were published on the Agency's website[8] to provide EU QPPVs with information on recent developments in EU pharmacovigilance activities including relevant projects.

At the end of July 2018 EudraVigilance was updated in order to use the EMA's Identity and Access Management platform. This new platform allows for harmonised organisation and user management across all EMA telematics systems and services contacted to this system. This enables users to have just one set of credential to access EMA services such as EudraVigilance. In addition, this system rationalises the registration process and makes it a more efficient for EudraVigilance stakeholders as they can now self-register and maintain their own users. It is acknowledged that the implementation of this platform into EudraVigilance was a more challenging exercise than initially expected due to the complexity of the pre-existing EudraVigilance registration data. This led to a significant number of EudraVigilance users experiencing access issues whilst the migrated registration data was cleaned and reconciled.

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 supports 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 9 working days. Approx. 40% 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 a large number of training, operational and technical support activities, many of which were open to all stakeholders:

- Two EudraVigilance and Signal Management information days (with combined attendance of 244 delegates),
- 27 training sessions on EudraVigilance ICSR submissions, with 469 participants,
- 2 training sessions on EVDAS for 36 experts from 17 NCAs,
- 5 training sessions on the XEVMPD, with 64 users participants,
- 153 XEVMPD users followed training via the dedicated e-learning platform,

[8] https://www.ema.europa.eu/documents/newsletter/whats-new-pharmacovigilance-qppv-update-issue-1-2018_en.pdf
https://www.ema.europa.eu/documents/newsletter/whats-new-pharmacovigilance-qppv-update-issue-2-2018_en.pdf

- 11 and 14 webinars were organised for NCAs and MAHs, respectively, to aid with the resolution of operational and technical questions and 5 additional signal management webinars were organised for MAHs,
- A large training offering is available online as e-learning[9] for all stakeholders and training for the EU network is available through the EU Network Training Centre.

6. Conclusion

EudraVigilance continues to be the central pillar of European medicine safety surveillance, as illustrated by the unprecedented receipt of more than 1 million ADR reports from the EEA in 2018. With currently over 14.5 million ADR reports, EudraVigilance is among the largest databases of its kind in the world and is used by EMA, EU NCAs and MAHs. With over 1 million ADRs forwarded to the WHO database, EudraVigilance also makes a major contribution to global surveillance.

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 contributes significantly to the protection of public health and the reduction of risks associated with the use of medicines.

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

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 November2017. 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.
Data quality review and duplicate management of adverse reaction reports in EudraVigilance. [Legal basis: Regulation (EC) 726/2004, Article 24(3)]	Continued during 2018.
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 2018.
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 2018.
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 2018.
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 2018.
Operation of the Medical Literature Monitoring service [Legal basis: Regulation (EC) 726/2004, Article 27]	Continued during 2018.

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 99.3% of the time throughout the year[10], exceeding the required 98% availability. There were two periods where this level was not met, in June at 96.95% and in October at 96.09% (figure 4). These were due to unforeseen technical issues and measures have been put in place to reduce the risk of recurrence.

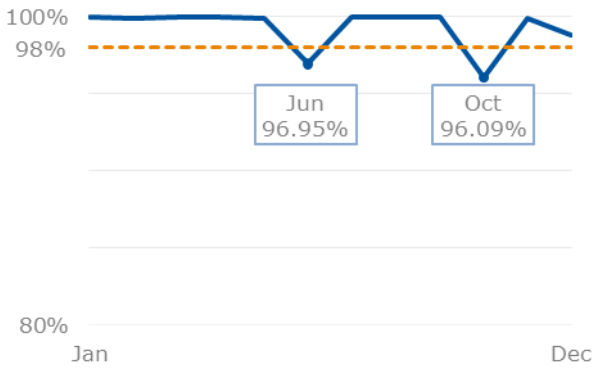


Figure 5. EudraVigilance gateway availability per month. The requirement is 98%. Please note that the scale starts at 80%. Planned downtime is excluded.

EudraVigilance database

For medicinal products authorised in the EEA, ADR reports are collected from both within and outside the EEA. By 31 December 2018, the EudraVigilance database held a total of 14,592,054 ADR reports (or ICSRs), referring to 8,331,075 individual cases (figure 5). The post-authorisation module (EVPM) contained 13,407,924 ADR reports (7,981,510 cases) and the clinical trial module (EVCTM) 1,184,130 reports (349,565 cases).

[10] Only unplanned downtime is taken into consideration

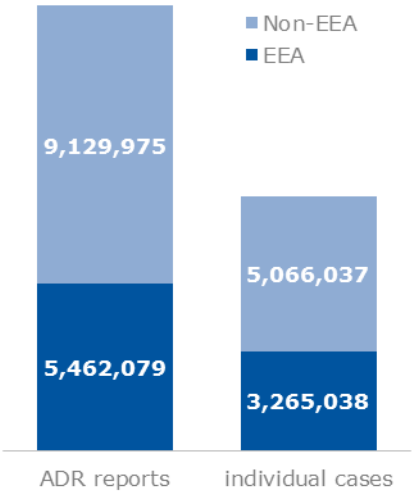


Figure 6. Number of ADR reports versus individual cases received in the EudraVigilance database from its inception in December 2001 until 31 December 2018 split by origin of the report in- or outside the EEA.

The numbers presented in figure 7 and 8 refer to the ADR reports received in the post-authorisation module (EVPM). A total of 13,407,924 EVPM ADR reports have been processed by the end of 2018 over a period of seventeen years. 2,015,881 EVPM ADR reports were processed in 2018. This is an increase of 37% as compared to last year (figure 7), and can largely be attributed to the transfer to the new EV system that went live on 22 November 2017 and 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.

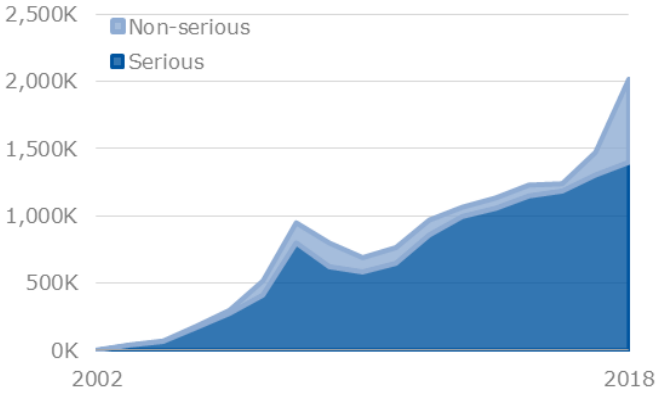


Figure 7. Number of ADR reports processed per year in EVPM.

Figure 8. Number of ADR reports processed per month in EVPM in 2018.

Figure 10 presents the total number of ADR reports received in EVPM grouped by EEA and non-EEA for 2018 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).

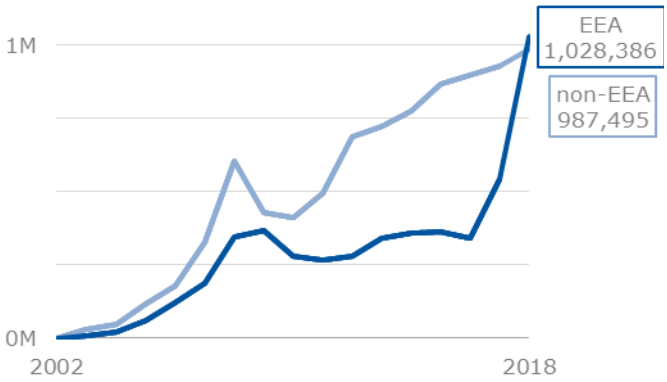


Figure 9. Number of ADR reports processed per year in EVPM split by cases occurred inside and outside the EEA.

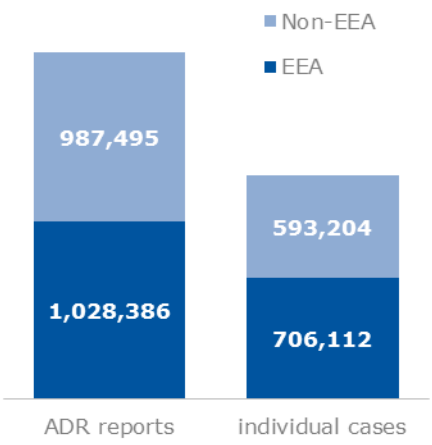


Figure 10. Number of ADR reports versus the number of individual cases in 2018 in EVPM.

In 2018, 172,762 ADR reports were submitted by European patients and consumers through the NCAs and MAHs, referring to 135,031 individual cases. This is an increase of 91% in such reports over the previous year (figure 11). Again, the mandatory reporting of non-serious cases to EudraVigilance since November 2017 is a key driver of this effect.

Figure 11. 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 1,405 MAHs (at headquarter level) have sent reports to EVPM in the period between 1 January 2002 and 31 December 2018, an approx. 31% increase compared to 2017.
- 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 2018, an approx. 10% increase compared to 2017.
- A total of 17,687 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). 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 and error reports are excluded from the compliance calculations. Only cases identified by the MAHs as serious are included in the calculations.

In 2018, 344,962 ICSRs were rerouted to NCAs following receipt of the reports from MAHs in EudraVigilance. 1,010,544 ICSRs were forwarded to WHO. A total of 233,759 download requests by MAHs were made resulting in 14,247,526 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 2018

EV Module	Transmission type	Count
EVPM	ADR reports	1,710,012
	Individual cases	1,010,397
EVCTM	ADR reports	113,392
	Individual cases	32,143

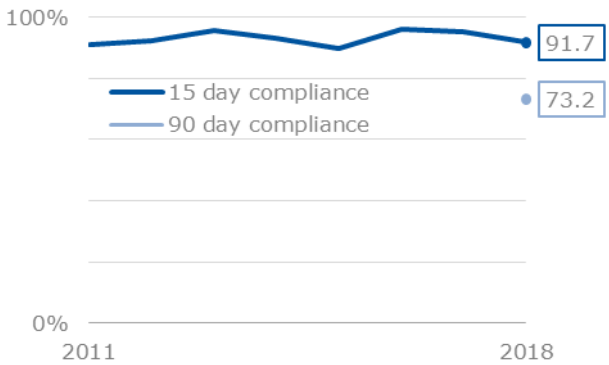


Figure 12. Compliance rate for serious (15-days) and non-serious (90-days) ADR reports to EVPM for all MAHs and sponsors by year.

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 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 1,317 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). The receipt date is treated as day 0, giving the NCA 15 days following that day to transmit the reports.

Nullification and error reports are excluded from the compliance calculations. Only cases flagged by the NCA as serious are included in the calculations.

Table 2. Number of ICSRs and unique cases transmitted by NCAs to EVPM and EVCTM during 2018

EV Module	Transmission type	Count
EVPM	ADR reports	305,869
	Individual cases	288,913
EVCTM	ADR reports	10,955
	Individual cases	7,352

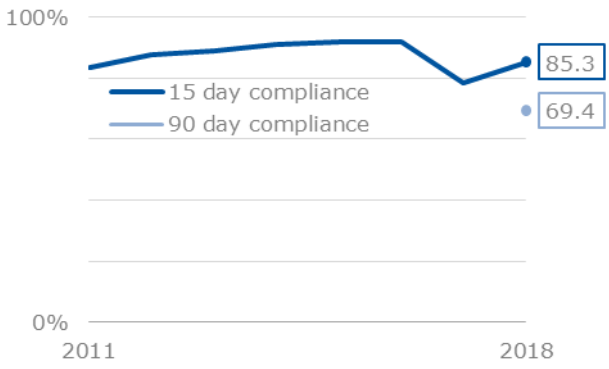


Figure 13. Compliance rate for serious (15-days) and non-serious (90-days) ADR reports to EVPM for all NCAs by year.

During 2018, 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)
- Finland (Finnish Medicines Agency)
- Germany (Federal Institute for Drugs and Medical Devices)
- Germany (Paul-Ehrlich-Institut)
- 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 23,292 eRMRs were generated in 2018 to facilitate the continuous monitoring of the safety of medicines by the Agency and NCAs in the EEA. Of these,

- 12,300 were routine eRMRs, produced monthly
- 2,620 were 3-monthly eRMRs
- 1,022 were 6-monthly eRMRs
- 7,350 were additional eRMRs – produced fortnightly.

Annex III - Total number of medicinal product submissions by MAHs

As described in Section 2 of this Annual Report, 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 2018). Table 3, below and its associated figures, provides a summary of the data resubmitted in the new format as of 28 January 2019.

Table 3. Summary of medicinal product submissions to the XEVMPD

Total number of medicinal product submissions in new format by MAHs by 28 January 2019 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) resubmitted in the new format.	816,765
Total number of MAHs (legal entities) established in the EU (corresponding to EudraVigilance codes).	5,152

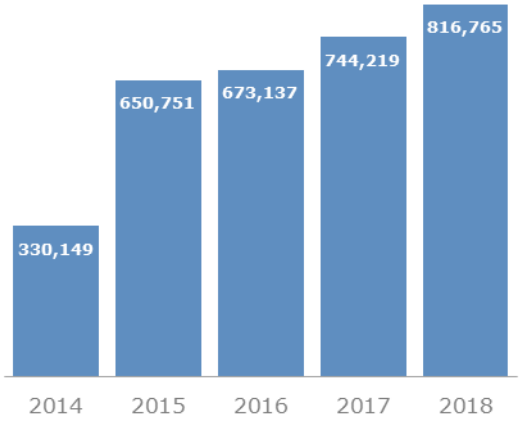


Figure 14. Total number of medicinal products (counted on the basis of EudraVigilance codes) submitted in the new format (cumulative by year)

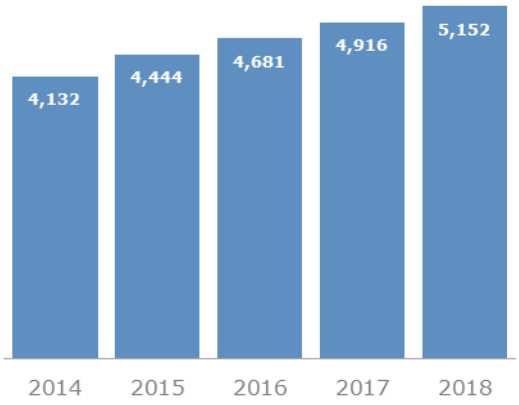


Figure 15. Total number of marketing authorisation holders (legal entities) established in the EU (corresponding to EudraVigilance codes) (cumulative by year)

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 2018 and provides 2016 and 2017 data for comparison.

Table 4. Summary of EudraVigilance data quality activities in 2018

Data quality area	Activities performed	2018	2017	2016
Identifying and managing duplicates	Duplicate couples assessed	177,811	275,020	72,655
	Master reports generated based on duplicated data	121,929	133,635	48,111
Coding of reported medicines and active substances	Reported medicinal products and active substance terms recoded	61,202	35,727	91,650
	ADR reports recoded (ICSRs)	56,756	41,124	64,686
Providing feedback on data quality	Organisations subject to ICSR data quality review	237	125	120
	Medicinal products in XEVMPD quality reviewed (and corrected if necessary)	292,367	369,073	235,058

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 2018, the EMA's signal management team reviewed in detail the information on 2,204 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 7% increase compared to the previous year.

Potential signals reviewed	2018	2017	2016	2015	2014
Total	2,204	2,062	2,076	2,372	2,030
difference	142	-14	-296	342	-419
% compared to previous	7%	-1%	-12%	17%	-17%

EudraVigilance screening continues to be the major source of EMA's potential signals with 78.7% of reviewed potential signals in 2018 originating from EV screening (compared to 81.8% in 2017). Scientific literature screening gave rise to 17.8% of potential signal in 2018 (16.5% in 2017). Additionally, cooperation with other regulatory authorities worldwide accounted for 1.8% of potential signals (1.2% in 2017), namely 11 from the FDA, 4 from PMDA/MHLW and 25 from Health Canada. 1.7% of potential signals originated from other sources. The overview by action taken is shown below:

Action taken	Number of potential signals 2018	% of total	Number of potential signals 2017	% of total
Not validated (closed)	1800	81.7%	1,669	80.9%
Monitored	152	6.9%	128	6.2%
Ongoing	178	8.1%	222	10.8%
Prioritised and assessed by PRAC	74	3.4%	43	2.1%
Total	2,204	100.00%	2,062	100.00%

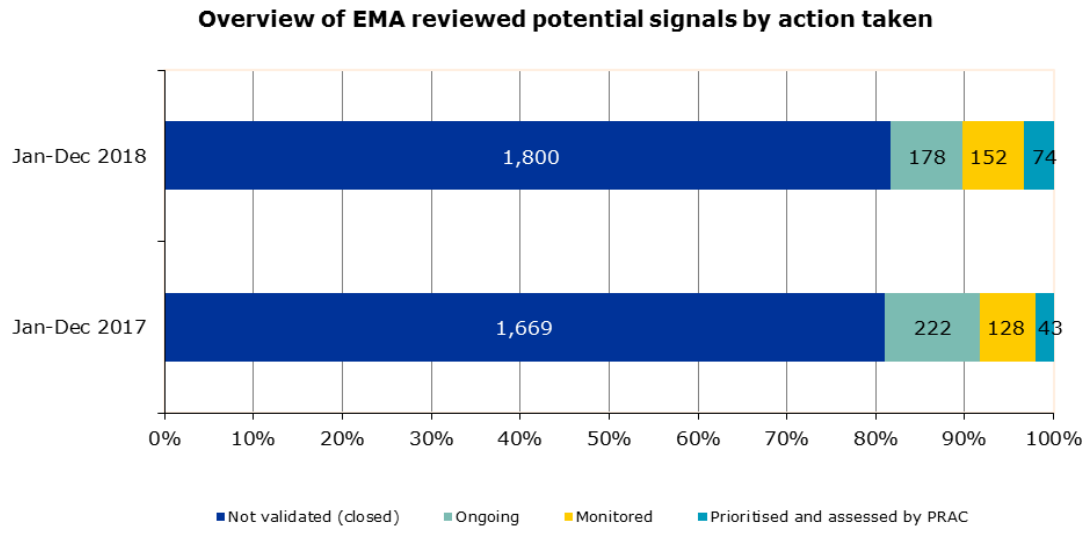


Figure 16. Overview of EMA reviewed potential signals by action taken.

Overview of signals prioritised and assessed by the PRAC

All detected validated signals which are confirmed by the Rapporteur or lead MS 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 2018 was 114, compared with 82 in 2017, representing a 39% increase. 74 were validated by the Agency and 40 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; overall 79% included data from EudraVigilance among their sources (63.4% in 2017).

Fifty of the assessed signals (44%) 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 six of these cases, the PRAC also recommended a DHPC to highlight new important safety information to prescribers and in two, also the update of the RMP. One additional signal led to the update of the RMP to fully characterise and investigate the concern. In 24 cases (21%) continuing with routine safety monitoring of the medicine was considered sufficient. The evaluation of 39 signals (34%) was ongoing at the data lock, including 22 via a follow up signal procedure and 17 in the next PSUR/PSUSA.

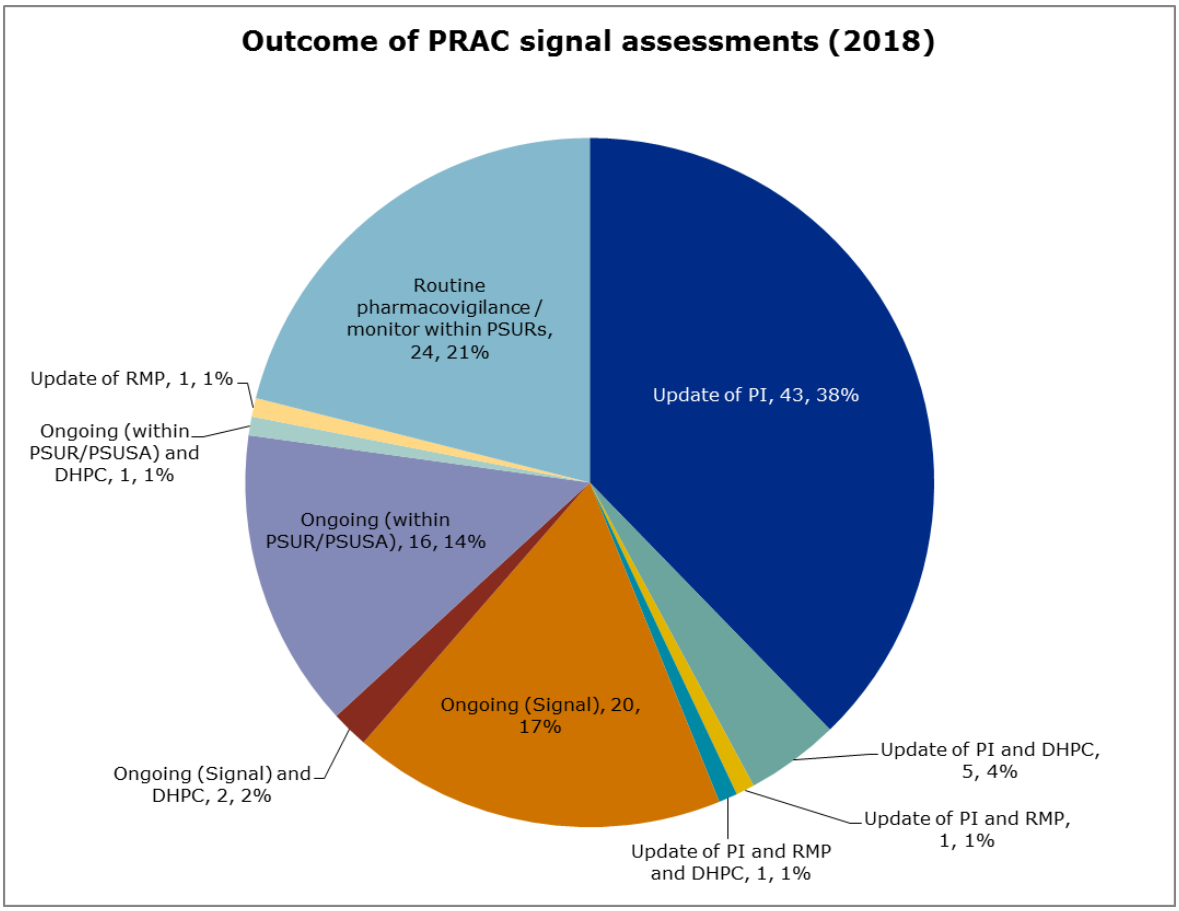


Figure 17. Outcomes of PRAC signal assessments (2018). PI: product information, DHPC: Direct Healthcare Professional Communication, RMP: Risk Management Plan, PSUR: Periodic Safety Update Report, PSUSA: PSUR Single Assessment.

A list of all signals prioritised and assessed by the PRAC in 2018 is provided below, noting the latest status or outcome as of 31 December 2018.

Drug	Issue / signal	Status or outcome
Abacavir, dolutegravir, lamivudine, zidovudine, atazanavir, cobicistat, darunavir, emtricitabine, tenofovir alafenamide, didanosine, rilpivirine, efavirenz, tenofovir disoproxil, elvitegravir, rilpivirine, enfuvirtide, etravirine, fosamprenavir, indinavir, zidovudine, lopinavir, maraviroc, nevirapine, raltegravir, saquinavir, stavudine, tipranavir	Autoimmune hepatitis	update of PI
Adalimumab	Lichenoid keratosis	update of PI
Alectinib	Erythema multiforme	ongoing (within PSUR/PSUSA)
Alemtuzumab	Cytomegalovirus infection	update of PI
Amitriptyline	Dry eye	update of PI
Amitriptyline; dosulepin; oxybutynin; paroxetine; procyclidine	Dementia	routine pharmacovigilance / monitor within PSURs
Apixaban	Neutropenia	routine pharmacovigilance / monitor within PSURs
Apixaban	Pancreatitis	ongoing (Signal)
Apixaban	Tubulointerstitial nephritis	routine pharmacovigilance / monitor within PSURs
Apixaban; edoxaban	Signal of drug interaction with selective serotonin reuptake inhibitors (SSRI) and/or serotonin and noradrenaline reuptake inhibitors (SNRI) leading to increased risk of bleeding	update of PI
Avelumab	Pancreatitis	ongoing (within PSUR/PSUSA)
Azithromycin	Increased rate of relapses of haematological malignancies and mortality in haematopoietic stem cell transplantation patients	ongoing (within PSUR/PSUSA) and DHPC
Baricitinib	Pneumonia	update of PI
Belimumab	Lupus nephritis	ongoing (Signal)

Drug	Issue / signal	Status or outcome
Benralizumab	Anaphylactic reaction	ongoing (within PSUR/PSUSA)
Biotin	Interference with clinical laboratory tests	ongoing (Signal)
Canagliflozin; dapagliflozin; empagliflozin; ertugliflozin	Fournier's gangrene	update of PI and DHPC
Carbimazole; thiamazole	New information on the known risk of birth defects and neonatal disorders in case of exposure during pregnancy	update of PI and DHPC
Carbimazole; thiamazole	Pancreatitis	update of PI and DHPC
Cefalexin	Acute generalised exanthematous pustulosis	update of PI
Certolizumab pegol; Etanercept; Golimumab; Infliximab	Lichenoid reactions for tumour necrosis factor alfa (TNFα) inhibitors	update of PI
Clomipramine; 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	ongoing (Signal)
Clopidogrel	Insulin autoimmune syndrome	update of PI
Clopidogrel; clopidogrel, acetylsalicylic acid	Interaction with boosted antiretroviral HIV therapy leading to insufficient inhibition of platelet aggregation	ongoing (Signal)
Concentrate of proteolytic enzymes enriched in bromelain	Haemorrhage	update of PI
Dabigatran	Hallucinations	ongoing (within PSUR/PSUSA)
Dabigatran Etexilate; Apixaban; Rivaroxaban; Edoxaban	Cholesterol embolisms	routine pharmacovigilance / monitor within PSURs
Daratumumab	Encephalopathy	routine pharmacovigilance /

Drug	Issue / signal	Status or outcome
		monitor within PSURs
Dasabuvir; ombitasvir, paritaprevir, ritonavir	Interstitial lung disease	routine pharmacovigilance / monitor within PSURs
Dasatinib	Cytomegalovirus reactivation	update of PI
Denosumab	Alopecia	ongoing (within PSUR/PSUSA)
Dienogest, ethinylestradiol	New information on the known risk of venous thromboembolism with combined hormonal contraceptives containing dienogest and ethinylestradiol	update of PI
Dimethyl fumarate	Immune thrombocytopenic purpura and thrombocytopenia	update of PI
Direct Acting Antivirals: daclatasvir dihydrochloride; sofosbuvir / velpatasvir; dasabuvir sodium; ledispavir / sofosbuvir; glecaprevir / pibrentasvir; sofosbuvir; ombitasvir / paritaprevir / ritonavir; sofosbuvir / velpatasvir / voxilaprevi; elbasvir / grazoprevir	Dysglycaemia	update of PI
Direct oral anticoagulants (DOACs): Rivaroxaban; apixaban; dabigatran; edoxaban	Recurrent thrombosis in patients with antiphospholipid syndrome	ongoing (Signal)
Dolutegravir; abacavir sulfate, dolutegravir sodium, lamivudine; dolutegravir, rilpivirine	Evaluation of preliminary data from an observational study on birth outcomes in HIV-infected women	update of PI and RMP and DHPC
Dulaglutide	Acute kidney injury	update of PI
Dulaglutide	Gastrointestinal stenosis and obstruction	update of PI
Dulaglutide; Exenatide; Liraglutide	Diabetic ketoacidosis	update of PI
Duloxetine	Interstitial lung disease	update of PI
Emicizumab	New information on the known risk of haemorrhagic events	routine pharmacovigilance / monitor within PSURs
Filgrastim; lenograstim; lipegfilgrastim; pegfilgrastim	Aortitis	update of PI

Drug	Issue / signal	Status or outcome
Fingolimod	Autoimmune haemolytic anaemia	ongoing (within PSUR/PSUSA)
Fluoroquinolones: ciprofloxacin; flumequine; levofloxacin; lomefloxacin; moxifloxacin; norfloxacin; ofloxacin; pefloxacin; prulifloxacin; rufloxacin	Aortic aneurysm and dissection	update of PI and DHPC
Gabapentin	Dysphagia	ongoing (Signal)
Hormonal contraceptives	New publication on suicidality with hormonal contraceptives	update of PI
Hormonal contraceptives: Chlormadinone acetate, ethinylestradiol; cyproterone, ethinylestradiol; cyproterone acetate, estradiol valerate; desogestrel; desogestrel ,ethinylestradiol; dienogest, estradiol; dienogest, ethinylestradiol; drospirenone, ethinylestradiol; estradiol, nomegestrol acetate; ethinylestradiol, etonogestrel; ethinylestradiol, gestodene; ethinylestradiol, gestodene; ethinylestradiol, levonorgestrel; ethinyl estradiol, norelgestromin; ethinylestradiol, norethisterone; ethinylestradiol, norgestimate; ethinylestradiol, norgestrel; levonorgestrel, ethinylestradiol; ethinylestradiol; levonorgestrel; medroxyprogesterone; norethisterone	Signal following a recent publication on known association between hormonal contraceptives and breast cancer	routine pharmacovigilance / monitor within PSURs
Human coagulation(plasma-derived) factor VIII: human coagulation factor VIII (antihemophilic factor A); human coagulation factor VIII (inhibitor bypassing fraction); human coagulation factor VIII, human von Willebrand factor Recombinant factor VIII: antihemophilic factor (recombinant); efmoroctocog alfa; lonoctocog alfa; moroctocog alfa; octocog alfa; simoctocog alfa; susoctocog alfa; turoctocog alfa	Signal of inhibitor development in previously untreated patients with haemophilia A treated with plasma-derived vs recombinant coagulation factor VIII concentrates	routine pharmacovigilance / monitor within PSURs
Human normal immunoglobulin	Lupus-like syndrome	update of PI
Hydrochlorothiazide	Skin cancer	update of PI and

Drug	Issue / signal	Status or outcome
		DHPC
Hydroxycarbamide	Cutaneous lupus erythematosus	update of PI
Hydroxycarbamide	Progressive multifocal leukoencephalopathy (PML)	routine pharmacovigilance / monitor within PSURs
Idelalisib	Arthritis and arthralgia	ongoing (Signal)
Inactivated poliomyelitis vaccine (including combination vaccines)	Case reports from outside the EU of immune thrombocytopenic purpura	ongoing (Signal)
Infliximab; Adalimumab	Risk of lymphoma in patients with inflammatory bowel disease	routine pharmacovigilance / monitor within PSURs
Ipilimumab	Gastrointestinal cytomegalovirus infection	update of PI
Ivacaftor; ivacaftor, tezacaftor	Increased blood creatine phosphokinase	ongoing (Signal)
Lapatinib	Pulmonary hypertension	update of PI
Lenalidomide	Progressive multifocal leukoencephalopathy (PML)	update of PI
Levothyroxine; ombitasvir, paritaprevir, ritonavir	Interaction possibly leading to decreased levothyroxine efficacy and hypothyroidism	update of PI
Megestrol; vitamin K antagonists: acenocoumarol, fluindione, phenprocoumon, warfarin	Drug interaction leading to elevated international normalised ratio (INR)/haemorrhage with megestrol and vitamin K antagonists	routine pharmacovigilance / monitor within PSURs
Meningococcal group b vaccine	Meningism	update of PI and RMP
Mepolizumab	Hypertensive crisis and hypertension	ongoing (within PSUR/PSUSA)
Methotrexate	Pulmonary alveolar haemorrhage	update of PI
Montelukast	Speech disorders (dysphemia)	ongoing (within PSUR/PSUSA)
Nabumetone	Drug reaction with eosinophilia and systemic symptoms (DRESS)	update of PI
Natalizumab	Human papillomavirus (HPV) infection and complications	ongoing (within PSUR/PSUSA)

Drug	Issue / signal	Status or outcome
Niraparib	Potential occurrence of embolic and thrombotic events	update of RMP
Niraparib	Sepsis	ongoing (within PSUR/PSUSA)
Nivolumab	Sclerosing cholangitis	routine pharmacovigilance / monitor within PSURs
Nivolumab	Hypoparathyroidism	ongoing (Signal)
Nivolumab	Keratoacanthoma	routine pharmacovigilance / monitor within PSURs
Nivolumab	Scleroderma	ongoing (Signal)
Norepinephrine	Stress cardiomyopathy	update of PI
Olanzapine	Gestational diabetes	ongoing (Signal)
Olanzapine	Somnambulism	routine pharmacovigilance / monitor within PSURs
Olmesartan	Autoimmune hepatitis	routine pharmacovigilance / monitor within PSURs
Oxybutynin; carbamazepine	Drug interaction between oxybutynin and carbamazepine resulting in seizures and carbamazepine overdose secondary to carbamazepine plasma level variations	routine pharmacovigilance / monitor within PSURs
Paracetamol	Maternal paracetamol use during pregnancy and premature ductus arteriosus closure in offspring	ongoing (Signal)
Paracetamol	Paracetamol use in pregnancy and child neurodevelopment and effects on the urogenital apparatus	ongoing (Signal)
Parathyroid hormone	Nephrolithiasis	update of PI
Pazopanib	Rhabdomyolysis	ongoing (within PSUR/PSUSA)
Pegfilgrastim; Lenograstim; Lipefilgrastim	Pulmonary haemorrhage	update of PI
Pembrolizumab	Aseptic meningitis	update of PI

Drug	Issue / signal	Status or outcome
Pembrolizumab	Sclerosing cholangitis	ongoing (within PSUR/PSUSA)
Pembrolizumab	Systemic inflammatory response syndrome (SIRS)	ongoing (within PSUR/PSUSA)
Pemetrexed	Nephrogenic diabetes insipidus	update of PI
Pemetrexed	Syncope	routine pharmacovigilance / monitor within PSURs
Peramivir	Hepatic failure	ongoing (within PSUR/PSUSA)
Perindopril	Raynaud's phenomenon	update of PI
Phenprocoumon	Risk of birth defects and fetal loss following first trimester exposure as a function of the time of withdrawal	update of PI
Propranolol	Increased risk of Parkinson's disease	routine pharmacovigilance / monitor within PSURs
Ranibizumab	Angioedema	routine pharmacovigilance / monitor within PSURs
Rivaroxaban	Acquired haemophilia	ongoing (within PSUR/PSUSA)
Rivaroxaban	Premature ending of the GALILEO study in patients who have received an artificial heart valve through a transcatheter aortic valve replacement	ongoing (Signal) and DHPC
Selective serotonin reuptake inhibitors (SSRI): citalopram; escitalopram	Drug interaction with fluconazole	ongoing (Signal)
Sildenafil	Pulmonary hypertension and fatal cases associated with use in an off-label indication, early-onset intrauterine growth restriction	ongoing (Signal) and DHPC
Sitagliptin; sitgaliptin, metformin	Potential drug interaction between sitagliptin and angiotensin-converting-enzyme (ACE)-inhibitors leading to an increased risk of angioedema	routine pharmacovigilance / monitor within PSURs

Drug	Issue / signal	Status or outcome
Sorafenib	Acute generalised exemanthous pustulosis)	ongoing (Signal)
Sunitinib	Aortic dissection	update of PI
Tacrolimus systemic formulation	Hepatitis E infection	update of PI
Teriflunomide	Dyslipidaemia	update of PI
Tocilizumab	Facial paralysis	ongoing (Signal)
Tocilizumab	Hypofibrinogenaemia	update of PI
Tocilizumab	Noninfectious encephalitis	routine pharmacovigilance / monitor within PSURs
Tocilizumab	Psoriasis	ongoing (Signal)
Trastuzumab emtansine	Sepsis	ongoing (within PSUR/PSUSA)
Trastuzumab; Trastuzumab emtansine; Pertuzumab	Multiple sclerosis relapse	routine pharmacovigilance / monitor within PSURs
Varenicline	Loss of consciousness	update of PI
Vascular endothelial growth factor (VEGF) inhibitors: aflibercept; axitinib; bevacizumab; cabozantinib; lenvatinib; nintedanib; pazopanib; pegaptanib; ponatinib; ramucirumab; ranibizumab; sorafenib; sunitinib; tivozanib; vandetanib	Artery dissections and aneurysms	ongoing (Signal)
Vemurafenib	Cardiac failure	routine pharmacovigilance / monitor within PSURs
Voriconazole	Drug reaction with eosinophilia and systemic symptoms (DRESS)	update of PI
Vortioxetine	Angioedema and urticaria	update of PI
Xylometazoline	Serious ventricular arrhythmia in patients with long QT syndrome	update of PI

Annex VI - Signal management process and methods

The Signal Management Review Technical Working Group (SMART) is a collaboration between Member States and EMA with the objective to strengthen and simplify the signal management process in the EU. Its two work streams are focused on signal management tools and processes (SMART Processes) and methodological guidance and signal detection methods (SMART Methods). SMART reports to PRAC. The progress achieved in 2018 is summarised below.

An updated work plan for SMART Processes has been endorsed. In addition to the established role of the group in supporting the overall signal management process and providing guidance, the work plan now reflects the new role of the group in overseeing the monitoring of EudraVigilance (EV) by MAHs. The group has been providing input to the implementation plan of the pilot on the EV monitoring by MAHs[11] and will continue to be involved in its evaluation. During a pilot period which started on 22 February 2018, MAHs of selected active substances[12] have to monitor them in EudraVigilance and inform EMA and NCAs of validated signals with their medicines. The pilot was initially planned for one year but has been extended until further notice.

Data on practices in place was collected from NCAs and shared to establish the periodicity of the monitoring of medicinal products, so the appropriate monitoring frequency is mainly driven by risk proportionality and the principles outlined in GVP IX.

Signal detection practices were further strengthened with the finalisation of guidance on signal detection and the processing of ADR terms linked to terms already included in the product information.

Guidance has been provided on scenarios when communication may be needed in relation to a signal, including EU DHPCs and national communications, as well as on the criteria to decide on whether plenary discussion at PRAC is needed, on confirmation/non confirmation and on how to deal with new publications (on previously confirmed signals) that do not change the previously adopted PRAC recommendations.

Work-sharing in signal management was further strengthened with respect to EV data monitoring for active substances authorised in more than one MS. Principles for the re-allocation of substances currently monitored by the UK to another lead member state were agreed.

The group also agreed on principles to ensure knowledge transfer from the UK and a smooth transition after March 2019. The eRMRs data will be shared by UK with the newly appointed signal leads, while signals whose evaluation cannot be finalised in time for endorsement at the PRAC March meeting will be proactively reallocated to the NCAs that will take over from UK.

In terms of SMART Methods, the group reviewed EudraVigilance data related to adverse pregnancy outcomes with the aim of identifying metrics that could best serve as a pregnancy flag, boosting both sensitivity and specificity in data retrieval.

The group also analysed in detail the results of the test done in collaboration with Columbia University on a new method to improve signal detection in EudraVigilance (Statistical Correction of Uncharacterised Bias). More work is needed to understand the potential of automatically correcting for confounding/bias.

[11] https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/signal-management
[12] 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

Another area of improvement concerns the implementation of a new algorithm at EMA to detect unexpected increases in frequency of reporting adverse reactions in EudraVigilance, supported by a new dashboard.

Annex VII - Requests for information and documents

In 2018, 28 requests for EudraVigilance data were responded to, two of which included one or more follow-up requests. This is a lower number compared to previous years (67 requests 2017), which is in large part due to the increased amount of information proactively provided on the public website of adverse drug report received in EudraVigilance via www.adrreports.eu.

Requests for information (referred to also as frequency tables) and requests for access to documents (line listings) accounted for 36% and 57% of requests, respectively, while the remaining 7% of requests concerned access to personal data of the patient about whom the report was notified or individual case forms. An increase, amounting to 25% of the total in 2018, was observed in research requests originating from academia, which were often complex and involved several substances, resulting in a higher workload. The highest number of external requests, as in previous years, was received from the UK and Germany.

The median response time for the requests was 9 working days (range 1-85 working days). The majority of requests (64%) were answered within 14 working days. Four research requests were responded to past the deadline due to their complexity and the amount of data involved. An overview is provided below by type of request, authorisation procedure of concerned product(s), requester type, and origin country (external requests only).

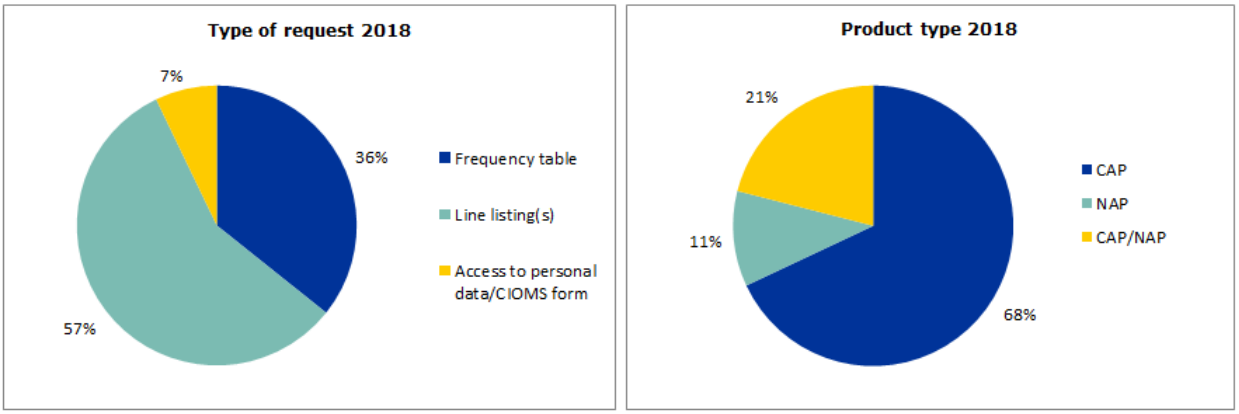
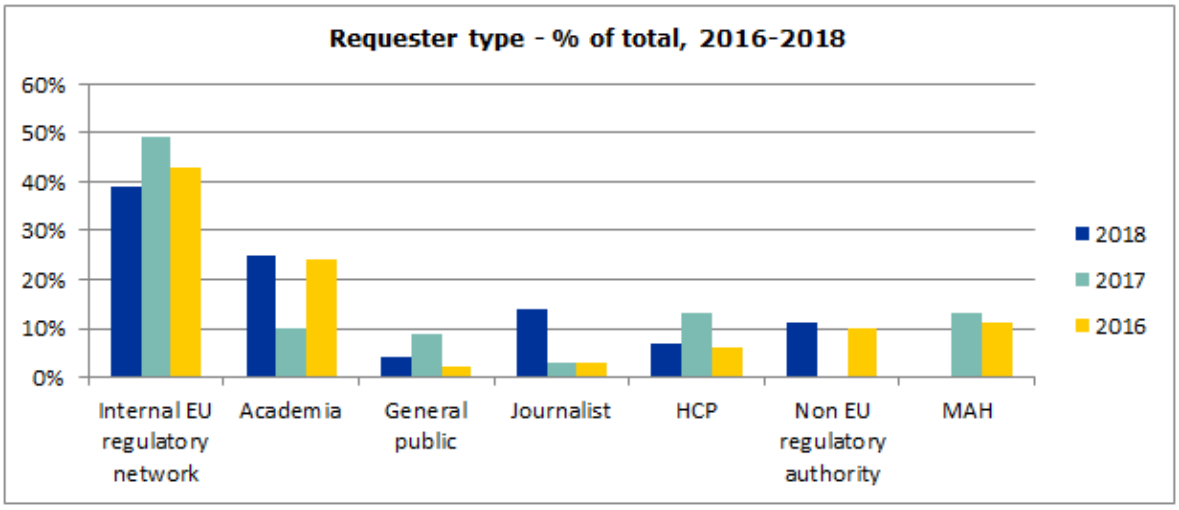


Figure 18. Overview of requests for EV data by type of request (left) and product type (right).



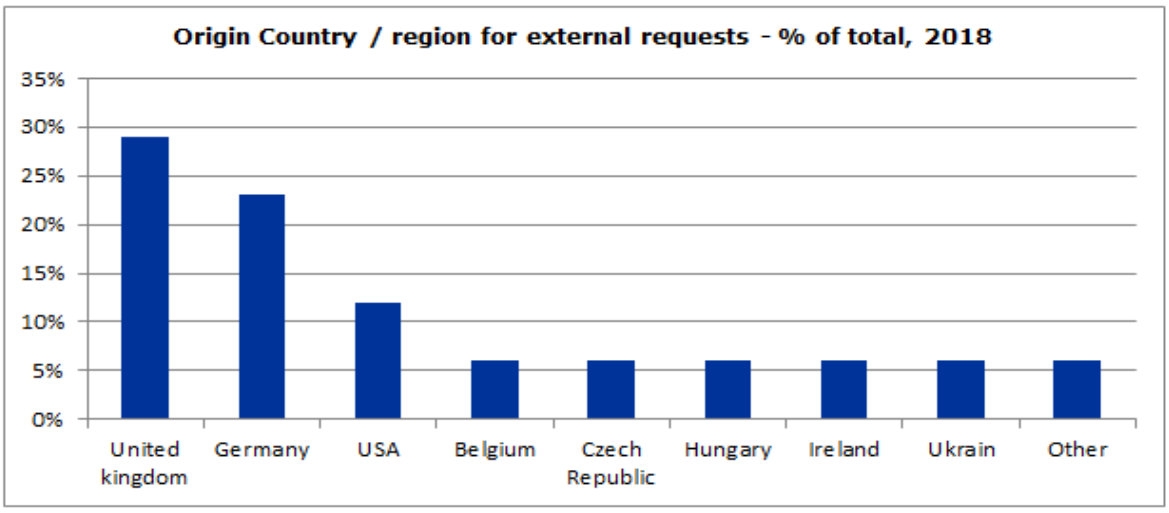


Figure 19. Overview of requests for EV data by requester type (top) and country or region of origin for external requests (bottom).

Overview of requests responded to in 2018

Type of requester	Substance / product	Issue	Type of request
Academia	Multiple	Eudravigilance data for multiple research questions	Frequency table(s)/RFI
Journalist	Sublingual Immunotherapy	Anaphylactic reaction	Frequency table(s)/RFI
Internal EU regulatory network	Buccolam	Pharmacovigilance data	Line listing(s)/ATD
Internal EU regulatory network	Gentamicin	Pharmacovigilance search request	Line listing(s)/ATD
Internal EU regulatory network	Praxbind	Medication errors	Line listing(s)/ATD
Internal EU regulatory network	Zoledronic	Allergic reactions	Frequency table(s)/RFI
Internal EU regulatory network	Tresiba (insulin degludec)	Medication errors	Line listing(s)/ATD
Internal EU regulatory network	Ella one	Hepatic disorder	Line listing(s)/ATD
Internal EU regulatory network	Daclizumab	DRESS	Line listing(s)/ATD

Type of requester	Substance / product	Issue	Type of request
Internal EU regulatory network	Zinbryta	Encephalomyelitis	CIOMS form(s)
Academia	Opioids	Misuse, abuse, dependence, withdrawal	Line listing(s)/ATD
Academia	Antidepressants	Misuse, abuse, dependence, withdrawal	Line listing(s)/ATD
Academia	Clozapine	Misuse, abuse, dependence, withdrawal	Line listing(s)/ATD
Academia	Metamizole	Agranulocytosis	Line listing(s)/ATD
Internal EU regulatory network	Methotrexate	Safety data for referral - discussion of scope and next step	Frequency table(s)/RFI
Academia	Zolpidem	ADRs	Frequency table(s)/RFI
General public	Gardasil	Access to personal data	Access to personal data
Academia	Multiple	Cardiovascular PTs	Line listing(s)/ATD
HCP	Pregabalin	Fatalities, suicides, blindness and total number of reports	Frequency table(s)/RFI
Internal EU regulatory network	Multiple	Identifying any concerning trends which may require action in regards to an invented name	Line listing(s)/ATD
Non EU regulatory network	Truberzi	Impact of the contra indication in patients with no gallbladder	Line listing(s)/ATD
Internal EU regulatory network	Ozurdex	Eye disorders	Line listing(s)/ATD
Non EU regulatory network	Pyramax	Individual reports	Frequency table(s)/RFI
Non EU regulatory network	Vaccines	Fatal ADRs	Line listing(s)/ATD
Journalist	Multiple	Musculoskeletal and connective tissue disorders of limbs congenital	Line listing(s)/ATD
HCP	Multiple	All PTs	Frequency table(s)/RFI
Journalist	Zinbryta	Fatal and serious cases	Frequency table(s)/RFI
Journalist	Colchicine	Overdoses and fatalities	Frequency table(s)/RFI D