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Inspections, Human Medicines Pharmacovigilance and Committees Division

2017 Annual Report on EudraVigilance for the European Parliament, the Council and the Commission

Reporting period: 1 January to 31 December 2017

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Table of contents

Abbreviations used in the document

ADR	Adverse Drug Reaction
CAP	Centrally Authorised Product
DHPC	Direct Healthcare Professional Communication
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
ICSR	Individual Case Safety Report
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

Introduction

EudraVigilance, the European database for adverse drug reaction (ADR) reports, is the tool that the European Medicines Agency (EMA) and the national competent authorities (NCAs) use for monitoring the safety of all authorised medicines on the EU market[1].

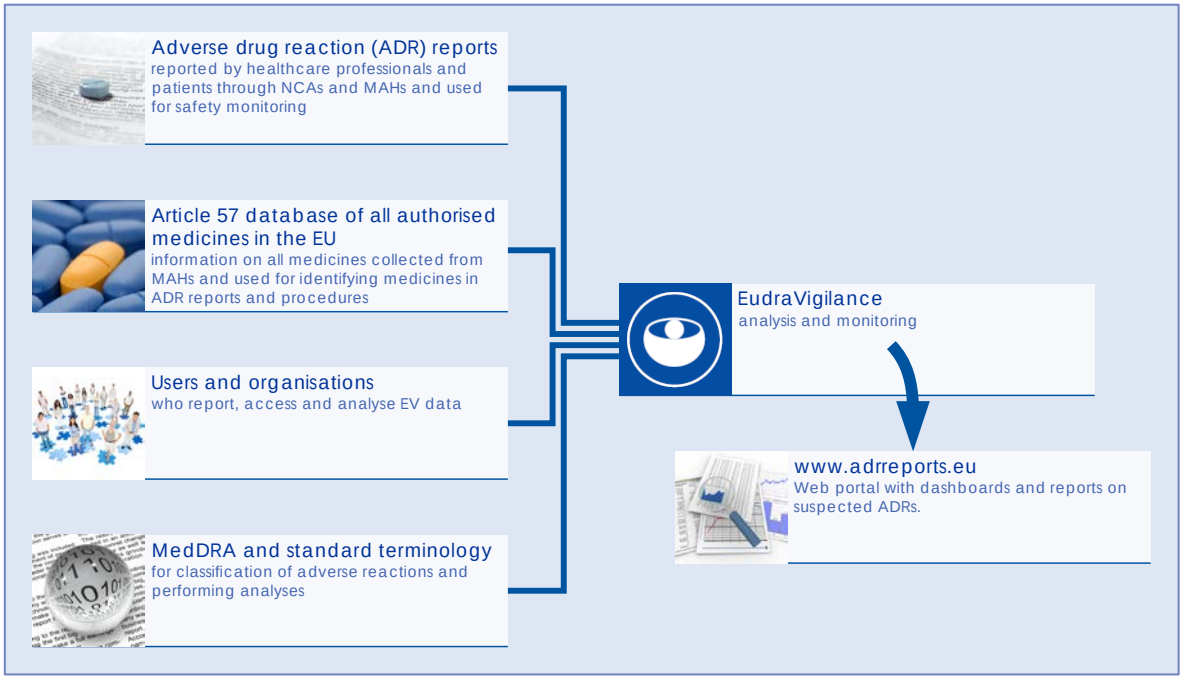


Figure 1. EudraVigilance actors and data sources.

The timely detection and assessment of drug safety signals, benefit-risk evaluation of periodic safety update reports and assessment and agreement of risk management plans by the Pharmacovigilance Risk Assessment Committee (PRAC) are the cornerstones of EU pharmacovigilance, optimising safe and effective use of medicines and supporting timely access to innovative medicines. EudraVigilance is essential to all these activities and is, therefore, the central pillar for pharmacovigilance activities in the European Economic Area (EEA).

The database currently holds over twelve million individual case safety reports (ICSRs) referring to nearly eight million cases and is one of the largest pharmacovigilance databases in the world. It is maintained by the EMA on behalf of the EU medicines regulatory network and 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 2017, notably:

- *Delivering the enhancements of the EudraVigilance database.* In February and April 2017, the new EudraVigilance system successfully passed an independent audit in accordance with Article 24 of Regulation (EC) 726/2004. The EMA Management Board confirmed[2] on 22 May 2017 that the full functionality of the EudraVigilance database had been achieved and the system met the defined functional specifications. The new EudraVigilance system was launched on 22 November 2017, providing enhanced functionalities to NCAs, EMA and marketing authorisation holders (MAHs) for

[1] EudraVigilance is also used to monitor safety in clinical trials conducted in the EU.
[2] http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/05/WC500228158.pdf

effective reporting and monitoring of ADR data and detection of risks related to the safety of medicines, thus contributing to the protection and promotion of public health.

- *Collecting and processing of adverse drug reaction reports.* In 2017, 1,471,596 reports related to suspected adverse reactions were collected and managed in EudraVigilance (a 19% increase compared to 2016). 543,548 of these reports originated from the EEA (a 60% increase compared to 2016). The number of reports submitted directly by European patients and consumers through the NCAs and MAHs (90,358) also increased significantly in 2017.
- *Maintaining and updating a database of information on all medicinal products authorised in the EU.* The database now contains information on 744,219 medicines. The availability of such a complete dataset allows identification of medicines in reports of suspected adverse drug reactions, supports the management of pharmacovigilance procedures (signals, PSURs, referrals) and facilitates the administration of pharmacovigilance fees. It also allows 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, including developing standards and guidance, detecting and managing duplicate reports,* review and feedback to reporters on the quality of reports they submitted, and quality review and corrections of data on authorised medicinal products have continued in 2017.
- *Production and provision of 21,496 data analysis reports on medicines safety to the EU network (electronic reaction monitoring reports - eRMRs) and provision of data analyses to support assessments in pharmacovigilance procedures.* EudraVigilance data allows monitoring of newly received ADR reports for identification of new risks or risks that have changed (e.g. in frequency or severity), and provides support for decision making in pharmacovigilance procedures.
- *Review of potential signals for centrally authorised products (CAPs) as well as nationally authorised products (NAPs)*. EMA staff lead on the monitoring of CAPs, while NCAs lead on the monitoring nationally authorised products (NAPs) in line with work-sharing in signal management. For CAPs, this resulted in 2,062 potential signals reviewed by the Agency, of which approximately 82% originated from analysis of ADR reports received in the EudraVigilance database, reflecting the importance of EudraVigilance for drug safety monitoring.
- *Supporting the central role of the PRAC in assessing and monitoring the safety of human medicines in the EU*, including prioritising and assessing safety signals. In 2017, the PRAC prioritised and assessed 82 signals, of which 63.4% included data from EudraVigilance as their source. Thirty-three (40%) of the assessed signals resulted in a recommendation for an update of the product information for patients and healthcare professionals, thus providing updated guidance and increasing the safe and effective use of the medicines. In two of these cases, the PRAC also recommended a Direct Healthcare Professional Communication (DHPC) to highlight new important safety information to prescribers. One signal is being further evaluated through a referral procedure. In 20 cases (24%) a continuation of routine safety monitoring of the medicine was considered sufficient. The evaluation of 28 signals (34%) was ongoing at the end of 2017.
- *Training and support activities*, many of which were open to all stakeholders, included 5 information days (3 EV, 1 Signal Management, and 1 on measuring impact of PV activities), 3 training sessions on EudraVigilance Data Analysis, including two sessions on the redesigned data analysis system (EVDAS) incorporating the enhanced functionalities which trained 46 experts from 23 NCAs. Additionally, 36 training sessions on EudraVigilance ICSR submissions (8 for the previous EV format, 28 for the new format) and 5 training sessions on submitting medicinal product information via the eXtended EudraVigilance Medicinal Product Dictionary (XEVMPD) were

delivered, while 226 users followed training on the XEVMPD via its e-learning platform. In preparation for the new EudraVigilance system, 15 and 26 webinars were organised for the NCAs and MAHs, respectively, to aid with operational and technical issues.

- *Continued public access to aggregated EudraVigilance data.* Public access has been available since 2012 via aggregated reports available at www.adrreports.eu. The functionality was enhanced in 2017 to include additional outputs such as case line listings and ICSR forms. At the beginning of 2018, data was publicly available for a total of 2,680 active substances (including 666 substances in 991 centrally authorised medicinal products (CAPs) and 2,014 substances in nationally authorised products).

1. Development of new functionalities

Technical improvements of EudraVigilance progressed over previous years. Following various phases of system development and user testing and a successful audit, the new improved EudraVigilance was launched on 22 November 2017. The EudraVigilance Expert Working Group (EV-EWG) advises the pharmacovigilance governance structure of the European Union (EU) regulatory network on aspects of the EudraVigilance system.

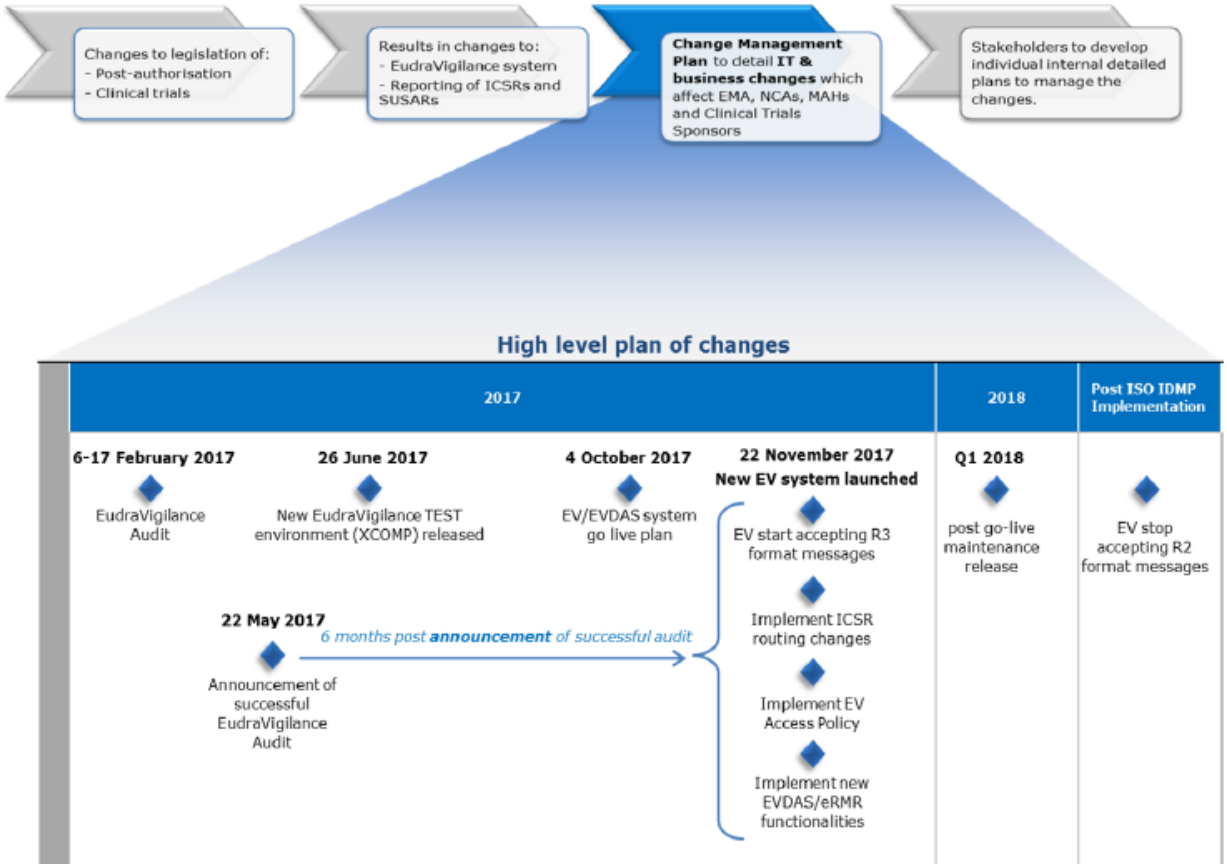


Figure 2. EudraVigilance change management plan[3] summarising the 2017 milestones in the delivery of new EV system launched on 22 November 2017.

[3] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000165.jsp&mid=WC0b01ac0580a69263

EudraVigilance functionalities subject to audit

The new EudraVigilance system successfully passed an independent audit in accordance with Article 24 of Regulation (EC) 726/2004 that took place in February and April 2017. On 22 May 2017, the EMA Management Board confirmed[4] that the full functionality of the EudraVigilance database had been achieved and that the system met the defined functional specifications. The new EudraVigilance system went live for users and stakeholders on 22 November 2017.

New and enhanced functionalities support:

- Simplification of the reporting of ADRs, in particular for MAHs for whom EudraVigilance has become the sole reporting point in the EEA, with subsequent re-routing of ICSRs to the Member States where the adverse reactions occurred;
- Direct and faster provision of EEA adverse reaction reports to the World Health Organisation (WHO) Uppsala Monitoring Centre;
- Enhancements to safety signal detection and analysis tools for NCAs and EMA;
- Increasing EudraVigilance access for MAHs to allow them to fulfil their pharmacovigilance obligations and to validate safety signals via examination of ICSRs;
- Increased access to EudraVigilance data for healthcare professionals, the public and researchers;
- The use of internationally agreed formats, standards and terminologies (such as the ISO ICSR E2B(R3) format) resulting in improved data quality and better data analysis possibilities.

To support EudraVigilance stakeholders and partners during this period of changes, EMA published important information on the EudraVigilance system including a stakeholder change management plan (revision 2 and 3), a communication plan, a training plan (revision 2), several e-learning materials and user manuals and the EudraVigilance go-live plan.

Medicinal product information

In compliance with Article 57 of Regulation (EC) No. 726/2004, the XEVMPD provides a dictionary of all medicinal products and substances on the EU market and is used to identify the products in reports of suspected ADRs, to coordinate pharmacovigilance procedures, to calculate pharmacovigilance fees and to facilitate transparency. To fully utilise the medicinal product data collected in the XEVMPD, the Agency increased its data validation activities to ensure the accuracy of the information. The Agency also created the Article 57 dashboards which were released to NCAs in 2016 and 2017. For the first time, these dashboards allow competent authorities to directly access the data held in the XEVMPD. The database is also relied upon to provide the name and contact details of the Qualified Person Responsible for Pharmacovigilance (QPPV) for each authorised medicine in the EU and the location of the Pharmacovigilance System Master File (PSMF) of the MAH. Details on the collection of submissions are in Annex III and on the data quality activities in Annex IV.

Medical literature monitoring

The EU pharmacovigilance legislation[5] introduced an obligation on the Agency to monitor selected medical literature for reports of suspected adverse reactions to medicinal products containing certain active substances and to enter relevant information into the EudraVigilance database. This enhances

[4] http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/05/WC500228158.pdf
[5] Regulation (EC) No. 726/2004, Article 27

the efficiency of reporting, reduces duplicate reports in the database and provides a simplification for industry stakeholders. The process aims to alleviate the burden for as many MAHs as possible, provide quality controlled literature-monitoring services and allow MAHs to comply with the regulatory requirements. The service has been in full operation since September 2015 and covers 300 chemical substance groups and 100 herbal substance groups.

In 2017, 222,937 unique literature references were reviewed and the outcome published on a daily basis. The review of these literature articles resulted in 14,193 adverse drug reaction reports, referring to 6,790 individual cases, being entered into EudraVigilance in 2017 and made available to NCAs and MAHs.

2. Data collection and data quality

One of the deliverables[6] of the pharmacovigilance legislation is the electronic submission by MAHs of a core dataset for all medicinal products authorised in the EU (Article 57 of Regulation (EC) No. 726/2004). In 2012, the Agency published a Legal Notice and an electronic submission format for this medicinal product data. In 2014, the format was amended to include additional elements, most notably the Summary of Product Characteristics, and data have subsequently been collected in this new format since 2015 (as part of the XEVMPD which currently supports the medicinal product submissions). The primary objective of this database was to facilitate data analysis and signal detection to support better safety monitoring for patients. In 2017, EMA published a note for clarification related to pharmacovigilance requirements and EudraVigilance access for traditional herbal medicinal products and simplified registrations for homeopathic medicinal products[7].

Medicinal product information

The total number of individual medicinal products for which submissions have been received from MAHs as of 24 January 2018 is 744,219 regardless of their current authorisation status (e.g. valid, withdrawn, etc.). These submissions provide a dataset of authorised medicines on the EU market (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 better identification of products in EudraVigilance ADR reports, better coordination of safety monitoring, faster implementation of new safety warnings and improved communication with and transparency for stakeholders. The dataset also includes information on the location of the Pharmacovigilance System Master File (PSMF), which was available for over 99.5% products. Full details on these are presented in Annex III.

Reporting of ADR reports and patient involvement

Every report of a suspected ADR submitted by a patient or healthcare professional contributes to safety monitoring and thus to the safe and effective use of medicines. Additionally, robust research[8] 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 EU pharmacovigilance system.

In 2017, 1,471,596 reports related to suspected adverse reactions were collected and managed in EudraVigilance, 543,548 of which originate from the EEA. This is an overall 19% increase and a 60% increase in EEA reporting compared to 2016. This can attributed to two factors. Throughout the year

[6] Regulation (EC) No. 726/2004, Article 57(2), second subparagraph
[7] http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2017/03/WC500222351.pdf
[8] 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.

there was slightly more reporting per month, but the major increase is due to the reporting of non-serious ICSRs after the go-live of the new EV system in November 2017. The number of reports submitted directly by European patients and consumers through the NCAs and MAHs (90,358) also increased significantly in 2017 for the same reasons.

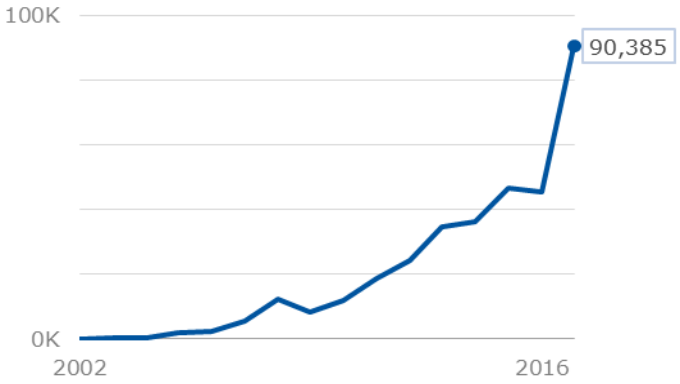


Figure 3. Trend of ADR reports received by European patients and consumers through the NCAs and MAHs.

In summary, the figures this year already show the effect of the new system that only went live on 22 November 2017, mainly due to the mandatory reporting of non-serious ICSRs in the EEA. 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[9] for which details are also provided in Annex II.

Data Quality

Data quality assurance is vital to support pharmacovigilance and provides the basis for successful data analysis, scientific assessment and decision making 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 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 and details on the development of EudraVigilance functionalities are provided in Section 1 of this report.

[9] 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

3. Data analysis

EudraVigilance monitoring is a collaborative effort between NCAs and the Agency. Since November 2017, MAHs also have access to comply with their signal detection and monitoring obligations. The safety information contained in EudraVigilance is continuously screened using statistical reports called electronic Reaction Monitoring Reports (eRMRs). These are produced every two weeks for products subject to additional monitoring and monthly, or less frequently, for other products. In 2017, a total of 21,496 such outputs were produced and provided to the EU network for review. All registered NCA and EMA users also have the option to perform further analyses in the EudraVigilance Data Analysis System (EVDAS). These include individual case line listings with detailed information on each case or disproportionality analyses to analyse reporting trends.

Screening of these outputs is one of the sources of validated signals, i.e. potential new associations or new aspects of known associations between medicines and adverse drug reactions which may be caused by the medicine. For active substances of nationally authorised products the monitoring of ADR reports is shared between the NCAs as per the 'List of substances and products subject to worksharing for signal management[10]', which indicates a Lead Member State for each included substance; the NCAs also monitor all nationally authorised medicines for which no Lead Member State has been appointed. For centrally authorised products, EMA leads the monitoring; of 2,062 potential signals which were reviewed by the Agency in 2017, around 82% originated from EudraVigilance, highlighting its central role for ADR data monitoring.

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 2017 was 82, compared with 94 in 2016. Of these 82 signals, 43 were validated by the Agency and 39 were validated by the MSs; overall, 63.4% included data from EudraVigilance as their source. The issues included disorders of the skin, kidneys, liver, drug interactions, cardiovascular issues, infections, issues arising from medication errors/drug abuse, drug use in pregnancy etc.

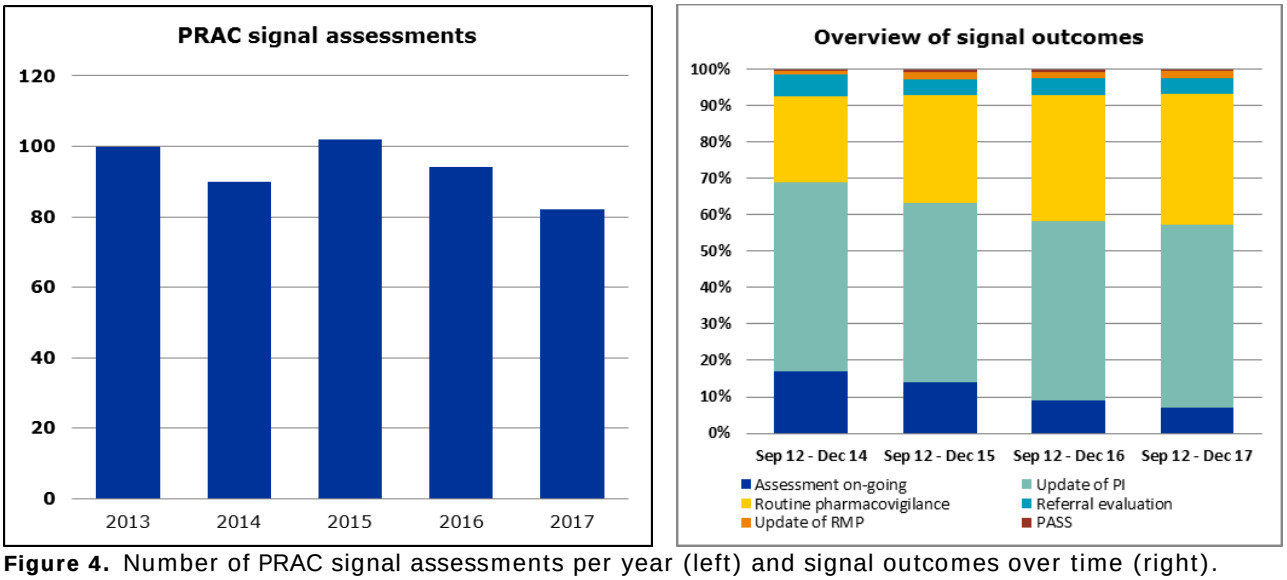


Figure 4. Number of PRAC signal assessments per year (left) and signal outcomes over time (right).

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

Thirty-three (40%) of the 82 assessed signals resulted in a recommendation for an update of the product information for patients and healthcare professionals (HCPs), thus providing updated guidance and increasing the safe and effective use of the medicines. In two of these cases, the PRAC also recommended a Direct Healthcare Professional Communications (DHPC) to highlight new important safety information to prescribers. One signal is being further evaluated through a referral procedure. In 20 cases (24%) continuing with routine safety monitoring of the medicine was considered sufficient. The evaluation of 28 signals (34%) is currently ongoing, including 17 via a follow up signal procedure and 11 in the next PSUR/PSUSA.

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 2017 can be found in Annex V. The progress of process improvements and simplifications in signal management is detailed in Annex VI.

4. 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, to include further outputs such as case line listings and case report forms. At the end of 2017, data was publicly available for a total of 2,680 active substances (including 666 substances in 991 centrally authorised medicinal products (CAPs) and 2,014 substances in nationally authorised products).

Access to EudraVigilance data is governed by the EudraVigilance Access Policy[11] which had previously been updated in preparation to enhanced access for Marketing Authorisation Holders (MAHs) as well as researchers. The revised policy entered into force in November 2017, six months after the Management Board announced that the EudraVigilance database had achieved full functionality[12], based on an independent audit report.

In 2017, the EMA organised three industry stakeholder platform meetings which supported further development of EudraVigilance and which were designed to aid MAHs with change management. Additionally, an annual stakeholder forum on the pharmacovigilance legislation was organised.

Three 'What's new in Pharmacovigilance QPPV updates' were published on the Agency's website[13]. These provided EU Qualified Persons responsible for Pharmacovigilance (QPPVs) with information on recent developments in EU pharmacovigilance relating to medicines for human use and included updates on the EU network activities and 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 supports better and faster updates to product information wording.

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, 67 requests were answered with a median of 10 working days. Nearly 50% of all requests were received from the

[11] http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/12/WC500218300.pdf
[12] http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/05/WC500228158.pdf
[13] http://www.ema.europa.eu/docs/en_GB/document_library/Newsletter/2017/04/WC500225787.pdf
http://www.ema.europa.eu/docs/en_GB/document_library/Newsletter/2017/08/WC500233161.pdf
http://www.ema.europa.eu/docs/en_GB/document_library/Newsletter/2017/12/WC500240764.pdf

EU regulatory network, supporting the scientific assessment of pharmacovigilance procedures. An increase was also observed in requests from HCPs and the public. 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:

- 5 information days (3 EV, 1 Signal Management, and 1 Measuring impact of PV activities),
- 3 training sessions on EudraVigilance Data Analysis in total including two sessions on the redesigned EVDAS incorporating the enhanced functionalities, training 46 experts from 23 NCAs,
- 36 training sessions on EudraVigilance ICSR submissions (8 for the previous EV format, 28 for the new format),
- 5 training sessions on the XEVMPD,
- 226 users followed training on XEVMPD via its e-learning platform,
- 15 and 26 webinars were organised for the NCAs and MAHs, respectively, to aid with operational and technical issues in preparation for the new EudraVigilance system.

5. Conclusion

EudraVigilance underwent a major development programme in recent years which in 2017 resulted in a successful audit outcome. Subsequently, on 22 November 2017 the new improved EudraVigilance system was launched.

EudraVigilance now holds information on more than 12.45 million safety reports, referring to 7.95 million cases, as well as information on 744,219 medicinal products on the EU market. This EU resource is now being used for regular signal detection by EMA and NCAs, support of other pharmacovigilance procedures in terms of scope and data analysis, and the calculation of pharmacovigilance fees. Furthermore, making all ICSRs from the EEA available to the World Health Organisation (WHO) Uppsala Monitoring Centre (UMC) directly from EudraVigilance contributes to global pharmacovigilance.

Access to EudraVigilance for MAHs was initiated in 2017, to allow them to comply with their monitoring obligations. Improved access to EudraVigilance data is also being provided for healthcare professionals, the public and academia. With the simplifications in reporting of ADRs and improvements in the tools for their analysis and monitoring, EudraVigilance is contributing to optimising the benefit-risk balance of medicines and thus to protection and promotion of public health.

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 implemented in 2017. Maintenance continued.
Data quality review and duplicate management of adverse reaction reports in EudraVigilance [Legal basis: Regulation (EC) 726/2004, Article 24(3)]	Continued during 2017
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 2017
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 2017
Operation of the signal management processes based on EudraVigilance data, including the monthly provision of e-RMRs to lead Member State for non-CAPs [Legal basis: Regulation (EC) 726/2004, Article 28a Directive 2001/83/EC, Article 107h Commission Implementing Regulation (EU) 520/212, Article 21]	Continued during 2017
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 2017
Operation of the Medical Literature Monitoring service [Legal basis: Regulation (EC) 726/2004, Article 27]	Continued during 2017

Annex II – EudraVigilance data-processing network and number of suspected adverse drug 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 99.7% of the time throughout the year with its lowest point in April at 97.38% (figure 4). This breached the requirement to be available 98% of the time. Only unplanned downtime is taken into consideration, so the downtime around the transfer to the new EV system is not displayed.

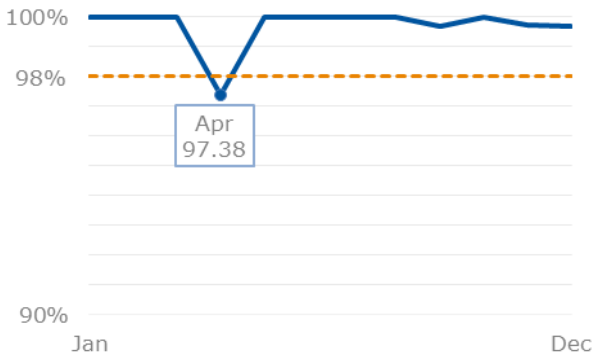


Figure 5. EudraVigilance gateway availability per month. The requirement is 98%. Please note that the scale starts at 90%. Planned downtime is excluded.

EudraVigilance database

For medicinal products authorised in the EEA, adverse drug reaction reports are collected from both within and outside the EEA. By 31 December 2017, the EudraVigilance database held a total of 12,451,826 ADR reports, referring to 7,948,873 individual cases (figure 5). The post-authorisation module (EVPM) contained 11,392,043 ADR reports (7,546,183 cases) and the clinical trial module (EVCTM) 1,059,783 reports (402,690 cases).

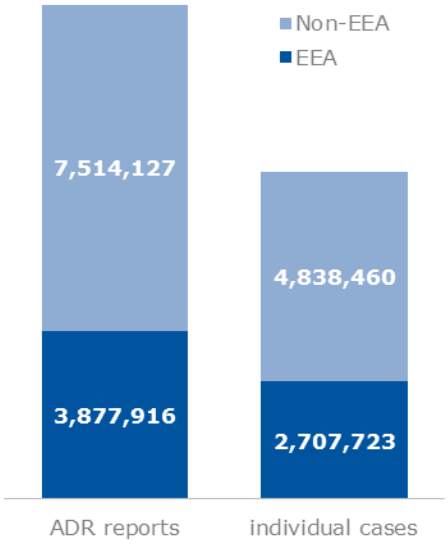


Figure 6. Number of ADR reports versus individual cases received in the EudraVigilance database from its inception in December 2001 until 31 December 2017 split by origin of the report in- or outside the EEA.

The numbers presented in figure 6 and 7 refer to the ADR reports received in the post-authorisation module (EVPM). A total of 11,392,043 EVPM ADR reports had been processed by the end of 2017 from the beginning sixteen years ago. 1,471,596 EVPM ADR reports were processed in 2017. This is a significant increase of 19% as compared to last year (figure 6), and can largely be attributed to the transfer to the new EV system that went live in November 2017 and which made it mandatory to submit non-serious ADR reports from within the EEA. Up to November on average 117,154 ADR reports were received and processed per month (figure 4) which was already higher than last year. In December, by contrast, 182,907 ADR reports were processed. ADR reports are subsequently made available for signal detection and data analysis by the Agency and national competent authorities in the Member States.

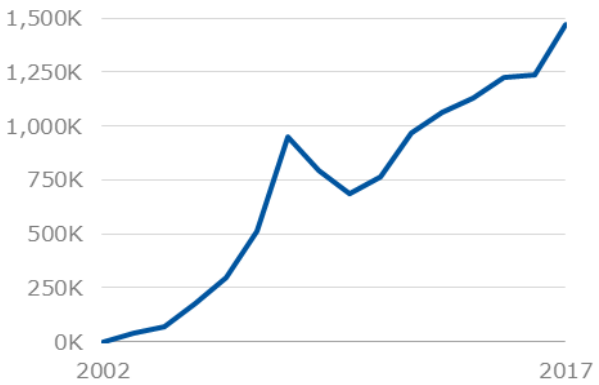


Figure 7. Number of ADR reports processed per year in EVPM.

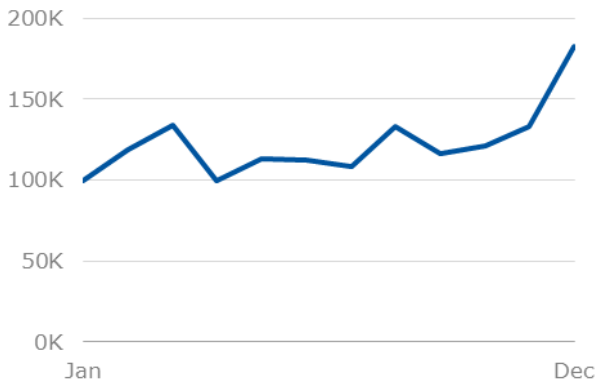


Figure 8. Number of ADR reports processed per month in EVPM in 2017.

Figure 9 presents the total number of ADR reports received in EVPM grouped by EEA and non-EEA for 2017 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).

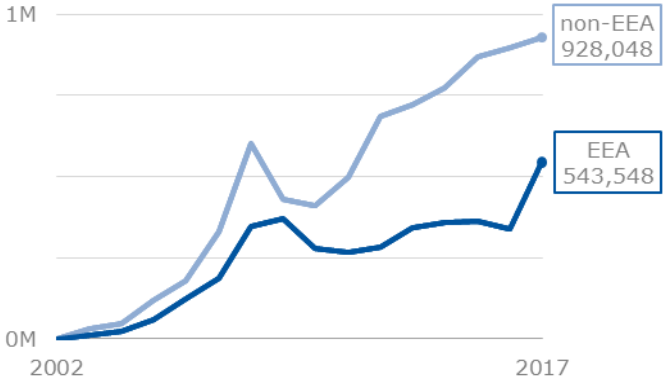


Figure 9. Number of ADR reports processed per year in EVPM split by cases occurred inside and outside the EEA.

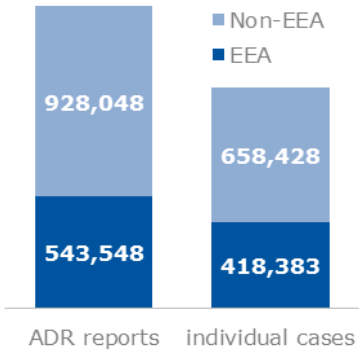


Figure 10. Number of ADR reports versus the number of individual cases in 2017 in EVPM.

In 2017, 90,385 ADR reports were submitted by European patients and consumers through the NCAs and MAHs, referring to 84,372 individual cases. This is an increase of 99% over the previous year (figure 11).

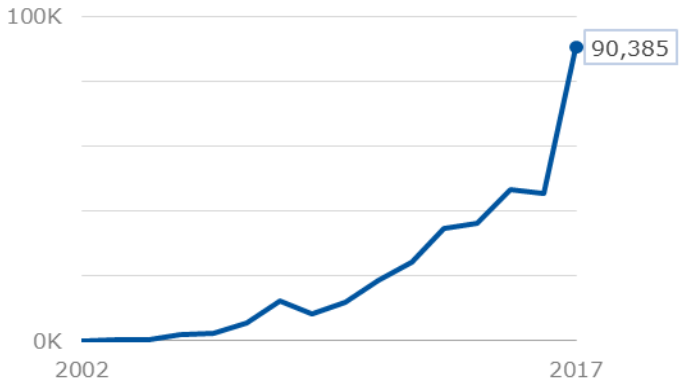


Figure 11. Number of ADR reports by European patients and consumers through the NCAs and MAHs.

E-reporting status for Marketing Authorisation Holders and sponsors of clinical trials

- A total of 1,070 MAHs (at headquarter level) have sent reports to the EudraVigilance Post-authorisation Module (EVPM) in the period between 1 January 2002 and 31 December 2017.
- A total of 1,042 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 2017.
- A total of 18,676 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 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.

Since 22 November 2017 until the end of the year, 65,251 ICSRs were rerouted to NCAs. 99,604 ICSRs were forwarded to WHO. A total of 26,653 download requests were made for a total of 1,851,433 ICSR downloads.

Table 1. Number of ADR reports and unique cases transmitted by MAHs and sponsors to EVPM and EVCTM in 2017.

EV Module	Transmission type	#
EVPM	ADR reports	1,096,891
	Individual cases	713,103
EVCTM	ADR reports	94,549
	Individual cases	34,160

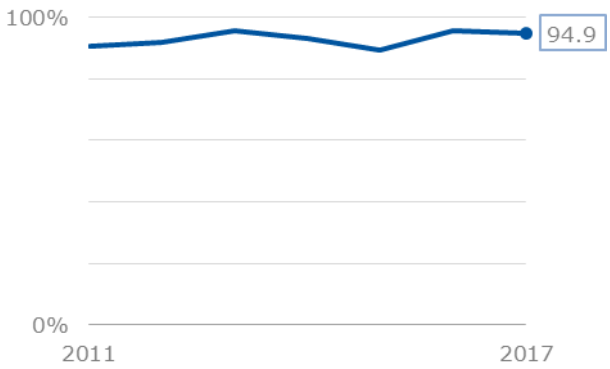


Figure 12. 15-day compliance rate to EVPM for all MAHs and sponsors by year.

E-reporting status for National Competent Authorities

- All 32 NCAs are authorised in production with 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 1,220 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.

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 following that day to transmit the reports.

For the re-transmission of reports originally transmitted to NCAs by MAHs, the receipt date is the date the NCA received the most recent information from the MAH, not the date that the MAH received the most recent information from the original reporter. 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 2017

EV Module	Transmission type	#
EVPM	ADR reports	256,650
	Individual cases	187,503
EVCTM	ADR reports	6,015
	Individual cases	2,636

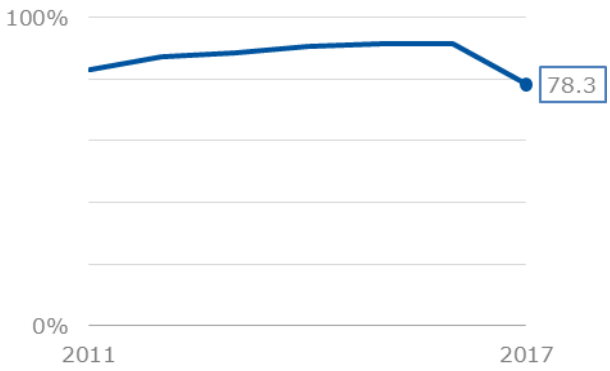


Figure 13. 15-day compliance rate to EVPM for all NCAs by year. The drop is caused by a large batch submission of ICSRs sent in 2017 from one NCA due to a system upgrade over the course of 2016 and 2017. Not considering the batch submission would show a compliance rate similar to previous years.

During 2017, 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)

- Romania (National Agency for Medicines and Medical Devices)
- United Kingdom (Medicines & Healthcare Products Regulatory Agency).

EudraVigilance database and support of signal management process

A total of 21,496 electronic Reaction Monitoring Reports (eRMRs) were generated in 2017 to facilitate the continuous monitoring of the safety of medicines by the Agency and NCAs in the EEA. Of these,

- 12,412 were routine eRMRs, produced monthly,
- 1,034 were 3-monthly eRMRs.
- 834 were 6-monthly eRMRs,
- 7,216 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 Periodic Safety Update Report(s) 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 being validated by the Agency (see Annex IV for a summary of the validations performed in 2017). Table 3, below and its associated figures, provides a summary of the data resubmitted in the new format as of 24 January 2018.

Table 3. Summary of medicinal product submissions to the XEVMPD

Total number of medicinal product submissions in new format by MAHs by 24 January 2018 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	744,219
Total number of marketing authorisation holders (legal entities) established in the EU (corresponding to EudraVigilance codes)	4,916

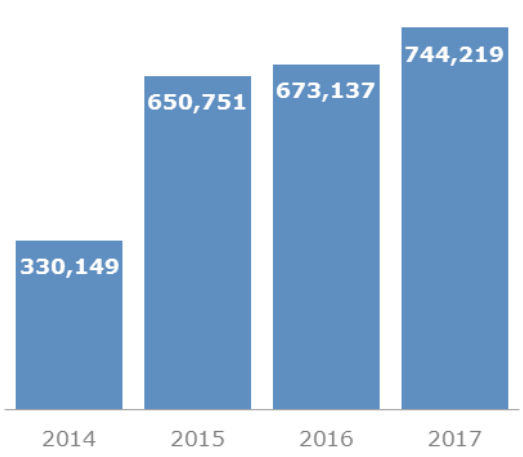


Figure 14. Total number of medicinal products (counted on the basis of EudraVigilance codes) resubmitted in the new format (cumulative by year)

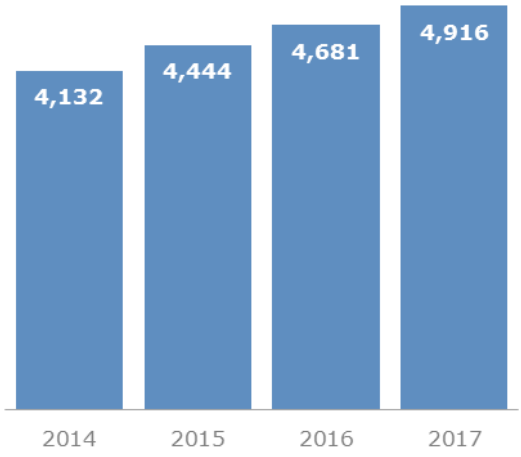


Figure 15. Total number of marketing authorisation holders (legal entities) established in the EU (corresponding to EudraVigilance codes) (cumulative by year)

The EudraVigilance code is the level to which a product is defined in the context of the Article 57(2).

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 2017.

Table 4. Summary of EudraVigilance data quality activities in 2017

Data quality area	Activities performed	2017	2016	2015
Identifying and managing duplicates	Duplicate couples assessed	275,020	72,655	31,797
	Master reports generated based on duplicated data	133,635	48,111	40,022
Coding of reported medicines and active substances	Reported medicinal products and active substance terms recoded	35,727	91,650	29,424
	ADR reports recoded (ICSRs)	41,124	64,686	54,535
Providing feedback on data quality	Organisations subject to ICSR data quality review	125	120	51
	Medicinal products in XEVMPD quality reviewed (and corrected if necessary)	369,073	235,058	362,858

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 2017, the EMA's signal management team reviewed in detail the information on 2,062 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 a minimal change (-1%) compared to the previous year.

Potential signals reviewed	2017	2016	2015	2014	2013
Total	2,062	2,076	2,372	2,030	2,449
difference	-14	-296	342	-419	236
% compared to previous	-1%	-12%	17%	-17%	11%

Overall the major source of EMA potential signals in 2017 continues to be EudraVigilance, from which 81.8% of potential signals originated (82.7% in 2016). In addition to EudraVigilance, an increase in potential signals from the scientific literature was also observed, now representing 16.5% of potential signals (13.9% in 2016). A further 1.2% originated from communications received from other regulatory authorities (5 from the FDA, 7 from PMDA/MHLW, 12 from Health Canada) and 0.5% from other sources. The overview by action taken is provided below:

Action taken	Number of potential signals 2017	% of total	Number of potential signals 2016	% of total
Not validated (closed)	1,669	80.9%	1,748	84.2%
Monitored	128	6.2%	100	4.8%
Ongoing	222	10.8%	180	8.7%
Prioritised and assessed by PRAC	43	2.1%	48	2.3%
Total	2,062	100.0%	2,076	100.0%

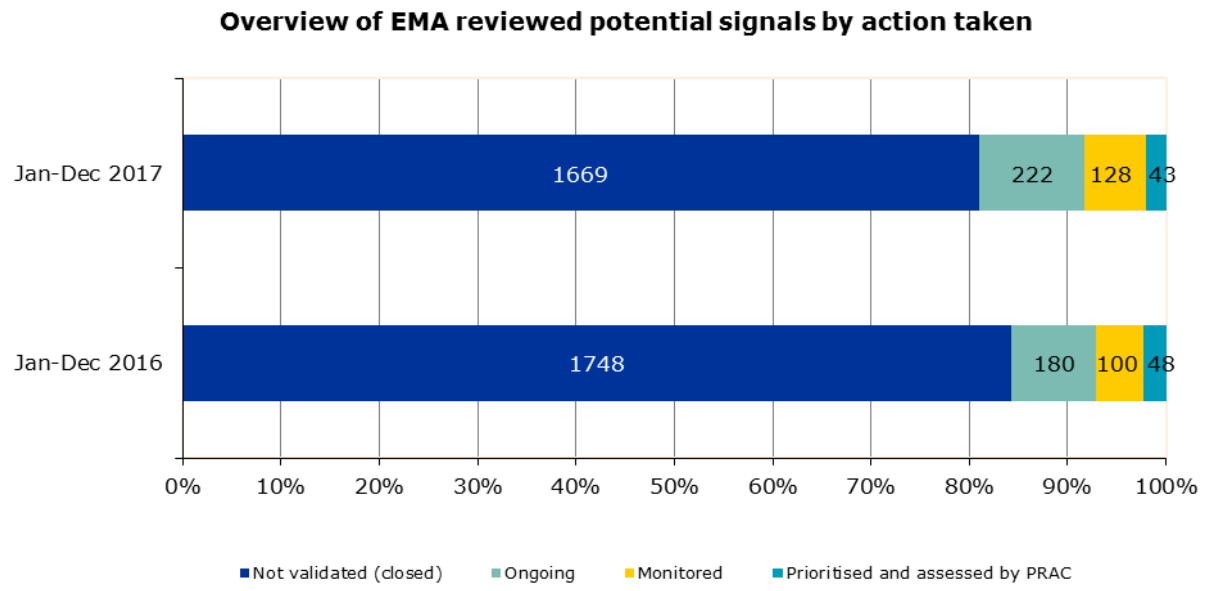


Figure 16. Overview of EMA reviewed potential signals by action taken.

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 2017 was 82, compared with 94 in 2016. Of these 82 signals, 43 were validated by the Agency and 39 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 63.4% included data from EudraVigilance as their source.

Thirty-three (40%) of the assessed signals resulted in a recommendation for an update of the product information for patients and healthcare professionals, thus providing updated guidance and increasing the safe and effective use of the medicines. In two of these cases, the PRAC also recommended a Direct Healthcare Professional Communication (DHPC) to highlight new important safety information to prescribers. One signal is being further evaluated through a referral procedure. In 20 cases (24%) continuing with routine safety monitoring of the medicine was considered sufficient. The evaluation of 28 signals (34%) is currently ongoing, including 17 via a follow up signal procedure and 11 in the next PSUR/PSUSA.

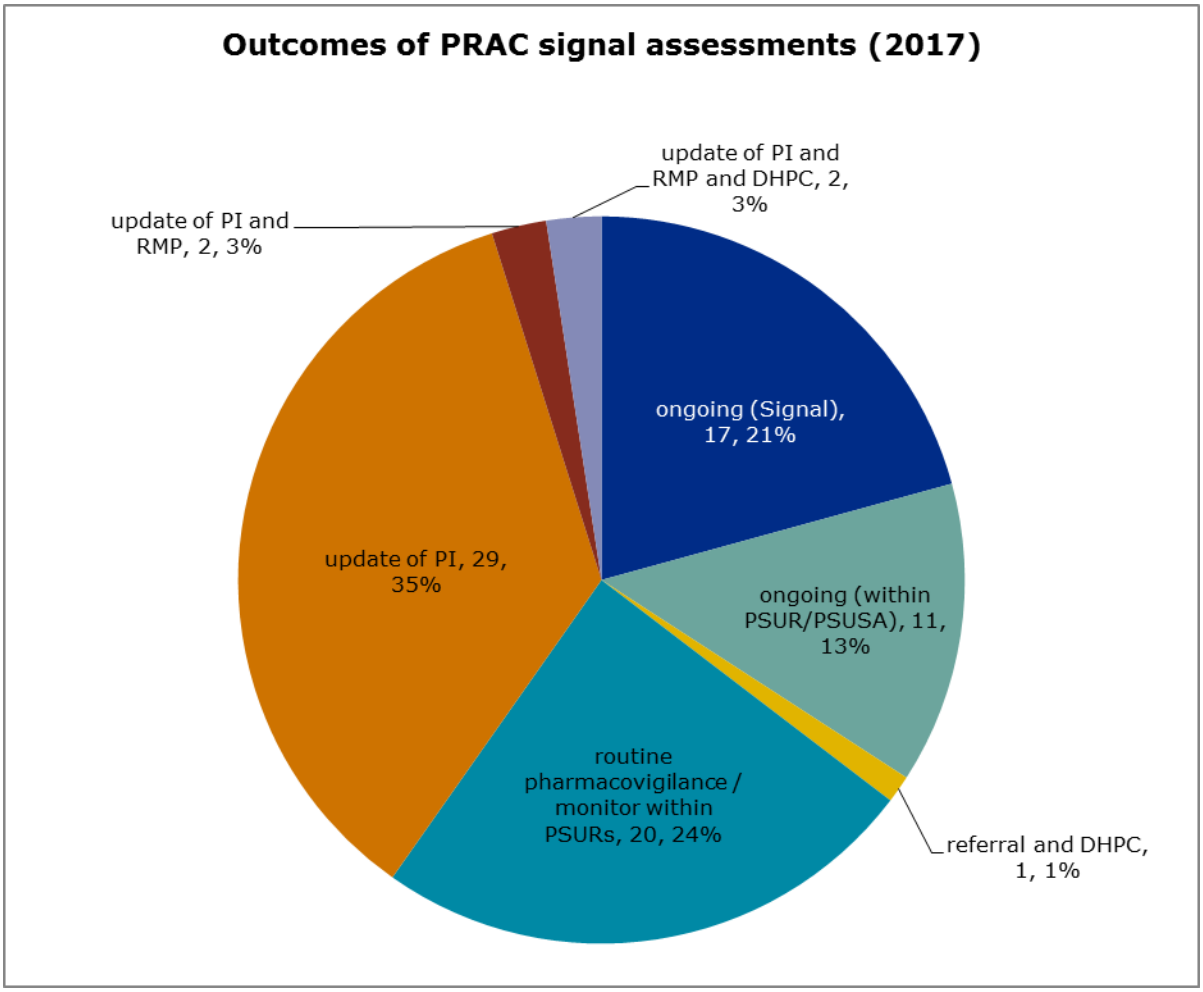


Figure 17. Outcomes of PRAC signal assessments (2017). PI: product information, DHPC: Direct Healthcare Professional Communication, RMP: Risk Management Plan, PSUR: Periodic Safety Update Report, PSUSA: PSUR Single Assessment.

A list of all signals prioritised and assessed by the PRAC in 2017 is provided below, noting the latest status or outcome as of 31 December 2017.

Drug	Issue / signal	Status or outcome
Acetazolamide	Acute generalised exanthematous pustulosis (AGEP)	update of PI
Albiglutide	Acute kidney injury	update of PI
Amitriptyline	Risk of drug induced liver injury (DILI) and hepatocellular injury	routine pharmacovigilance / monitor within PSURs
Amlodipine; rifampicin	Drug interaction between amlodipine and rifampicin leading to reduced antihypertensive effect of amlodipine	update of PI
Amoxicillin	Drug Rash Eosinophilia Systemic Symptoms (DRESS) syndrome	update of PI
Apixaban; dabigatran etexilate; edoxaban; rivaroxaban	Cholesterol embolisms	ongoing (Signal)
Azacitidine	Pericarditis and pericardial effusion	update of PI
Azithromycin	Increased rate of relapses of haematological malignancies and mortality in haematopoietic stem cell transplantation (HSCT) patients with azithromycin	ongoing (Signal)
Azithromycin; tobramycin inhaled	Possible interaction between tobramycin and azithromycin leading to lower effectiveness of tobramycin	routine pharmacovigilance / monitor within PSURs
Baricitinib	Pneumonia	ongoing (Signal)
Brentuximab vedotin	Cytomegalovirus (CMV) reactivation	update of PI
Cefalexin	Acute generalized exanthematous pustulosis (AGEP)	ongoing (Signal)
Cladribine	Progressive multifocal leukoencephalopathy (PML)	update of PI and RMP and DHPC
Clarithromycin; erythromycin; azithromycin; roxithromycin	Acute generalised exanthematous pustulosis (AGEP)	update of PI
Dabigatran; lovastatin; simvastatin	Major haemorrhage following dabigatran interaction with simvastatin or lovastatin	routine pharmacovigilance / monitor within PSURs
Dabrafenib; trametinib	Sepsis	routine pharmacovigilance / monitor within PSURs
Daratumumab	CMV reactivation	ongoing (within PSUR/PSUSA)
Darbepoetin alfa	Incorrect use of device associated with adverse reactions including underdose, drug dose omission, accidental exposure to product	update of PI

Drug	Issue / signal	Status or outcome
	and injection site reactions	
Darbepoetin alfa; epoetin alfa; epoetin beta; epoetin theta; epoetin zeta Methoxy polyethylene glycol-epoetin beta	Severe cutaneous adverse reactions (SCARs) including Stevens - Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)	update of PI and RMP and DHPC
Dasatinib	CMV reactivation	ongoing (Signal)
Dasatinib; warfarin	Signal of serious adverse drug reactions (ADRs) including bleeding events following potential drug interaction between dasatinib and warfarin	ongoing (within PSUR/PSUSA)
Dexlansoprazole; lansoprazole	Unexpected histopathological findings from a juvenile rat toxicity study	routine pharmacovigilance / monitor within PSURs
Dexmedetomidine	Polyuria	update of PI
Docetaxel	Unexpected seriousness of the reported adverse drug reactions with docetaxel and suspicion of an increase in the adverse drug reactions (ADR) reporting rate in France with docetaxel containing-products	routine pharmacovigilance / monitor within PSURs
Doxycycline	Doxycycline induced Jarisch-Herxheimer reaction	update of PI
Dulaglutide	Gastrointestinal stenosis and obstruction	ongoing (Signal)
Efavirenz, tenofovir, emtricitabine	Autoimmune hepatitis	ongoing (Signal)
Eltrombopag	Laboratory test interference, interference with bilirubin assay	ongoing (within PSUR/PSUSA)
Enzalutamide	Hepatotoxicity	ongoing (within PSUR/PSUSA)
Everolimus; sirolimus; temsirolimus	Optic neuropathy and papilloedema	routine pharmacovigilance / monitor within PSURs
Exenatide	Cardiac arrhythmias	ongoing (within PSUR/PSUSA)
Exenatide	Incorrect use of device associated with (serious) adverse reactions including hyperglycaemia and hypoglycaemia	routine pharmacovigilance / monitor within PSURs
Filgrastim; lenograstim; lipegfilgrastim; pegfilgrastim	Aortitis	ongoing (Signal)
Flucloxacillin	High anion gap metabolic acidosis (HAGMA)	update of PI
Fluconazole	Spontaneous abortion and stillbirth	update of PI
Fulvestrant	Anaphylactic reactions	update of PI
Gabapentin	Respiratory depression without	update of PI

Drug	Issue / signal	Status or outcome
	concomitant opioid use	
Gefitinib	Recall phenomenon	routine pharmacovigilance / monitor within PSURs
GnRH Agonists:buserelin; goserelin; leuprorelin; triptorelin	Thromboembolic events	routine pharmacovigilance / monitor within PSURs
Human normal immunoglobulin	Lupus-like syndrome and related terms	ongoing (Signal)
Hydroxycarbamide	Cutaneous lupus erythematosus	ongoing (Signal)
Iloprost	Bradycardia	ongoing (within PSUR/PSUSA)
Insulin aspart; insulin degludec; insulin degludec, liraglutide; insulin detemir;insulin glargine; insulin glulisine; insulin human; insulin human, insulin isophane; insulin lispro; insulin porcine	Signal of potential increased risk of medication error associated with withdrawing insulin from pre-filled pens and cartridges, leading to dysglycaemia	update of PI
Intravenous fluids containing electrolytes and/or carbohydrates	Hyponatraemia	update of PI
Ipilimumab	Haematophagic histiocytosis	update of PI
Lapatinib	Pulmonary hypertension	ongoing (Signal)
Ledipasvir, sofosbuvir	Blood cholesterol increased, low density lipoprotein increased	routine pharmacovigilance / monitor within PSURs
Leflunomide; teriflunomide	Falsely decreased ionised calcium levels	update of PI
Lenalidomide	Hemophagocytic lymphohistiocytosis (HLH)	routine pharmacovigilance / monitor within PSURs
Levonorgestrel	Arthralgia	routine pharmacovigilance / monitor within PSURs
Levonorgestrel intrauterine device (IUD)	Anxiety, panic attacks, mood changes, sleep disorders and restlessness	routine pharmacovigilance / monitor within PSURs
Loperamide	Serious cardiac events with high doses of loperamide, mainly from abuse and misuse	update of PI and RMP
Lopinavir, ritonavir	Interaction possibly leading to decreased levothyroxine efficacy and hypothyroidism	ongoing (Signal)
Loratadine and desloratadine	Weight increased in children	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	ongoing (Signal)
Meningococcal group B vaccine (rDNA, component, adsorbed)	Arthritis and synovitis	ongoing (within PSUR/PSUSA)

Drug	Issue / signal	Status or outcome
Meropenem; ciprofloxacin	Incompatibility leading to possible precipitation when co-administered intravenously	update of PI
Mesalazine	Risk of photosensitivity reactions	update of PI
Methotrexate	Pulmonary alveolar haemorrhage	ongoing (Signal)
Nivolumab	Pemphigoid	update of PI
Nivolumab	Tumour lysis syndrome	ongoing (within PSUR/PSUSA)
Nivolumab; pembrolizumab	Transplant rejection	update of PI and RMP
Paracetamol	Paracetamol use in pregnancy and child neurodevelopment	routine pharmacovigilance / monitor within PSURs
Pembrolizumab	Sarcoidosis	update of PI
Pemetrexed	Nephrogenic diabetes insipidus	ongoing (Signal)
Phenprocoumon	Risk of birth defects and foetal loss following first trimester exposure as a function of the time of withdrawal	ongoing (Signal)
Pirfenidone	Colitis	routine pharmacovigilance / monitor within PSURs
Pramipexole	Dystonia	update of PI
Prednisolone; prednisone	Induced scleroderma renal crisis	update of PI
Propofol; valproate and related substances	Pharmacokinetic drug interaction between propofol and valproate leading to an increased propofol exposure	update of PI
Proton pump inhibitors (PPIs): dexlansoprazole; esomeprazole; lansoprazole; omeprazole; pantoprazole; rabeprazole	Chronic kidney disease (CKD) and progression to end stage renal disease (ESRD)	routine pharmacovigilance / monitor within PSURs
Radium-223	Signal of fractures and fatal cases in chemotherapy-naive patients	referral and DHPC
Rivaroxaban	Increased risk of bleeding due to an interaction with macrolide antibiotics	ongoing (within PSUR/PSUSA)
Rivaroxaban	Oesophagitis	ongoing (within PSUR/PSUSA)
Selexipag	Fatal cases in patients with pulmonary arterial hypertension (PAH)	routine pharmacovigilance / monitor within PSURs
Sodium iodide [131I]	Hyperparathyroidism and parathyroid adenomas	update of PI
Telmisartan; telmisartan, hydrochlorothiazide; telmisartan, amlodipine	Risk of psoriasis or exacerbation of psoriasis	routine pharmacovigilance / monitor within PSURs
Temozolomide	Herpetic meningoencephalitis	update of PI
Teriflunomide	Lymphoma	ongoing (within PSUR/PSUSA)
Tick-borne encephalitis vaccine	Potential vaccination failure in	routine pharmacovigilance /

Drug	Issue / signal	Status or outcome
(inactivated)	children	monitor within PSURs
Tofacitinib	Angioedema	update of PI
Vortioxetine	Angioedema	ongoing (Signal)

Annex VI - Signal management in the EU

The Signal Management Review Technical Working Group is a working group of PRAC members supported by EMA staff, working on improvements and simplifications in 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). The progress achieved in 2017 is summarised below.

A major revision of the 'Good pharmacovigilance practices module IX – Signal management' was published in October 2017, updating the module with experience and with new provisions in preparation for MAH access to EudraVigilance for compliance with their monitoring requirements. The group also developed a standalone form for MAHs to notify the regulatory authorities of signals validated based on their monitoring of EV.

Work-sharing in signal management was further strengthened with respect to EV data on active substances authorised in more than one MS. More than 600 extra substances were allocated to lead MSs, bringing the total of substances in the work-sharing to nearly 1,700.

The group also advised on the monitoring frequency and the resulting production frequency of eRMRs, and advised on the practicalities of production of eRMRs to avoid peaks of workload.

The SMART Processes workstream implemented a pilot for adopting PRAC recommendations for signals without plenary discussion to optimise the use of PRAC time and resources. This applies to signals at the initial step of prioritisation and assessment where standard timetables are applied. The group also advised on the current practice of providing assessment reports for signals to MAHs leading to an earlier provision of the AR to MAHs (i.e. at the time of the first PRAC recommendation).

In the area of emerging safety issues (ESIs), a list of contact points at national authorities was provided on the EMA website to streamline communication from MAHs. The collated list of received ESIs is being routinely provided to the network, together with a list of safety issues communicated from non-EU regulatory agencies.

In terms of methods, the eRMR user manual was updated following the implementation of the ICH E2B(R3) standard on ICSRs.

The group performed a validation study on a new algorithm to detect unexpected increases in the frequency of reporting in EudraVigilance to aid the detection of safety issues. The study also resulted in a published scientific paper.

Lastly, in collaboration with Columbia University the group has tested a new method to improve signal detection in EV, automatically correcting for confounding and bias, referred to as SCRUB (Statistical Correction of Uncharacterised Bias).

Annex VII - Requests for information and documents

Further to the ADR information provided proactively on the website www.adrreports.eu, the EMA continued to answer requests for EV data. In 2017, 67 EudraVigilance requests were responded to and five of those received included one or more follow-up requests. A higher percentage of requests (49%) than in previous years originated from the EU regulatory network.

Requests for information (referred to also as frequency tables) and requests for access to documents (line listings) accounted for 29% and 64%, respectively, while the remaining 7% of requests concerned access to both information and documents or access to personal data and CIOMs forms. Requests related to centrally authorised products (CAPs) alone accounted for 41% of the total number of requests and 44% of requests were related to nationally authorised products (NAPs). An increase of 7% was observed in requests from the general public. The highest number of external requests was received from the UK and Germany (12% each).

The median response time for the requests was 10 working days (range 1-56 days). Two requests were responded to past the deadline due to their complexity, whilst a majority of the requests (70%) 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).

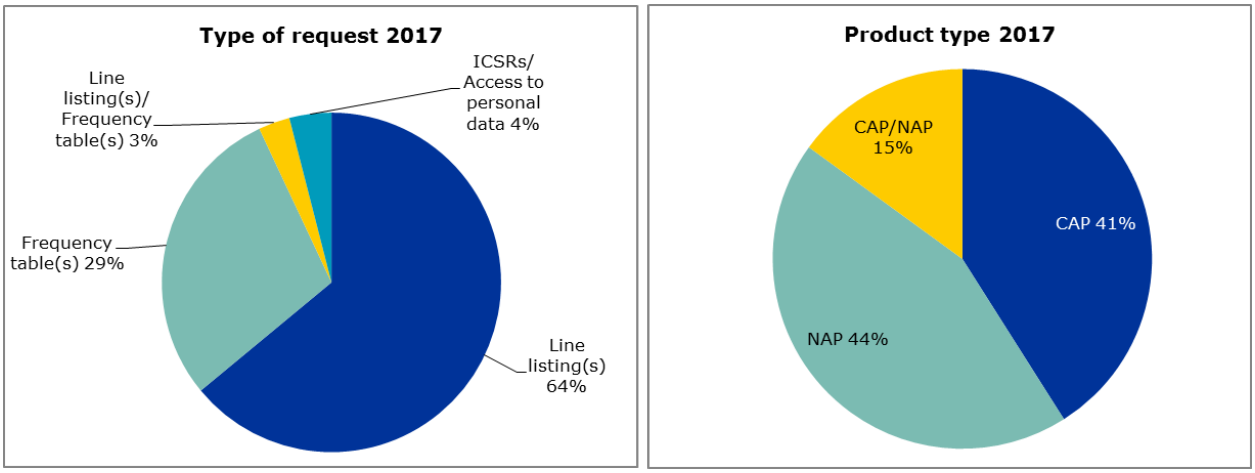
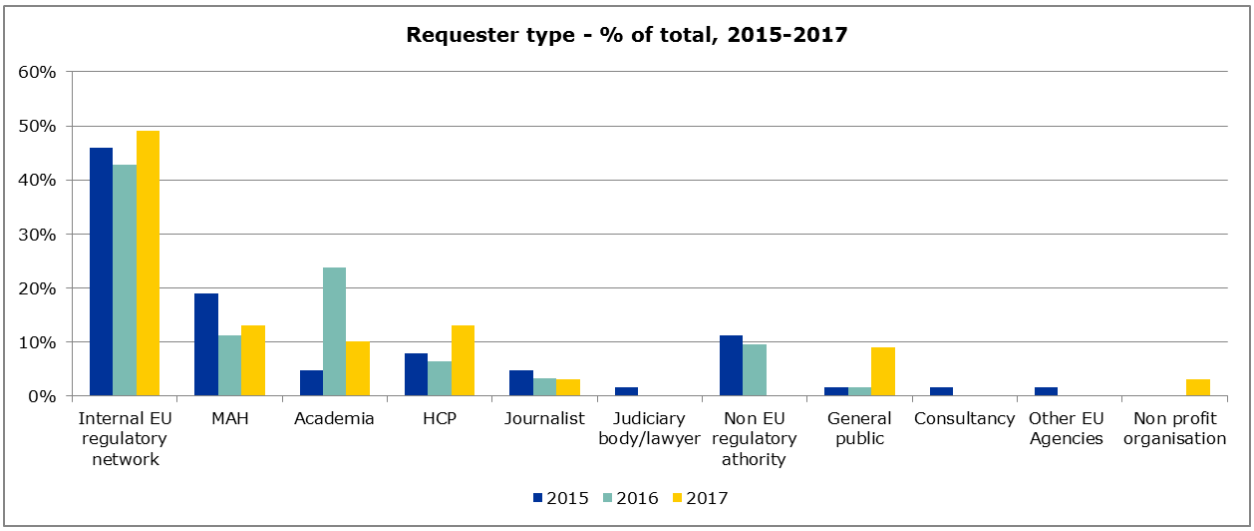


Figure 18. Overview of requests for EV data by type of request (left) and product type (right).



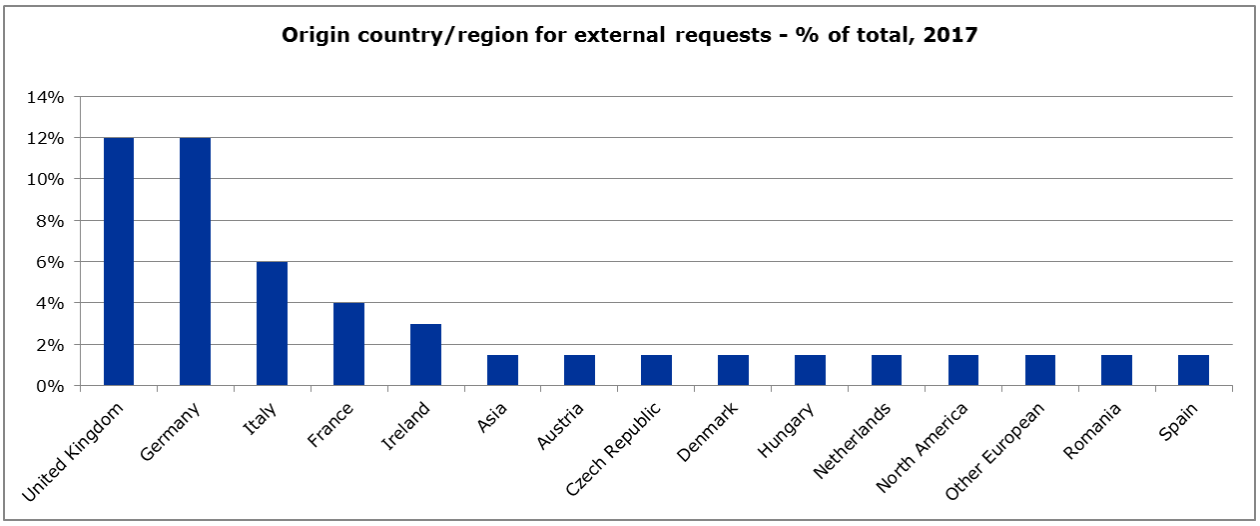


Figure 19. Overview of requests for EV data by requester type (top) and country or region of origin for external requests (bottom).

Overview of requests responded to in 2017

Type of requester	Substance / product	Issue	Type of request
Internal EU regulatory network	Uvesterol D	Information needed to support PRAC discussion	Frequency table(s)/RFI
Internal EU regulatory network	Selexipag	EV analysis	Line listing(s)/ATD
Internal EU regulatory network	Quinolones and fluoroquinolones	Art. 31 PhV - possible timetables	Frequency table(s)/RFI
Internal EU regulatory network	Dabigatran	Interaction with statins	Frequency table(s)/RFI
HCP	Multiple	Literature references (ICH E2B (R2) A.2.2) from ICSRs reported to EudraVigilance for ICSRs	Line listing(s)/ATD
Internal EU regulatory network	Docetaxel	Fatal cases	Line listing(s)/ATD
Academia	Clenbuterol and Salbutamol	All reported ADRs	Line listing(s)/ATD
Internal EU regulatory network	Canagliflozin, Dapagliflozin and Empagliflozin	SGLT2-fatal ketoacidosis	Line listing(s)/ATD

Type of requester	Substance / product	Issue	Type of request
Patient	Gardasil	Access to personal data	Access to personal data
MAH	Humalog/Humulin	EudraVigilance data	Line listing(s)/ATD
MAH	Dimethyl fumarate therapy	Reported cases of PML	Frequency table(s)/RFI
Internal EU regulatory network	Gentamicin	All reported ADRs	Line listing(s)/ATD
Patient	Allergy desensitisation vaccines	Reports of narcolepsy and epilepsy	Frequency table(s)/RFI
HCP	Pazopanib, Sorafenib, Sunitinib	Reported cases of retinal detachments/tears	Line listing(s)/ATD
Internal EU regulatory network	Enalapril	EudraVigilance data	Line listing(s)/ATD
Internal EU regulatory network	Raxone	PRAC recommendation on PSUR	Line listing(s)/ATD
Internal EU regulatory network	Inhaler products	Medication errors reporting for inhaler products	Frequency table(s)/RFI
Internal EU regulatory network	IV fluids containing electrolytes and/or carbohydrates	Signal of hyponatraemia	Line listing(s)/ATD
Academia	Tick-borne encephalitis vaccine	Reported cases of narcolepsy	Line listing(s)/ATD
HCP	Lyrica	Reported incidents since 1996	Frequency table(s)/RFI
HCP	Ketamine	Renal and urinary disorders	Line listing(s)/ATD
Journalist	Tresiba, Humalog, Toujeo	Reported cases of medication errors	Frequency table(s) and Line listing(s)
Internal EU regulatory network	Multiple	Severe signals recorded in neonates	Frequency table(s)/RFI

Type of requester	Substance / product	Issue	Type of request
Internal EU regulatory network	INOmax	Reported case of death of a neonate	Line listing(s)/ATD
Internal EU regulatory network	Epipen	Worldwide recall	Line listing(s)/ATD
Internal EU regulatory network	Albiomin – all ADRs	All reported ADRs	Line listing(s)/ATD
HCP	Humira	Reports of systemic lupus	Line listing(s)/ATD
MAH	Amisulpride	Reported ADRs	Line listing(s)/ATD
MAH	Leuprorelin/leuprolide	Reported ADRs	Line listing(s)/ATD
Academia	Ketamine	Reported cases related to psychiatric disorders	Line listing(s)/ATD
Internal EU regulatory network	Victoza	Reported cases of medication errors	Line listing(s)/ATD
Internal EU regulatory network	Valproate	EudraVigilance data	Frequency table(s)/RFI
Academia	Ivermectin	Reports in children under 5 years old	Line listing(s)/ATD
MAH	Boric acid 3% solution	Reported ADRs to topically applied boric acid	Line listing(s)/ATD
Internal EU regulatory network	Levonorgestrel	Reported cases of anxiety, panic attack, restlessness and sleep disorder	Line listing(s)/ATD
Academia	Promethazine	Reported cases of abuse/misuse/dependence/ withdrawal reactions	Line listing(s)/ATD
Internal EU regulatory network	Tramadol	Tramadol project	Frequency table(s)/RFI
Patient	Influenza vaccine (split virion)	All reported ADRs	Line listing(s)/ATD
HCP	Tienam	EudraVigilance data	Line listing(s)/ATD

Type of requester	Substance / product	Issue	Type of request
Internal EU regulatory network	Paracetamol	Reported cases of overdose with modified-release paracetamol products for oral use	Line listing(s)/ATD
Non-profit Organisation	Levonorgestrel	All reported ADRs	Frequency table(s)/RFI
Internal EU regulatory network	Flupirtine	EudraVigilance analysis on reported cases of hepatotoxicity	Line listing(s)/ATD
Internal EU regulatory network	Rifampicin and Amlodipine	Drug-drug interaction	Line listing(s)/ATD
Academia	Protein kinase inhibitors	Research request	Line listing(s)/ATD
Internal EU regulatory network	Zinbryta	Reported fatal case	Line listing(s)/ATD
Non-profit Organisation	Rituximab	Request for CIOMS reports	CIOMS reports
HCP	Durvalumab	Clinical trial	Frequency table(s)/RFI
MAH	Depakine injectable	Information about clarity issue on reconstituted solution	Line listing(s)/ATD
MAH	Loperamide	Reported cases of misuse	Line listing(s)/ATD
Internal EU regulatory network	Truberzi	Reported cases of Pancreatitis or Sphincter of Oddi dysfunction	Line listing(s)/ATD
HCP	Multiple	Reported cases of agrysytocis [sic]	Line listing(s)/ATD
Internal EU regulatory network	Infanrix hexa and Synflorix vaccines	Reported cases on psychomotor retardation	Line listing(s)/ATD
Internal EU regulatory network	Levothyrox	Complaints in relation to changes to formulation	Line listing(s)/ATD
MAH	Hydroxyethylstarch	EudraVigilance data	Frequency table(s)/RFI
Internal EU regulatory network	Januvia and Janumet	Reported cases of medication errors	Frequency table(s) and Line listing(s)

Type of requester	Substance / product	Issue	Type of request
Internal EU regulatory network	Keppra	Batches verification	Frequency table(s)/RFI
Internal EU regulatory network	Omega-3-acid triglyceride	EDQM	Frequency table(s)/RFI
Internal EU regulatory network	Keytruda	Transplant rejection	Line listing(s)/ATD
Internal EU regulatory network	Esmya	Ulipristal endometrial safety	Frequency table(s)/RFI
Internal EU regulatory network	Multiple	Leaking needle issues	Frequency table(s)/RFI
Internal EU regulatory network	Levonorgestrel	Reported cases of arthralgia	Line listing(s)/ATD
Patient	Bendamustine	Request for CIOMS reports	CIOMS reports
Internal EU regulatory network	Ulipristal	Reported cases of hepatic disorders	Line listing(s)/ATD
HCP	Zolpidem, Zopiclone and Zaleplon	All reported ADRs	Line listing(s)/ATD
Patient	Gardasil	All reported ADRs	Frequency table(s)/RFI