EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16 March 2017
EMA/9942/2017
Inspections, Human Medicines Pharmacovigilance & Committees Division

2016 Annual Report on EudraVigilance for the European Parliament, the Council and the Commission

Reporting period: 1 January to 31 December 2016

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Abbreviations used in this document

ADR	Adverse Drug Reaction
CAP	Centrally Authorised Product
DHPC	Direct Healthcare Professional Communication
DME	Designated Medical Event
EC	European Commission
EEA	European Economic Area
EMA	European Medicines Agency
eRMR	electronic Reaction Monitoring Report
EU	European Union
EVCTM	EudraVigilance Clinical Trials Module
EVPM	EudraVigilance Post-authorisation Module
FDA	Food and Drug Administration
GVP	Good Pharmacovigilance Practice
ICSR	Individual Case Safety Report
ISO	International Standards Organisation
IT	information technology
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
PRR	Proportional Reporting Ratio
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
SMQ	Standardised MedDRA Query
SUSAR	Suspected Unexpected Serious Adverse Reaction
WHO	World Health Organization
xEVMPD	eXtended EudraVigilance Medicinal Product Dictionary

1. Introduction

Pharmacovigilance is essential for optimising the benefit-risk balance of medicines on the market in the European Union (EU). The EU regulatory network for medicines includes the National Competent Authorities (NCAs) in the EU Member States (MSs), the European Medicines Agency (the Agency) and the European Commission (EC). This network constantly monitors, assesses and takes action regarding newly detected risks of medicines or when known risks have changed.

A key tool for these pharmacovigilance activities is EudraVigilance, the European database for adverse drug reaction reports, which MSs and the Agency use for monitoring the safety of authorised medicines on the EU market. EudraVigilance now holds 10.8 million reports referring to 6.7 million cases and therefore is one of the biggest adverse drug reaction databases in the world. The database, which has two modules (EudraVigilance Post-authorisation Module, EVPM, and EudraVigilance Clinical Trials Module, EVCTM), is maintained on behalf of the EU network by the Agency.

This Annual report is prepared in accordance with EU legislation[1] and summarises the EudraVigilance-related activities performed in 2016. These include:

- *Maintaining and updating a database of information on all medicinal products authorised in the EU*. The availability of such a dataset allows for identification of medicines in reports of suspected adverse drug reactions, as well as supporting the management of pharmacovigilance procedures (signals, PSURs, referrals) and facilitates the administration of pharmacovigilance fees. It also allows Marketing Authorisation Holders (MAHs) to easily update details of the qualified person responsible for pharmacovigilance (QPPV) and the pharmacovigilance system master file (PSMF) without the need for submission of variations.
- *Collecting and processing of adverse drug reaction (ADR) reports*. The number of reports received by EudraVigilance in 2016 was 1% higher than the previous year (1,238,178 reports received in 2016). The number of reports received originating from the EEA decreased by approximately 6% (339,544 reports received in 2016). The number of reports submitted directly by European patients and consumers through the NCAs and MAHs (47,238) was similar to but slightly lower than in 2015.
- *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.
- *Provision of 22,429 data analysis reports to the EU network monitoring EudraVigilance data on medicines safety (electronic reaction monitoring reports - eRMRs) and provision of data analyses to support assessments in pharmacovigilance procedures*. EudraVigilance monitoring is performed in collaboration between the NCAs and the Agency. NCAs monitor EudraVigilance data for potential signals (i.e. drug-event pairs, potential safety issues or associations between medicines and adverse reactions detected from screening of the EudraVigilance database, the medical literature, or information from other regulatory authorities etc.) relating to substances used in nationally authorised products.
- *Review of potential signals for centrally authorised products*. EMA staff led on monitoring these and this resulted in 2,076 potential signals reviewed by the Agency, of which approximately 83% originated from analysis of ADR reports received in the EudraVigilance database, reflecting the central role of EudraVigilance for ADR data monitoring.

[1]Regulation (EC) No. 726/2004, Article 24(2), paragraph 2

- *Supporting the central role of the Pharmacovigilance Risk Assessment Committee (PRAC) in assessing and monitoring the safety of human medicines in the EU*, including prioritising and assessing safety signals (94 confirmed signals previously validated by the MSs and the Agency were prioritised and assessed by the PRAC in 2016). Approximately 30% resulted directly in an update of product information, providing prescribers and patients with information aimed at minimising the risks from these ADRs. Others were to be monitored in the context of the PRAC's assessment of periodic safety update reports (PSURs) or in four cases handled via an EU referral procedure. The PRAC assessed the available evidence and where necessary, made timely recommendations to minimise the risks and provide information to patients and prescribers.
- *Training activities*, many of which were open to all stakeholders (see also chapter 4): Five training sessions on the EudraVigilance Data Warehouse and Analysis System were delivered, training 74 experts from 16 NCAs within the EU network on activities related to pharmacovigilance analysis of ADR report data, screening electronic reaction monitoring reports and aiding PSUR assessments. Additionally, 16 training sessions on EudraVigilance data submission and 7 training sessions on the XEVMPD were organised in 2016 and 263 users underwent training on XEVMPD via its e-learning platform.
- *Development of Introduction to EMA's training offering as well as a comprehensive set of training materials,* delivered ahead of time to support EudraVigilance stakeholders and partners in their preparation for new EudraVigilance functionalities.
- *Delivering enhancements of the EudraVigilance database, internal and stakeholder testing and implementing fixes*. This prepares the way for an independent audit in 2017 with the aim of bringing enhanced functionalities into operation. These functionalities will simplify ADR notifications by MAHs through centralising reporting to EudraVigilance and rerouting of the reports to NCAs in EEA Member States. Furthermore, new functionalities will give unprecedented stakeholder access to ADR data including healthcare professionals, patients, academia but also MAHs to the extent necessary to fulfil their pharmacovigilance obligations. Improved data quality and better data analysis is being achieved through the use of the internationally agreed ISO/ICH E2B(R3) ICSR standard and the Medical Dictionary for Regulatory Activities (MedDRA). Adverse reactions reports from within the EU will be delivered directly and in a faster way from EudraVigilance to the World Health Organization (WHO) Uppsala Monitoring Centre.

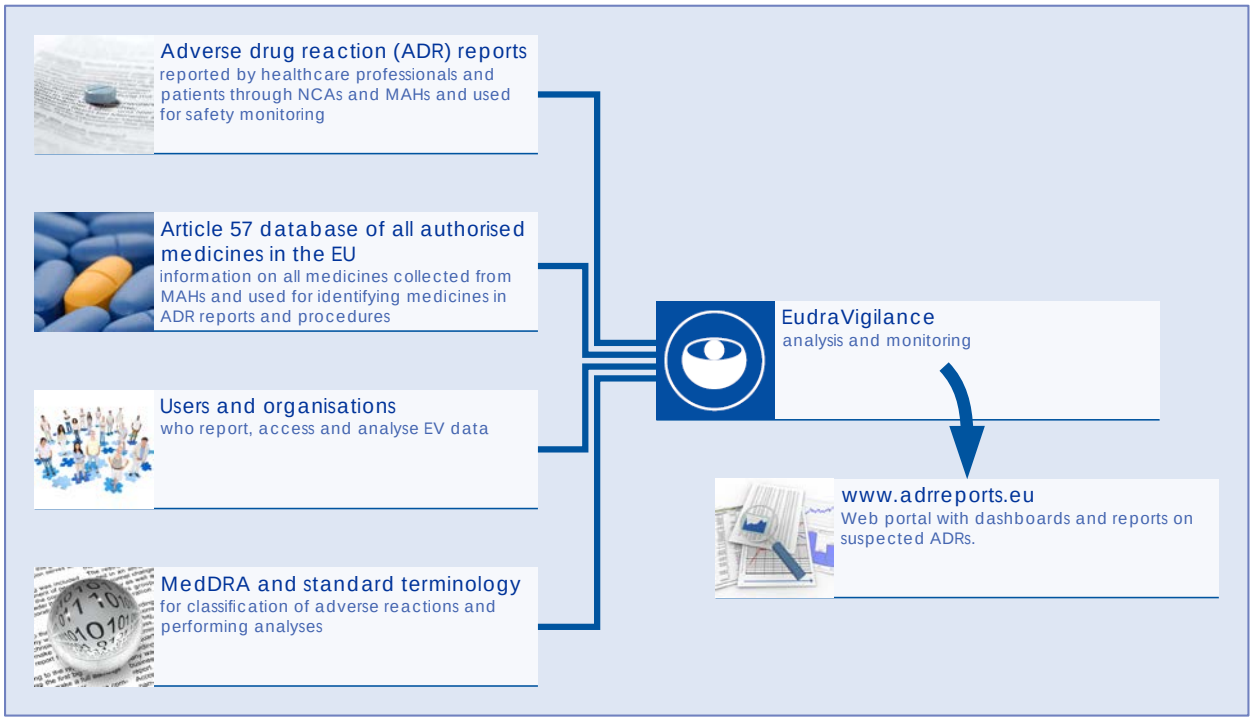


Figure 1: EudraVigilance actors and data sources

2. Data collection and data quality

One of the deliverables[2] 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 through 2015 and 2016 (as part of the XEVMPD which currently supports the medicinal product submissions). The primary objective of this database was facilitating data analysis and signal detection to support better safety monitoring for patients.

Medicinal product information

The total number of individual medicinal products received from MAHs as of 12 January 2017 is 673,137 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 nationally by the NCAs) 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. Full details on these are presented in Annex III.

[2] Regulation (EC) No. 726/2004, Article 57(2), second subparagraph

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[3] has demonstrated that collating reports into big datasets and using statistical analyses of the data allows safety issues to be detected, and therefore dealt with, more rapidly. In this context, the reporting of suspected ADRs underpins the EU pharmacovigilance system.

In 2016, 1,238,178 reports related to suspected adverse reactions were collected and managed in EudraVigilance, 339,544 of which originate from the EEA. This is an overall 1% increase but a 6% decrease in EEA reporting compared to 2015. The number of reports submitted directly by European patients and consumers through the NCAs and MAHs (47,238) was similar to but slightly lower than in 2015.

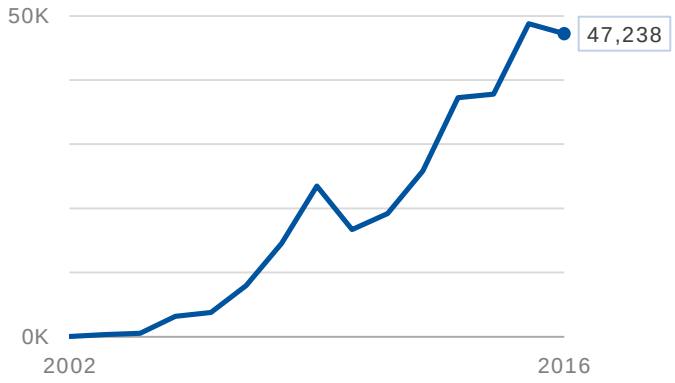


Figure 2: Trend of ADR reports received by European patients and consumers through the NCAs and MAHs.

In summary, the figures this year indicate that the ongoing increase since the introduction of the new legislation in 2012 has slowed down in 2016, showing more or less equal numbers as compared to 2015. Detailed information relating to these figures is provided in Annex II.

EudraVigilance also continues to support the reporting of suspected unexpected serious adverse reactions (SUSARs) in accordance with EU clinical trial legislation[4] and details are 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. 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.

[3] Alvarez Y et al. Validation of statistical signal detection procedures in EudraVigilance post-authorization data: a retrospective evaluation of the potential for earlier signalling. Drug Saf. 2010; 33(6):475-487.
[4] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

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 individual case safety reports (ICSRs), performing data quality reviews of XEVMPD submissions and conducting recoding 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 5 of this report.

3. Data analysis

Statistical outputs called electronic reactions monitoring reports (eRMRs) are produced from ADR reports received in EudraVigilance every two weeks for products subject to additional monitoring, and monthly for all other monitored products. In 2016, a total of 22,429 such reports were produced and shared with the EU network. 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. EudraVigilance monitoring is a collaborative effort between NCAs and the Agency. 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', which indicates a Lead Member State for each included substance; the NCAs are also monitoring all nationally authorised medicines for which no Lead Member State has been appointed. For centrally authorised products, EMA is leading the monitoring; of 2,076 potential signals which were reviewed by the Agency in 2016, around 83% 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 for assessment. The number of confirmed signals prioritised and assessed by the PRAC in 2016 was 94, compared with 102 in 2015. Of these 94 signals, 48 were validated by the Agency and 46 were validated by the MSs; overall 66% included data from EudraVigilance as their source. Of the assessed signals, 28 (30%) resulted in a recommendation for an update of the product information for patients and healthcare professionals, thus increasing the safe and effective use of the medicines. In three of these cases, Direct Healthcare Professional Communications (DHPCs) were also recommended by the PRAC to highlight new important safety information. Four signals are being evaluated through a referral procedure, one signal will be further assessed through a Post-Authorisation Safety Study (PASS) and the evaluation of one signal led to the update of the Risk Management Plan (RMP) for the affected medicine. In 30 cases (32%) continuing routine safety monitoring of the medicine was considered sufficient. The evaluation of 30 signals (32%) is ongoing, including 21 via a follow up signal procedure and 9 in the next PSUR/PSUSA.

Serious adverse reactions assessed by the PRAC in 2016 included, among others, ADRs occurring in children, disorders of the blood, skin, liver, kidneys, cardiovascular, gastrointestinal and neuropsychiatric reactions, medication errors and drug interactions.

Early detection and timely assessment of new ADRs or new aspects of already known ADRs (such as changes in their frequency or severity) 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 2016 can be found in Annex V. The progress of process improvements and simplifications in signal management is detailed in Annex VI.

EudraVigilance also includes up-to-date information on over 670,000 medicinal products in the EU (Art. 57 database), authorised via centralised, national, decentralised or mutual recognition procedures. This, together with ADR data is used to support a wide array of pharmacovigilance procedures

including the assessment of PSURs and PSUR single assessments and EU referral procedures. Data on medicinal products is also used for the computation of pharmacovigilance fees.

4. Transparency, communication and training

Public access to aggregated EudraVigilance data has been available since 2012 via aggregated reports available at www.adrreports.eu. At the end of 2016, this included data for a total of 2,246 active substances (including 618 substances in 912 centrally authorised medicinal products and 1,628 substances in nationally authorised products).

The EudraVigilance Access Policy[5] had been revised in 2015 with minor updates of Annex B published in 2016 to further increase the amount of information made available to patients, prescribers, academia and MAHs. The revised policy will enter into force six months after the Management Board announces that the EudraVigilance database has achieved full functionality, based on an independent audit report.

In 2016, the EMA organised three industry stakeholder platform meetings which supported further development of EudraVigilance and were designed to aid with change management. Additionally, an annual stakeholder forum on pharmacovigilance legislation was organised.

Three 'What's new in Pharmacovigilance QPPV updates' were published on the Agency's website[6]. These provide 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 the 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 aims to increase the harmonisation of the 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, 63 requests were answered in 2016 with a median time for a response of 7 working days. Over 40% of all requests were received from the EU regulatory network, supporting the scientific assessment of pharmacovigilance procedures. Additionally, an increase of approximately 19% was observed in requests from academia. For further details please refer to Annex VII.

The Agency organised a large number of training activities, many of which were open to all stakeholders:

- 7 information days/stakeholder platforms (2 EudraVigilance information days, 1 ICSR information day, and 3 industry stakeholder platform meetings as well as the Annual stakeholder forum on the operation of the pharmacovigilance legislation);
- 5 training sessions on EudraVigilance Data Analysis, training 74 experts from 16 NCAs;
- 16 training sessions on EudraVigilance data submission, 7 organised at the EMA and 9 organised in the Member States;

[5] http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/12/WC500218300.pdf
[6] http://www.ema.europa.eu/docs/en_GB/document_library/Newsletter/2016/04/WC500205595.pdf
http://www.ema.europa.eu/docs/en_GB/document_library/Newsletter/2016/08/WC500211746.pdf
http://www.ema.europa.eu/docs/en_GB/document_library/Newsletter/2016/12/WC500219047.pdf

- 7 training sessions on the eXtended EudraVigilance Medicinal Product Dictionary (XEVMPD), 4 organised at the EMA and 3 organised in the Member States;
- 263 users followed training on xEVMPD via its e-learning platform.

Furthermore, as part of the launch of the new EudraVigilance system, the Agency has released a comprehensive set of training modules[7] focusing on pharmacovigilance, EudraVigilance and IT related matters based on a dedicated training curriculum to prepare stakeholders for the changes introduced by the 2010 pharmacovigilance legislation regarding adverse reaction reporting and signal detection. Additionally, an introduction to EMA's training offering module (PhV-M0) explains which courses are required for each stakeholder group, as summarised in table 1 below.

PhV-M0: Introduction to EMA's training offering		
Pharmacovigilance	**EudraVigilance**	**EudraVigilance -IT**
PhV-M1: New EV functionalities & 2010 pharmacovigilance legislation	EV-M2: Introduction to EV system components and system functionalities	IT-M1: ISO ICSR standard implementation for IT system developers
PhV-M2a: Implementing ISO ICSR/ICH E2B(R3): Impact on adverse reaction reporting	EV-M3a: EV Reporting process for users: EV Gateway, Web-Trader, EV-Post functions	ISO ICSR (E2B(R3)) system implementers workshop
PhV-M2b: Implementing ISO ICSR/ICH E2B(R3): Backwards and forwards conversion	EV-M3b: EV Reporting process for users: Introduction to EVWEB	EV-M5a: EVDAS training for National Competent Authorities
PhV-M3: How to prepare for simplified adverse drug reaction reporting in the European Union	EV-M3c: EV Reporting process for users: Export functions in EVWEB	EV-M5b: EVDAS training for Marketing Authorisation Holders
PhV-M4: Revised EudraVigilance access policy: impact on stakeholders	EV-M3d: EV Reporting process for users: Create and send ICSRs using EVWEB	EV-M6: ADRreports.eu portal

Table 1: Overview of available training modules in the EudraVigilance training plan

5. Development of EudraVigilance functionalities

To optimise delivery, the EMA Management Board conducted a prioritisation exercise for the implementation of the EU pharmacovigilance legislation in December 2011. They gave the highest priority to measures positively impacting public health, second priority to transparency and communication measures and third priority to administrative simplification. The delivery of new information management systems was judged to be for administrative simplification and hence was third priority. Consequently, technical improvements of the EudraVigilance system progressed in 2016, reaching user testing phase and implementation of fixes in anticipation of the independent audit in 2017. Further development and enhancement in collaboration with the Member States will continue through 2017.

[7] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000162.jsp&mid=WC0b01ac0580a1a1fb

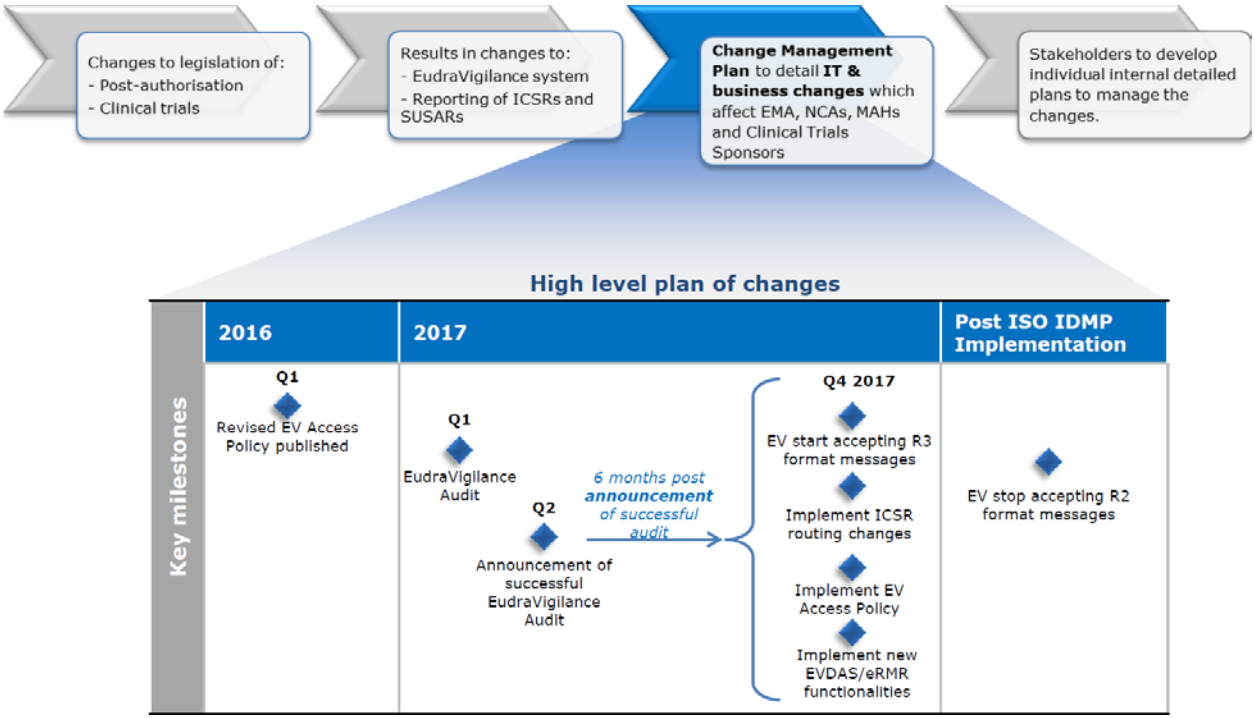


Figure 3: High level plan of changes in EudraVigilance

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 adverse drug reactions (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 and also created the Article 57 dashboards. The first set of dashboards was released in 2016 and a further set of dashboards will be released to NCAs in 2017. This has allowed competent authorities to directly access the data held in the XEVMPD for the first time. 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[8] 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 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. An independent audit of the EMA MLM service provider's internal quality management and control systems and of the output of the service was conducted in early 2016. Two surveys were conducted to assess industry and NCAs' experience with

[8] Regulation (EC) No. 726/2004, Article 27

the service and a workshop was held in September 2016 to obtain detailed proposals for future enhancements, leading to continuous process improvements.

In 2016, 275,954 unique literature references were reviewed and the outcome published on a daily basis. The review of these literature articles resulted in 8,495 adverse drug reaction reports, referring to 5,595 individual cases, being entered into EudraVigilance in 2016 and made available to NCAs and MAHs.

EudraVigilance functionalities that will be subject to audit

Before the move to centralised reporting, the new EudraVigilance system has to undergo an independent audit in accordance with Article 24 of Regulation (EC) 726/2004, scheduled to take place in February 2017. In preparation for the independent audit the Agency has continued developing the EudraVigilance database together with the MSs. Many of the IT testing activities of the new EudraVigilance system functionalities have been completed in 2016, including internal testing performed by EMA and testing by external stakeholders (i.e. testers from NCAs, MAHs and the WHO-UMC). The auditing company has been selected and preparation of the audit fieldwork started in 2016.

New and enhanced functionalities will support:

- Simplification of the reporting of ADRs, in particular for MAHs for whom EudraVigilance will become the sole reporting point in the EEA, with subsequent re-routing of ICSRs to the Member States where the adverse reactions occurred;
- Provision of EEA adverse reaction reports to the World Health Organisation (WHO);
- Enhancements to signal detection and analysis tools for NCAs;
- The broadening of EudraVigilance access to MAHs to the extent necessary to fulfil their pharmacovigilance obligations as well as to validate signals as appropriate based on an examination of ICSRs;
- The use of internationally agreed formats, standards and terminologies (such as the ISO ICSR format).

To support EudraVigilance stakeholders and partners during this period of changes, the EudraVigilance website was redesigned in June 2016 and enhanced to publish important information on the new and existing EudraVigilance system including a stakeholder change management plan (revision 2), a communication plan, a training plan (revision 2) and e-learning materials (see chapter 4.)

6. Conclusion

EudraVigilance continues to have a central role for the EU Regulatory Network in the safety monitoring of medicines on the EU market. It collects adverse drug reaction reports, underpins detection of new risks and identification of risks which have changed through screening ADR reports, and provides routine support of all pharmacovigilance procedures. EudraVigilance now contains 10.8 million ADR reports referring to 6.7 million cases, and a database of information on over 670,000 medicinal products on the EU market.

The reporting of adverse drug reaction reports to EudraVigilance continued at levels similar to 2015, with minor decreases observed in the number of EEA reports submitted by healthcare professionals as well as reports submitted directly by European patients and consumers. The NCAs and the Agency jointly received in excess of 22,000 statistical outputs (electronic reaction monitoring reports - eRMRs)

for review of newly received ADR reports. The timely detection and assessment of signals together with benefit-risk evaluation in periodic safety update reports and assessment of risk management plans by the PRAC are the cornerstone of EU pharmacovigilance, allowing safe and effective use of medicines and supporting timely access to innovative medicines.

The development of EudraVigilance continued in collaboration with the MSs throughout 2016, with successful completion of user testing in preparation of its independent audit in early 2017. The enhanced functionalities are planned to become operational in late 2017 subject to a successful audit outcome.

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]	Continued during 2016
Data quality review and duplicate management of adverse reaction reports in EudraVigilance [Legal basis: Regulation (EC) 726/2004, Article 24(3)]	Continued during 2016
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 2016
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 28(a) • Directive 2001/83/EC, Article 107(h) • Commission Implementing Regulation (EU) 520/212, Article 21]	Continued during 2016
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 2016
Operation of the Medical Literature Monitoring service [Legal basis: Regulation (EC) 726/2004, Article 27]	Continued during 2016

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. Last year availability of the system was maintained above the required target of 98%. On average the system was available 99.8% of the time throughout the year with its lowest point 98.92% in September (figure 4).

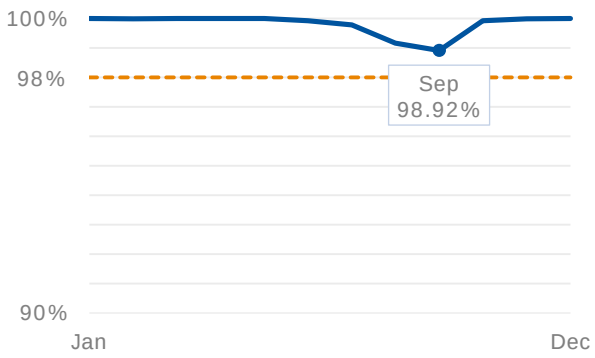


Figure 4: EudraVigilance gateway availability per month. The requirement is 98%. Please note that the scale starts at 90%.

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 2016, the EudraVigilance database held a total of 10,888,388 ADR reports, referring to 6,703,735 individual cases (figure 5). The post-authorisation module (EVPM) contained 9,928,217 ADR reports (6,367,422 cases) and the clinical trial module (EVCTM) 960,171 reports (336,313 cases).

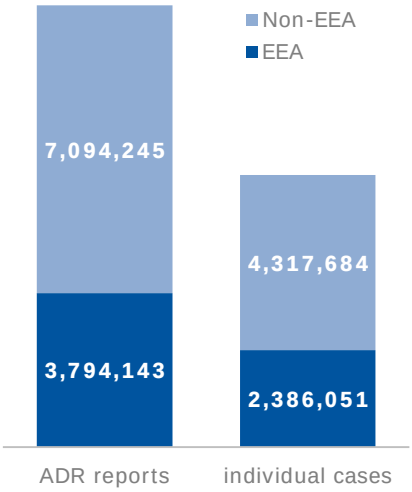


Figure 5: Number of ADR reports versus individual cases received in the EudraVigilance database from its inception in December 2001 until 31 December 2015 split by origin of the report in- or outside the EEA.

The numbers presented in figure 6 and 7 refer to the ADR reports received in the post-authorisation module (EVPM). A total of 9,928,217 EVPM ADR reports had been processed by the end of 2016 since the beginning fifteen years ago. 1,238,178 ADR reports were transmitted in 2016 which was 1% higher than last year. With 1% more ADR reports than in 2015, the increase from the last couple of years has stabilised in 2016 (figure 6). On average 103,182 ADR reports were received and processed per month (figure 7) in 2016 and subsequently made available for signal detection and data analysis by the Agency and national competent authorities in the Member States.

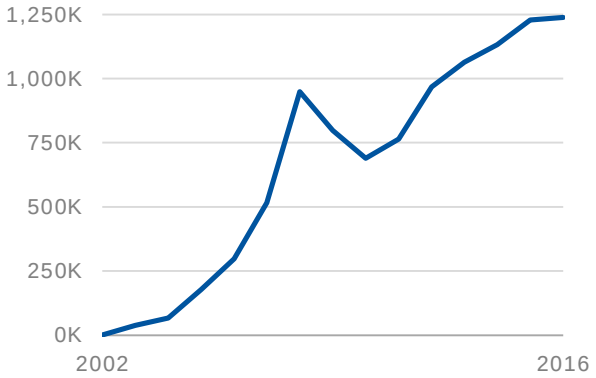


Figure 6: Number of ADR reports processed per year in EVPM

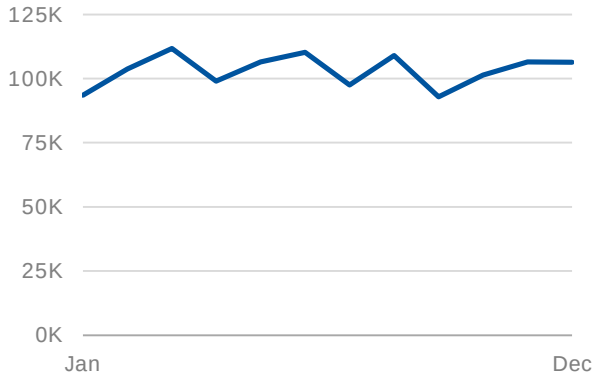


Figure 7: Number of ADR reports processed per month in EVPM in 2016

Figure 8 presents the total number of ADR reports received in EVPM grouped by EEA and non-EEA for 2016, compared to the number of cases they are referring to (figure 9). In 2016, 339,544 ADR reports were received from the EEA, a decrease of approximately 6% from the previous year. 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 are known as adverse drug reaction (ADR) reports or individual case safety reports (ICSRs).

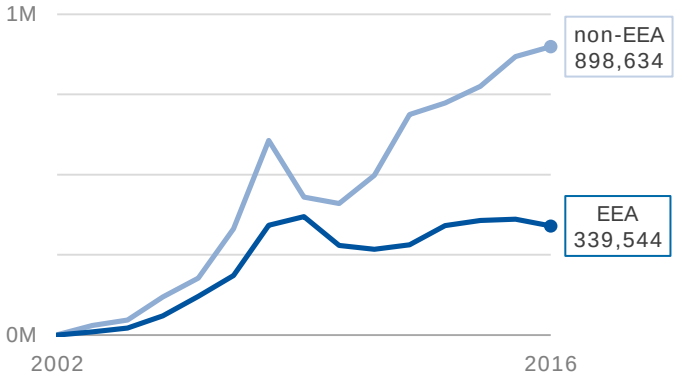


Figure 8: Number of ADR reports processed per year in EVPM split by cases occurred inside and outside the EEA

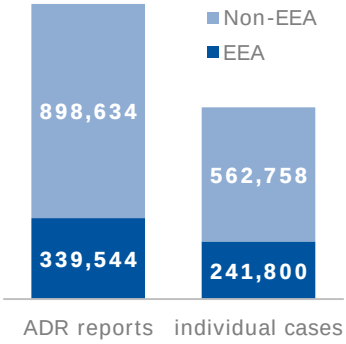


Figure 9: Number of ADR reports versus the number of individual cases in 2016 in EVPM

In 2016, 47,238 ADR reports were submitted by European patients and consumers through the NCAs and MAHs as spontaneous reports, referring to 34,583 individual cases. This is broadly similar to, but approximately 3% lower compared to 2015 (figure 10).

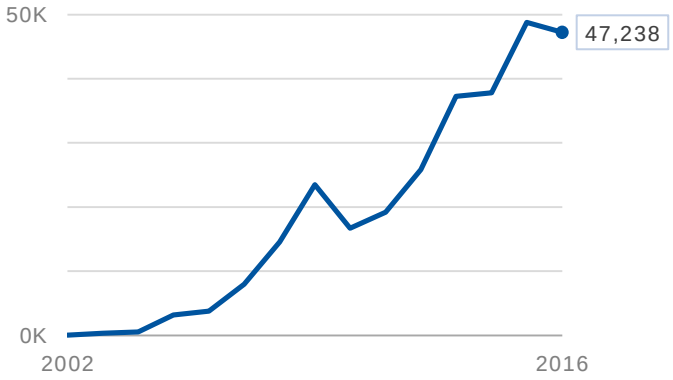


Figure 10: Number of ADR reports by European patients and consumers through the NCAs and MAHs

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

- A total of 960 MAHs (at headquarter level) have sent reports to the EudraVigilance Post-authorisation Module (EVPM) in the period between 1 January 2002 and 31 December 2016.
- A total of 982 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 2016.

Table 2 below shows the total number of unique cases and ICSRs transmitted by MAHs and sponsors to EVPM and EVCTM. Figure 11 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 following 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.

Table 2. Number of ADR reports and unique cases transmitted by MAHs and sponsors to EVPM and EVCTM in 2016.

EV Module	Transmission type	2016	2015
EVPM	ADR reports	981,828	944,822
	Individual cases	617,055	618,831
EVCTM	ADR reports	88,097	74,193
	Individual cases	33,516	29,539

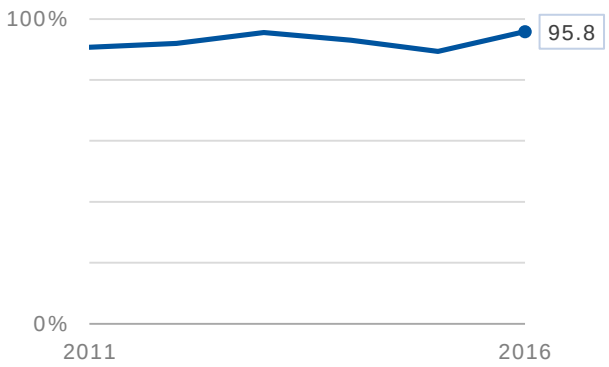


Figure 11: 15-day compliance rate to EVPM for all MAHs and sponsors by year

E-reporting status for National Competent Authorities

- All 32 NCAs in the EEA have been authorised to enter into production with EudraVigilance.
- All NCAs have reported ICSRs to EVPM, except for AFLUV (Liechtenstein) and the Division de la Pharmacie et des Médicaments (Luxembourg), for whom 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.

Table 3 below shows the total number of unique cases and ICSRs transmitted by NCAs to EVPM and EVCTM. Figure 12 shows the 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 3. Number of ICSRs and unique cases transmitted by NCAs to EVPM and EVCTM during 2016

EV Module	Transmission type	2016	2015
EVPM	ADR reports	256,650	283,520
	Individual cases	187,503	212,095
EVCTM	ADR reports	6,756	7,098
	Individual cases	2,769	2,880

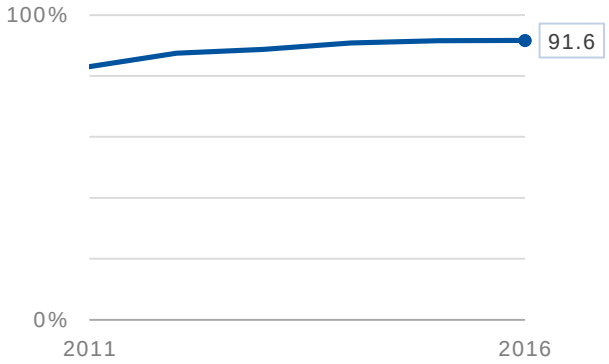


Figure 12: 15-day compliance rate to EVPM for all NCAs by year

During 2016, the following 6 NCAs transmitted SUSARs to EVCTM (SUSARs from other countries were received directly from sponsors of clinical trials):

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

EudraVigilance database and support of signal management process

A total of 22,429 electronic Reaction Monitoring Reports (eRMRs) were generated in 2016 to facilitate the continuous monitoring of the safety of medicines by the Agency and NCAs in the EEA. Of these, 5,926 were produced from ADR reports received in EudraVigilance every two weeks for products subject to additional monitoring and 16,503 were produced monthly for all other monitored products.

Annex III - Total number of medicinal product submissions by MAHs

As described in section 2, 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 (see section 5),
  - proactively:

    to MAHs to enable the performance of signal detection activities in accordance with Article 24(2) 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 2016). Table 4, below, provides a summary of the data resubmitted in the new format as of 12 January 2017.

Table 4. Summary of medicinal product submissions to the XEVMPD

Total number of medicinal product submissions in new format by MAHs by 12 January 2017 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	673,137
Total number of marketing authorisation holders (legal entities) established in the EU (corresponding to EudraVigilance codes)	4,681

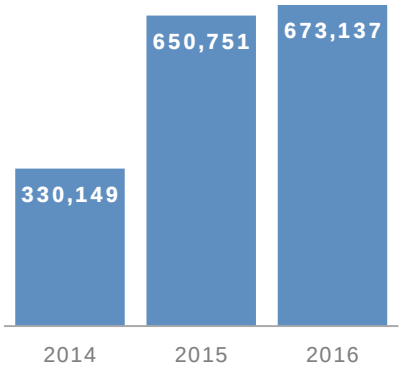


Figure 13: Total number of medicinal products (counted on the basis of EudraVigilance codes) resubmitted in the new format (cumulative by year)

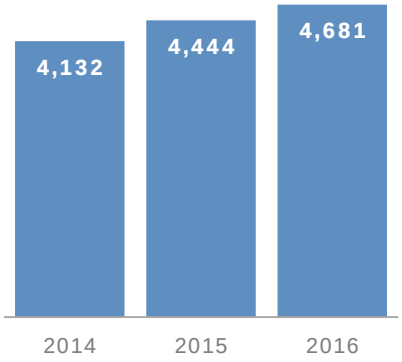


Figure 14: Total number of marketing authorisation holders (legal entities) established in the EU (corresponding to EudraVigilance codes) (cumulative by year)

The EudraVigilance code is the level to which a product is defined in the context of the 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 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 2016. The decrease in quality reviews in XEVMPD is as expected. The number of resubmissions since 2014 is levelling off and revisions are performed as data is received. The backlog of validations was mainly done in the previous year.

Table 5. Summary of EudraVigilance data quality activities in 2016

Data quality area	Activities performed	2016	2015
Identifying and managing duplicates	Duplicate couples assessed	72,655	31,797
	Master reports generated based on duplicated data	48,111	40,022
Coding of reported medicines and active substances	Reported medicinal products and active substance terms recoded	91,650	29,424
	ADR reports recoded (ICSRs)	64,686	54,535
	ADR reports recoded (cases)	37,774	30,245
Providing feedback on data quality	Organisations subject to ICSR data quality review	120	51
	Medicinal products in XEVMPD quality reviewed (and corrected if necessary)	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 2016, the Agency's Signal Management Team reviewed in detail a total of 2,076 potential signals (i.e. drug-event pairs from screening of the EudraVigilance database, medical literature, information received from other regulatory authorities etc.). This represents an approx. 12.5% decrease compared to the previous year.

Potential signals reviewed	2016	2015	2014	2013	2012
Total	2,076	2,372	2,030	2,449	2,213
Difference	-296	342	-419	236	627
% compared to previous year	-12.5%	17.0%	-17.1%	10.7%	39.5%

Overall the major source of EMA potential signals in 2016 continues to be EudraVigilance, from which 82.7% of potential signals originated (87.8% in 2015). In addition to EudraVigilance, an increase in potential signals from the scientific literature was also observed, representing 13.9% of potential signals (8.7% in 2015). A further 2.1% originated from communications received from other regulatory authorities (20 from the FDA, 13 from PMDA/MHLW, 7 from Health Canada, 1 from Swissmedic and 3 from the WHO) and 1.3% from other sources. The overview by action taken is provided below:

	Number of potential signals			
Action taken	**2016**	**%**	**2015**	**%**
Not validated (closed)	1,748	84.2%	2,045	86.2%
Monitored	100	4.8%	90	3.8%
Ongoing	180	8.7%	176	7.4%
Prioritised and assessed by PRAC	48	2.3%	61	2.6%
Total	2,076	100.0%	2,372	100.0%

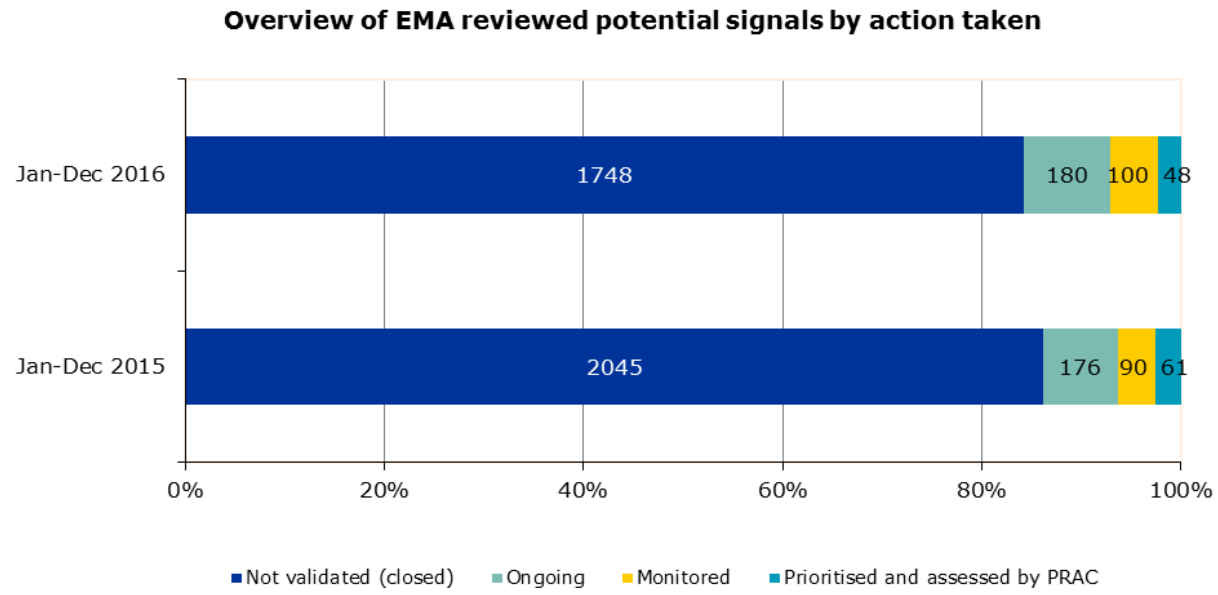


Figure 15: Overview of EMA reviewed potential signals by action taken.

Overview of signals prioritised and assessed by the PRAC

All detected validated signals which are confirmed by the Rapporteur or 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 2016 was 94, compared with 102 in 2015. Of these 94 signals, 48 were validated by the Agency and 46 were validated by the MSs in the course of ongoing ADR reports monitoring through screening of reaction monitoring reports, ADR reports, medical literature and other safety data; overall 66% included data from EudraVigilance as their source.

Twenty-eight (30%) of the assessed signals resulted in a recommendation for an update of the product information that provides guidance to patients and healthcare professionals, thus increasing the safe and effective use of the medicines. In three of these cases, Direct Healthcare Professional Communications (DHPC) were also recommended by the PRAC to highlight new important safety information. Four signals are being evaluated through a referral procedure, one signal will be further assessed through a Post-Authorisation Safety Study (PASS) and the evaluation of one signal led to the update of the Risk Management Plan (RMP). In 30 cases (32%) continuing routine safety monitoring of the medicine was considered sufficient. The evaluation of 30 signals (32%) is currently ongoing, including 21 via a follow up signal procedure and 9 in the next PSUR/PSUSA.

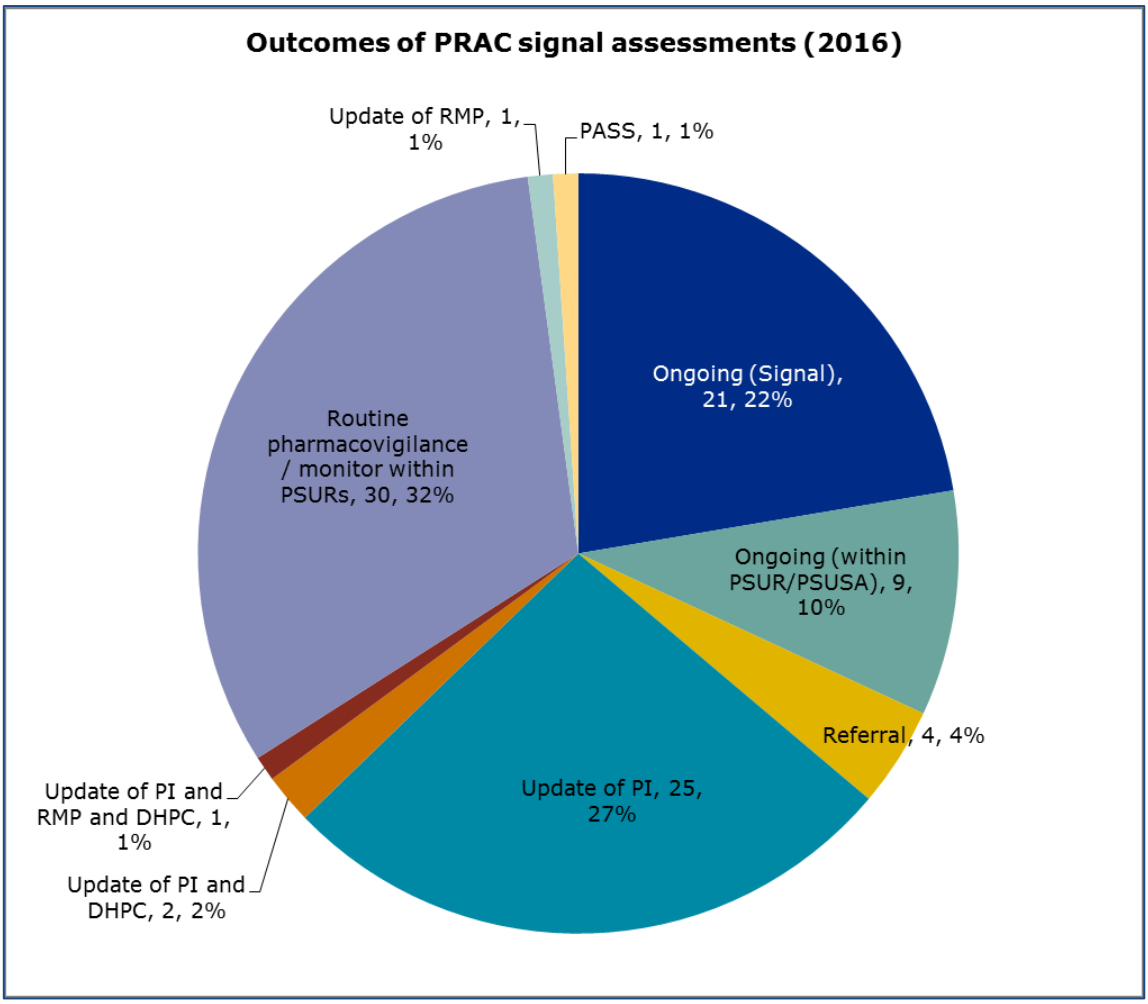


Figure 16: Outcomes of PRAC signal assessments (2016). PI: product information, DHPC: Direct Healthcare Professional Communication, RMP: Risk Management Plan, PASS: Post-Authorisation Safety Study, PSUR: Periodic Safety Update Report, PSUSA: PSUR Single Assessment.

A list of all signals prioritised and assessed by the PRAC in 2016 is provided below, noting the latest status or outcome as of 31 December 2016.

Drug	Issue / Signal	Status or outcome
Acenocoumarol; phenprocoumon; fluindione; phenindione	Calciphylaxis	update of PI
Adalimumab	Acute febrile neutrophilic dermatosis (Sweet's Syndrome)	routine pharmacovigilance / monitor within PSURs
Adalimumab	Autoimmune haemolytic anaemia (AIHA) and haemolytic anaemia (HA)	routine pharmacovigilance / monitor within PSURs
Adalimumab	Glomerulonephritis	routine pharmacovigilance / monitor within PSURs
Agomelatine	Leukopenia	routine pharmacovigilance / monitor within PSURs
Agomelatine	Urinary retention	update of PI
Albiglutide	Acute kidney injury	ongoing (Signal)
Alogliptin; alogliptin, metformin; alogliptin, pioglitazone; linagliptin; linagliptin, metformin	Arthralgia	update of RMP
Anakinra, canakinumab	Weight increased	routine pharmacovigilance / monitor within PSURs
Aripiprazole	Compulsive shopping	ongoing (within PSUR/PSUSA)
Axitinib	Nephrotic syndrome	update of PI
Azacitidine	Pericarditis and pericardial effusion	ongoing (Signal)
Bcr-abl tyrosine kinase inhibitors	HBV reactivation	update of PI and DHPC
Boceprevir; daclatasvir; dasabuvir; ledipasvir, sofosbuvir; ombitasvir, paritaprevir, ritonavir; simeprevir; sofosbuvir	Drug interaction between direct-acting antivirals and vitamin K antagonists leading to a reduced international normalized ratio (INR)	update of PI
Brentuximab vedotin	Cytomegalovirus (CMV) reactivation	ongoing (Signal)
Canagliflozin; canagliflozin, metformin	Increased risk of lower limb amputations in CANVAS trial	referral and DHPC
Carbidopa, levodopa (intestinal gel)	Intussusception	update of PI
Ceftriaxone	Drug reaction with eosinophilia and systemic symptoms (DRESS)	routine pharmacovigilance / monitor within PSURs

Drug	Issue / Signal	Status or outcome
Cisplatin	Peripheral arterial thromboembolic events (ATEs) and arterial occlusion	routine pharmacovigilance / monitor within PSURs
Clozapine	Myocarditis	routine pharmacovigilance / monitor within PSURs
Cobicistat containing products: cobicistat; cobicistat, atazanavir sulfate; cobicistat, darunavir; cobicistat elvitegravir, emtricitabine, tenofovir alafenamide; cobicistat elvitegravir, emtricitabine, tenofovir disoproxil fumarate	Drug interaction with corticosteroids leading to adrenal suppression	update of PI
Cytarabine	Benign intracranial hypertension	routine pharmacovigilance / monitor within PSURs
Dabrafenib; trametinib	Sepsis	ongoing (Signal)
Dapagliflozin	Pancreatitis	routine pharmacovigilance / monitor within PSURs
Daratumumab	Tumour lysis syndrome	ongoing (within PSUR/PSUSA)
Darbepoetin alfa	Incorrect use of device associated with adverse reactions including underdose, drug dose omission, accidental exposure to product and injection site reactions	ongoing (Signal)
Direct-acting antivirals (DAAV) indicated for the treatment of hepatitis C (interferon free): daclatasvir; dasabuvir; ombitasvir, paritaprevir, ritonavir; simeprevir; sofosbuvir; sofosbuvir, ledipasvir	Unexpected early hepatocellular carcinoma recurrence	referral
Enzalutamide	Hepatotoxicity	ongoing (Signal)
Exenatide	Incorrect use of device associated with (serious) adverse reactions including hyperglycaemia and hypoglycaemia	ongoing (Signal)
Ferrous sulfate	Mouth ulceration	update of PI
Flucloxacillin	Acute generalised exanthematous pustulosis (AGEP)	update of PI
Fluconazole	Signal of spontaneous abortion during pregnancy and stillbirth	ongoing (Signal)
Fluoroquinolones ciprofloxacin; enoxacin; flumequine;	Aortic aneurysm and dissection	routine pharmacovigilance /

Drug	Issue / Signal	Status or outcome
levofloxacin; lomefloxacin; moxifloxacin; norfloxacin; ofloxacin; pefloxacin; prulifloxacin; rufloxacin		monitor within PSURs
Fluoroquinolones ciprofloxacin; enoxacin; flumequine; levofloxacin; lomefloxacin; moxifloxacin; norfloxacin; ofloxacin; pefloxacin; prulifloxacin; rufloxacin	Retinal detachment	routine pharmacovigilance / monitor within PSURs
Fluoroquinolones ciprofloxacin; enoxacin; flumequine; levofloxacin; lomefloxacin; moxifloxacin; norfloxacin; ofloxacin; pefloxacin; prulifloxacin; rufloxacin	Uveitis	routine pharmacovigilance / monitor within PSURs
Fulvestrant	Interference with estradiol assay, false estradiol results	update of PI
Gefitinib	Pneumatosis intestinalis	routine pharmacovigilance / monitor within PSURs
Human albumin solutions	Increased risk of death in patients with severe traumatic brain injury and in patients with burns	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); moroctocog alfa; octocog alfa; simoctocog alfa; turoctocog alfa	Signal of inhibitor development in previously untreated patients (PUPs) with haemophilia A treated with plasma-derived vs recombinant coagulation factor VIII concentrates	referral
Human normal immunoglobulin	Posterior reversible encephalopathy syndrome (PRES)	routine pharmacovigilance / monitor within PSURs
Infliximab	Thyroid gland disorders	routine pharmacovigilance / monitor within PSURs
Intravenous fluids containing electrolytes and/or carbohydrates	Hyponatraemia	routine pharmacovigilance / monitor within PSURs
Iomeprol	Haemolysis	update of PI
Ipilimumab	Type 1 diabetes mellitus	ongoing (within PSUR/PSUSA)
Lansoprazole; dexlansoprazole (proton pump inhibitor)	Unexpected histopathological findings from a juvenile rat toxicity	ongoing (Signal)

Drug	Issue / Signal	Status or outcome
	study	
Leflunomide; teriflunomide	Falsely decreased ionised calcium levels	ongoing (Signal)
Lenalidomide	Haemophagocytic lymphohistiocytosis (HLH)	ongoing (Signal)
Lenvatinib	Cholecystitis	ongoing (Signal)
Levetiracetam	Risk of medication errors due to a new presentation of syringes	update of PI and DHPC
Loperamide	Serious cardiac events with high doses of loperamide, mainly from abuse and misuse	ongoing (Signal)
Loratadine	Risk of QT prolongation/torsade de pointes associated	ongoing (within PSUR/PSUSA)
Mercaptopurine; azathioprine	Lymphoproliferative disorders	update of PI
Meropenem; ciprofloxacin	Incompatibility leading to possible precipitation when co-administered intravenously	ongoing (Signal)
Methotrexate	Congenital cardiovascular anomaly	routine pharmacovigilance / monitor within PSURs
Methotrexate	Progressive multifocal leukoencephalopathy (PML), JC virus infection	routine pharmacovigilance / monitor within PSURs
Methylphenidate	Priapism	update of PI
Metronidazole	Severe hepatic and neurologic toxicity in patients with Cockayne syndrome	update of PI
Mitotane	Sex hormone disturbances and development of ovarian macrocysts	update of PI
Natalizumab	Necrotising retinitis	update of PI
Nivolumab	Pemphigoid	ongoing (Signal)
Nivolumab; pembrolizumab	Transplant rejection	ongoing (Signal)
Olanzapine	Drug reaction with eosinophilia and systemic symptoms (DRESS)	update of PI
Olanzapine	Restless leg syndrome (RLS)	update of PI
Ombitasvir, paritaprevir, ritonavir, dasabuvir	Depression and suicidal ideation	ongoing (within PSUR/PSUSA)
Oxybutynin	Psychiatric disorders	update of PI
Paracetamol	Signal of paracetamol use in pregnancy and child neurodevelopment	ongoing (Signal)

Drug	Issue / Signal	Status or outcome
Paracetamol; phenylephrine	Pharmacokinetic drug interaction: increased bioavailability of phenylephrine when co-administered with paracetamol	routine pharmacovigilance / monitor within PSURs
Pazopanib	Polycythaemia	update of PI
Peginterferon alfa-2a	Acquired haemophilia	routine pharmacovigilance / monitor within PSURs
Peginterferon alfa-2a	Guillain-Barré syndrome (GBS)	routine pharmacovigilance / monitor within PSURs
Penicillins of the beta-lactamase resistant group: cloxacillin; dicloxacillin; flucloxacillin; nafcillin; oxacillin	Metabolic acidosis following administration of flucloxacillin in association with paracetamol	routine pharmacovigilance / monitor within PSURs
Pirfenidone	Colitis	ongoing (Signal)
Propofol	Diabetes insipidus	routine pharmacovigilance / monitor within PSURs
Propofol; valproate and related substances	Pharmacokinetic drug interaction between propofol and valproate leading to an increased propofol exposure	ongoing (Signal)
Proton pump inhibitors (PPIs): dexlanzoprazole; esomeprazole; lansoprazole; omeprazole; pantoprazole; rabeprazole	Elevated circulating levels of chromogranin A	update of PI
Proton pump inhibitors (PPIs): dexlansoprazole; esomeprazole; lansoprazole; omeprazole; pantoprazole; rabeprazole	Gastric polyps	update of PI
Proton pump inhibitors (PPIs): dexlansoprazole; esomeprazole; lansoprazole; omeprazole; pantoprazole; rabeprazole	Incident chronic kidney disease (CKD) and progression to end stage renal disease (ESRD)	ongoing (Signal)
Quinine	Increased mortality risk in heart failure patients with/without concomitant use of beta-blockers	ongoing (within PSUR/PSUSA)
Recombinant factor VIII: antihemophilic factor (recombinant); moroctocog alfa; octocog alfa	Inhibitor development in previously untreated patients	routine pharmacovigilance / monitor within PSURs
Regorafenib	Angioedema	routine pharmacovigilance / monitor within PSURs
Riociguat	Increased mortality and serious	update of PI and RMP and

Drug	Issue / Signal	Status or outcome
	adverse effects in patients with pulmonary hypertension (PH) associated with idiopathic interstitial pneumonias (IIP) in a single clinical trial	DHPC
Ritonavir	Retinal pigment epitheliopathy	ongoing (within PSUR/PSUSA)
Rivaroxaban	Spontaneous spinal haematoma	ongoing (within PSUR/PSUSA)
Saxagliptin; saxagliptin, metformin	Acute kidney injury	PASS
Selective serotonin reuptake inhibitors (SSRIs): citalopram; escitalopram; fluoxetine; fluvoxamine; mirtazapine; paroxetine; sertraline Serotonin–norepinephrine reuptake inhibitors (SNRIs): duloxetine; sibutramine; venlafaxine	Risk of autism spectrum disorders (ASD) after maternal use of SSRI/SNRI	routine pharmacovigilance / monitor within PSURs
Sofosbuvir	Hepatitis B reactivation	referral
Temozolomide	Meningoencephalitis herpetic	ongoing (Signal)
Thioctic acid	Insulin autoimmune syndrome (IAS)	update of PI
Tigecycline	Hypofibrinogenaemia	update of PI
Tramadol; paracetamol, tramadol	Risk of hyponatraemia and syndrome of inappropriate antidiuretic hormone secretion (SIADH)	routine pharmacovigilance / monitor within PSURs
Ustekinumab	Pemphigoid	routine pharmacovigilance / monitor within PSURs
Vedolizumab	Hepatotoxity	ongoing (within PSUR/PSUSA)
Vildagliptin; vildagliptin, metformin	Pemphigoid	update of PI
Warfarin	Calciphylaxis	update of PI

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 and methodological guidance and signal detection methods. In 2016, the following progress was achieved:

- The applicability of PRAC recommendations on safety signals to homeopathic products was clarified. MAHs of homeopathic products should consider updates of the PI of their products based on scientific grounds and considering the dilution of their product.
- Further reflections were made on how product information updates stemming from signal assessments impact on the outer packaging of medicinal products. This is particularly relevant for regulatory decisions leading to changes to posology/method of administration or dose.
- Considerations were made for assessments of drug interactions in case of nationally authorised products (NAPs) and when the respective SmPCs are not aligned.
- Improvements for signal detection were proposed by considering signals which relate to information included in the SmPCs, but may differ in terms of severity, outcomes or possibilities for prevention and risk management.
- A new process for prioritisation of new signals by the PRAC without plenary discussion was devised, allowing efficient use of time during the PRAC plenary. All signals remain subject to a rigorous assessment and adoption of a PRAC recommendation.
- The processes for tracking and communicating the timetables for signals for NAPs, communicating safety issues for NAPs received from other regulatory authorities and tracking and communicating of Emerging Safety Issues were streamlined for simplicity and clarity.
- The publication of the list of Designated Medical Events (DMEs), or medical conditions that are inherently serious and often medicine-related. EMA and Member States use it to focus on reports of suspected adverse reactions that deserve special attention, irrespective of statistical criteria used to prioritise safety reviews. The list[9] can be found on the Signal management section of the EMA website.
- Work continued on the revision of the Module IX of the GVP – Signal management, taking into comments received during the public consultation phase.
- The Signal Management worksharing list[10] was updated, aligning it with PSUSA leads and allocating a further 600 substances to Lead Member States for worksharing in monitoring of EudraVigilance and signal management. Publication is foreseen in spring 2017.
- The group closely followed the work of the Strengthening Collaborations for Operating Pharmacovigilance in Europe joint action (SCOPE). Work packages 4 and 5 which deal with ADR collection and signal management from the perspective of MSs reached important milestones, including the finalisation of the Best Practice guide, training materials and associated workshops.

[9] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000587.jsp&mid=WC0b01ac0580727d1b

[10] http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/10/WC500133308.xls

Annex VII - Requests for information and documents

In 2016, 63 requests were responded to (the same as in 2015). Several requests involved multiple substances, whole therapeutic classes or required complex analyses. Three queries received one or more follow-up requests. A similar percentage of all requests (43%), as in previous years, originated from the EU regulatory network, as part of ongoing safety reviews, including five requests in the context of EU referrals (i.e. metformin, trimetazidine, direct acting antivirals, Symbioflor and retinoids).

Requests for information (referred to also as frequency tables) and requests for access to documents (line listings) accounted for 40% and 44%, respectively; the remaining 16% of requests concerned access to both information and documents (comparable to 2015). Requests related to centrally authorised products (CAPs) alone accounted for 47% of the total number of requests and 22% of requests were related to nationally authorised products (NAPs), compared to 40% and 29%, respectively, in 2015. An increase of 19% was observed in requests from academia, including two research requests requiring large volume of data. The highest number of external requests (19%) was received from the UK.

The median response time for the requests was seven working days (range 0.5-76 days). Three requests (4.8%) were responded to past the deadline due to their complexity, whilst a majority of the requests (73%) were answered within 14 days. A pilot with the AskEMA team was undertaken from May to November 2016, to align the process with other access to documents requests across the Agency. The results concluded that the changes did not seem to lead to non-compliance with the deadlines.

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

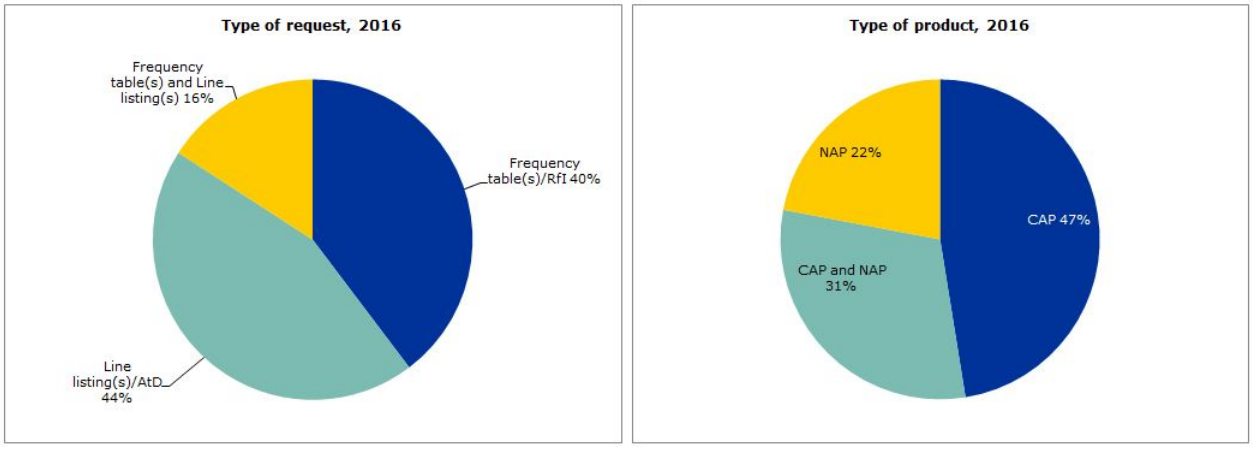
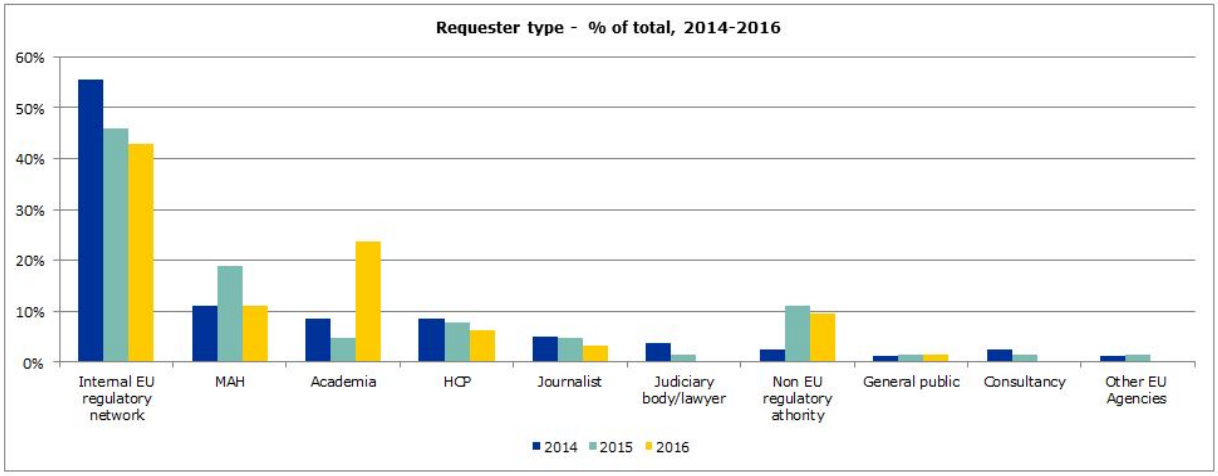


Figure 17: Overview of requests for EV data by type of request (left) and type of product (right).



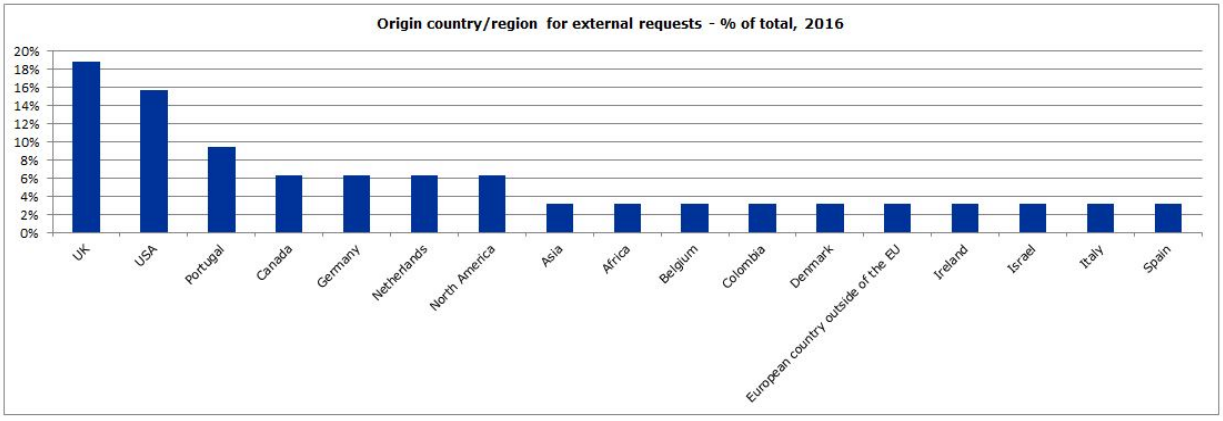


Figure 18: Overview of requests for EV data by type of requester (top) and country or region of origin for external requests (bottom).

Overview of requests responded to in 2016

Type of requester	Substance / product	Issue	Type of request
HCP	Cervarix, Gardasil, Enzira, M-M-Rvaxpro and Priorix	Aggregate number of reported adverse events by year	Frequency table(s)/RFI
Academia	All products	Cardiac ADRs	Line listing(s)/ATD
Internal EU regulatory network	Cloxacillin, dicloxacillin, flucloxacillin, nafcillin and oxacillin	Metabolic acidosis	Frequency table(s)/RFI and Line
Journalist	Tecfidera	Reported cases of PML	Line listing(s)/ATD
Consultancy	Aubagio/Teriflunomide	Cases with fatal outcome	Line listing(s)/ATD

Type of requester	Substance / product	Issue	Type of request
Non-EU regulatory network	Lixisenatide/Lyxumia	Post-marketing cases of serious allergic reactions/hypersensitivity	Frequency table(s)/RFI
MAH	Pradaxa	Pulmonary alveolar haemorrhage	Line listing(s)/ATD
Internal EU regulatory network	Metformin	EV data on lactic acidosis	Frequency table(s)/RFI
Internal EU regulatory network	Natalizumab	PML and other risks related to viral infection	Frequency table(s)/RFI
Internal EU regulatory network	Fatty acid amide hydrolase (FAAH) inhibitors	EudraVigilance data of clinical trials with FAAH inhibitors	Frequency table(s)/RFI and Line listing(s)/ATD
Internal EU regulatory network	Trimetazidine	EudraVigilance analysis of cases of parkinsonism per year	Frequency table(s)/RFI
MAH	Pramipexole	Paraphilia	Line listing(s)/ATD
HCP	Pazopanib	Retinal detachment and retinal tear	Line listing(s)/ATD
Internal EU regulatory network	HPV vaccines	Reporting of adverse reactions over time	Frequency table(s)/RFI
Academia	Oncology drugs and vaccines	Research proposal	Line listing(s)/ATD
MAH	Almagate	Reported adverse events in EudraVigilance	Line listing(s)/ATD
Academia	Kinase inhibitors	Adverse events of kinase inhibitors used in oncology	Frequency table(s)/RFI
Internal EU regulatory network	Denosumab	Data in the paediatric population	Frequency table(s)/RFI
Internal EU regulatory network	N/a	Cases on the ingestion of the desiccant in medicinal products	Frequency table(s)/RFI
MAH	All	Listings of all PTs from Eudravigilance, and total number of cases for each PT	Frequency table(s)/RFI

Type of requester	Substance / product	Issue	Type of request
Non-EU regulatory network	Talc	Cases of cancer	Frequency table(s)/RFI
Journalist	Eslicarbazepine	Specific case reports	Frequency table(s)/RFI
Internal EU regulatory network	Mylan Generics products	Medication errors involving similar pack design	Frequency table(s)/RFI
Academia	Remicade and Adalimumab	Adverse events per year	Frequency table(s)/RFI
Academia	Etanercept	Adverse events per year	Frequency table(s)/RFI
MAH	Dimetindene	All cases	Frequency table(s)/RFI
Patient	Gardasil	Particular ADR report	Line listing(s)/ATD
Academia	Paediatric drugs	Paediatric data	Line listing(s)/ATD
Non-EU regulatory	Velcade	Medication errors	Frequency table(s)/RFI and
Academia	Nexplanon	Case reports of contraceptive implants in the lung	Line listing(s)/ATD
Internal EU regulatory network	Lenalidomide	Secondary malignant neoplasms in children	Frequency table(s)/RFI
Academia	Inflecta and Remsima	Adverse events per year	Line listing(s)/ATD
Internal EU regulatory network	Direct-acting antivirals	Hepatic ADRs	Frequency table(s)/RFI
Internal EU regulatory network	Briviact and Brivirac	Possible cases involving name confusion	Line listing(s)/ATD
Internal EU regulatory network	Imbruvica/ Ibrutinib	Cases of PML	Line listing(s)/ATD
HCP	Gadolinium	Anaphylaxis deaths from radiological contrast media	Line listing(s)/ATD
Academia	Metoclopramide	Anxiety	Line listing(s)/ATD

Type of requester	Substance / product	Issue	Type of request
Academia	Respiratory medicines	Data for research	Frequency table(s)/RFI
MAH	All fumaric acid esters	PML and malignant neoplasms	Line listing(s)/ATD
Internal EU regulatory network	Fluoroquinolones	EV analysis for uveitis	Frequency table(s)/RFI and Line
Academia	Bupropion, clenbuterole, olanzapine, quetiapine, salbutamol, venlafaxine, zaleplon, zopiclone, zolpidem	Data related to abuse/dependence cases	Line listing(s)/ATD
Academia	All drugs in the database	Nephropathies	Line listing(s)/ATD
Internal EU regulatory network	Empagliflozin	Hepatic disease/injury	Line listing(s)/ATD
Internal EU regulatory network	Proton pump inhibitors	Proton pump inhibitors and gastric polyps	Line listing(s)/ATD
Non-EU regulatory network	All products containing aspirin and/or sodium bicarbonate	GI bleeding	Frequency table(s)/RFI and Line listing(s)/ATD
Internal EU regulatory network	Symbioflor	Art. 31 referral analysis	Frequency table(s)/RFI and Line listing(s)/ATD
MAH	Brintellix	Fatal cases/completed suicide	Line listing(s)/ATD
Internal EU regulatory network	Guanfacine	Analysis of hypertensive encephalopathy/PRES	Frequency table(s)/RFI and Line
Internal EU regulatory network	Retinoids	Art. 31 referral analysis	Frequency table(s)/RFI and Line
Academia	Various products	Adverse event reporting compliance rates in EU	Frequency table(s)/RFI
Internal EU regulatory network	Fluoroquinolones	Musculoskeletal and neuropsychiatric ADRs	Frequency table(s)/RFI
Non EU regulatory authority	Rituximab	Medication errors regarding formulations	Line listing(s)/ATD

Type of requester	Substance / product	Issue	Type of request
Non EU regulatory authority	Homeopathic teething tablets	Neurological adverse events	Line listing(s)/ATD
Academia	Metformin and daclatasvir	Cases of hypoglycaemia	Frequency table(s)/RFI
Internal EU regulatory network	DPP4-inhibitors	ADRs reports in narrow SMQ Pancreatitis	Frequency table(s)/RFI
Internal EU regulatory network	Paracetamol	Data of overdose with modified-release paracetamol products for oral use	Line listing(s)/ATD
Internal EU regulatory network	Cerdelga, Cerezyme, Vpriv, Zavesca	Reported adverse events in Gaucher disease	Frequency table(s)/RFI
Internal EU regulatory network	Zalviso	Reported cases	Frequency table(s)/RFI and Line
Academia	Ceftriaxone	PRR values	Frequency table(s)/RFI
Internal EU regulatory network	Cyclosphosphamide	Fatal cases	Line listing(s)/ATD
Internal EU regulatory network	All drugs in the database	SCARs (severe cutaneous adverse reactions)	Frequency table(s)/RFI
Internal EU regulatory	Gentamicin	Reported adverse events	Line listing(s)/ATD
HCP	Natalizumab, rituximab	PML cases	Line listing(s)/ATD