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Inspections and Human Medicines Pharmacovigilance Division

2015 Annual Report on EudraVigilance for the European Parliament, the Council and the Commission

Reporting period: 1 January to 31 December 2015

[1] 'Figure 1' which had been inserted in error in the Table of contents (p. 2) was removed on 4 May 2016, consequently the numbering of figures has changed.

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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
MHLW	Ministry of Health, Labor and Welfare (Japan)
MS	Member State
NAP	Nationally Authorised Product
NCA	National Competent Authority
PASS	Post-Authorisation Safety Study
PI	Product information
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
PRAC	Pharmacovigilance Risk Assessment Committee
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Review
PSUSA	Periodic Safety Update Single Assessment
QPPV	Qualified Person responsible for Pharmacovigilance
RMP	Risk Management Plan
SUSAR	Suspected Unexpected Serious Adverse Reaction
WHO	World Health Organization
xEVMPD	eXtended EudraVigilance Medicinal Product Dictionary

1. Introduction

Pharmacovigilance is essential for optimising the benefit-risk balance of medicines on the market in the European Union (EU). The EU regulatory network 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 reporting of adverse drug reaction reports, which all MSs and the Agency use for monitoring the safety of authorised medicines on the EU market. EudraVigilance now holds 9.5 million reports referring to 6.2 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 the EU legislation[1] and summarises the EudraVigilance-related activities performed in 2015. These include:

- Collecting and maintaining information on all medicinal products authorised in the EU. The availability of such a complete dataset supports identifying the medicines in reports of suspected adverse drug reactions, as well as the scope of pharmacovigilance procedures (signals, PSURs, referrals) and the administration of pharmacovigilance fees. It also allows Marketing Authorisation Holders (MAHs) to update the details of the qualified person responsible for pharmacovigilance (QPPV) and the pharmacovigilance system master file (PSMF) in a more convenient way without the need for variations.
- Collecting and processing of adverse drug reaction (ADR) reports. The number of reports received continued to increase (1,228,342 reports received in 2015, an increase of 10 percent), as did the number of reports submitted directly by European patients and consumers through the NCAs and MAHs (48,872 reports received in 2015, an increase of 29 percent).
- Ongoing data quality activities, including setting of standards, detecting and managing duplicate reports as well as review and feedback to reporters on the quality of reports they submitted.
- Provision of 21,618 data analysis reports to NCAs for monitoring of EudraVigilance data on medicines safety (electronic reaction monitoring reports - eRMRs) and provision of data analyses in support of detailed assessment of pharmacovigilance product safety issues.
- Review of 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.). EudraVigilance monitoring is performed in collaboration between the NCAs and the Agency. For substances found in 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 and the NCAs also monitor all medicines for which no Lead Member State has been appointed. EMA staff lead on monitoring centrally authorised products and this resulted in 2,372 potential signals reviewed by EMA, of which approximately 88% originated from analysis of data in the EudraVigilance database, reflecting its central role for ADR data monitoring.

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

- The central role of the Pharmacovigilance Risk Assessment Committee (PRAC) including prioritising and assessing safety signals (102 confirmed signals previously validated by the MSs and the Agency were assessed by the PRAC in 2015). Approximately a third of these 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 one case handled via an EU referral procedure, for which the PRAC has made recommendations to minimise the risk.
- A large number of training activities, many of which were open to all stakeholders were organised (see chapter 4):
  - Eight information days/stakeholder platforms: ICSR information day, ISO IDMP information day, 'New services and systems in pharmacovigilance: preparing for business change' information day and five industry stakeholder platform meetings on the operation of the pharmacovigilance legislation
  - Four training sessions on EudraVigilance Data Analysis, training experts from 16 NCAs
  - Twenty training sessions on EudraVigilance data submission, 11 organised at the EMA and 9 organised locally
  - Seven training sessions on the eXtended EudraVigilance Medicinal Product Dictionary (xEVMPD), 5 organised at the EMA and 2 organised locally
  - Four "Introduction to EudraVigilance" training sessions
  - 249 users followed training on xEVMPD via its e-learning platform
- Enhancements of the EudraVigilance database in preparation for its independent audit in 2016 with the aim to bring enhanced functionalities into operation. These functionalities will allow for simplifications based on centralised reporting of ADR reports to EudraVigilance and rerouting to national Competent Authorities in EEA Member States, unprecedented access to ADR data by stakeholders including healthcare professionals, patients and academia, improved data quality and better data analysis as well as faster provision of adverse reactions reports from within the EU to WHO.

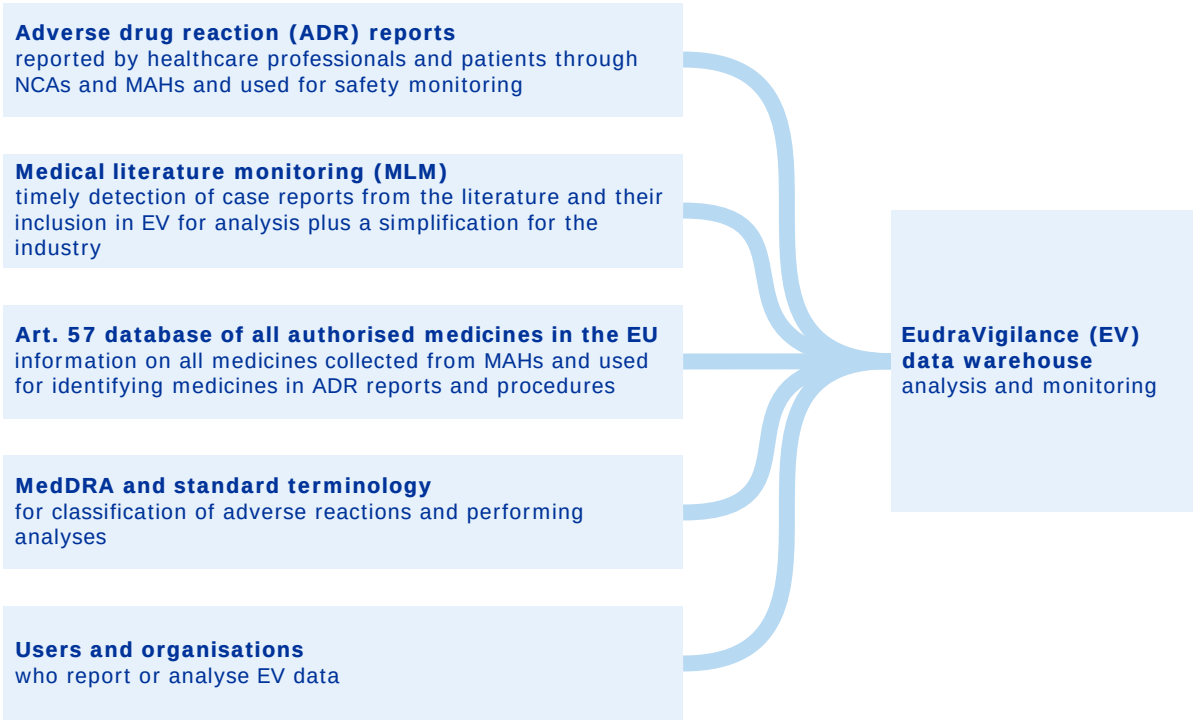


Figure 1. All data sources feeding into the EudraVigilance data warehouse

2. Data collection and data quality

One of the deliverables[1] of the pharmacovigilance legislation is the electronic submission by MAHs of a core data set 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 throughout 2014 and 2015, data were collected in this new format (as part of the xEVMPD). The primary objective of this was facilitating data analysis and signal detection to support better safety monitoring for patients. The total number of individual medicinal products submitted by MAHs as of 1 February 2016 was 650,751. These submissions provide, for the first time, a dataset of all 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.

Reporting of ADRs and patient involvement

Every report of a suspected ADR submitted by a patient or healthcare professional contributes to safety monitoring and thus the safe and effective use of medicines. Additionally, robust research[2] 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 sustained high levels of reporting of suspected ADRs reflect a well-functioning EU pharmacovigilance system. In 2015, 1,228,342 reports related to suspected adverse reactions were collected and managed in

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

EudraVigilance, 360,838 of which originate from the EEA. This is an increase of 2.3 percent over 2014 and 38 percent compared to the year before the introduction of the new legislation. The number of reports submitted directly by European patients and consumers through the NCAs and MAHs is 48,782, an increase of 29 percent. Detailed information relating to these reports is provided in Annex II.

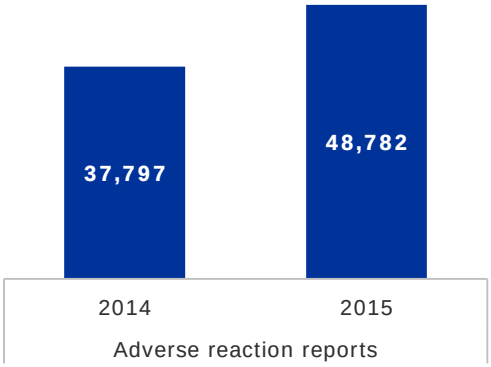


Figure 2. The number of adverse reaction reports by European patients and consumers through the NCAs and MAHs

EudraVigilance continues to support the reporting of suspected unexpected serious adverse reactions (SUSARs) in accordance with EU clinical trial legislation[1] and details are provided in Annex II.

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 as well as adequate case documentation.

EMA's efforts to improve data quality include the provision of training to reporters, detecting and merging duplicate reports, performing data quality reviews of individual case safety reports (ICSRs), providing feedback to individual reporting organisations concerning xEVMPD submissions and conducting recoding of adverse reaction reports utilising the medicinal product data of the xEVMPD. These activities are summarised in Annex IV.

3. Data analysis

Statistical outputs called electronic reactions monitoring reports 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 2015, a total of 21,618 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. Other sources of potential signals include national reviews, studies, the medical literature and information from other regulatory authorities.

[1] 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

EudraVigilance monitoring is performed in collaboration between the NCAs and the Agency. For substances found in 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 and the NCAs also monitor all medicines for which no Lead Member State has been appointed. EMA staff lead on monitoring centrally authorised products and of 2,372 potential signals which were reviewed by the Agency in 2015, around 88% originated from EudraVigilance, highlighting its central role for ADR data monitoring.

All detected validated signals which are confirmed by the Rapporteur or lead MSs 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 2015 was 102, compared with 90 in 2014. Of these 102 signals, 61 were validated by the Agency and 41 were validated by the MSs; overall 64% included data from EudraVigilance as their source. Thirty-four (33%) of the assessed signals resulted directly in a recommendation for an update of the product information that informs patients and healthcare professionals in the safe and effective use of the medicines. In four of these cases, a Direct Healthcare Professional Communications (DHPC) was also recommended by the PRAC to highlight new important safety information. The evaluation of another four signals led to an update of the RMP, one signal is being accessed through a referral procedure and one will be assessed through a Post-Authorisation Safety Study (PASS). Twenty seven (26%) signals were closed and will be subject to routine safety monitoring. The evaluation of 35 signals (35%) is currently ongoing, including 20 via a follow up signal procedure and 15 in the next PSUR/PSUSA. Serious adverse reactions assessed by the PRAC in 2015 included, among others, ADRs occurring in children, disorders of the blood, cardiovascular, gastrointestinal, musculoskeletal, respiratory, neurological and psychiatric reactions and drug interactions.

Early detection and timely assessment of new adverse drug reactions, or new aspects of already known adverse drug reactions (such as changed frequency or severity) results in prompt provision of information to prescribers and patients, or the introduction of additional risk minimisation activities. Further details on all signals assessed by the PRAC 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 650,000 medicinal products authorised in the EU (Art. 57 database), regardless of their authorisation procedure. This, together with ADR data is used to support a wide array of pharmacovigilance procedures including the assessment of Periodic Safety Update Reports and PSUR single assessments and EU referral procedures. Data on medicinal products is also used for the administration of pharmacovigilance fees.

4. Transparency, communication and training

Public access to aggregated EudraVigilance data has been available since 2012 via www.adrreports.eu. At the end of 2015, this included data for a total of 2,160 active substances (including 569 substances in 815 centrally authorised medicinal products and 1,591 substances in nationally authorised products).

Furthermore, the EudraVigilance Access Policy underwent a major revision[1] in preparation for enhanced access to EudraVigilance, and this policy was adopted by the Agency's Management Board in December 2015. This will result in an increased amount of information available for patients, healthcare providers and academia, access for MAHs to comply with their monitoring obligations, and

[1] http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/12/WC500199048.pdf

provision of ADR data to the WHO Uppsala Monitoring Centre taking into account the need to protect personal data in compliance with EU data protection law. The enhanced access is planned to come into effect in the third quarter of 2017.

In 2015, the EMA organised five industry stakeholder platform meetings which supported the further development of EudraVigilance and to aid with change management. Additionally, an Annual stakeholder forum on implementation of pharmacovigilance legislation was organised. Four "updates" on the Pharmacovigilance Programme were published on the Agency's website[1], summarising the latest developments regarding medical literature monitoring, database of medicinal products (Art. 57), PSUR repository, pharmacovigilance fees and ADR reporting/signal management. These specify the corresponding actions for the MAHs in preparation for business change and the timelines for their implementation.

The PRAC agendas, minutes and signal recommendations continue to be published every month. Starting in January 2015, PRAC recommendations for changes to the product information following signal assessments are now routinely translated into all official EU languages and published on the EMA website. This enhances harmonisation of the product information wording and decreases the workload for the MAHs and MSs in submitting and assessing variations.

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. Approximately half of all requests were received from the EU regulatory network, in support of scientific assessment of pharmacovigilance procedures. An increase was noted in requests from non-EU regulatory authorities and from MAHs. In total, 63 requests were answered in 2015. All requests were answered within agreed timelines, with a median of 14 days. For further details please refer to Annex VII.

Four training sessions on the EudraVigilance Data Warehouse and Analysis System were delivered, training 62 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.

In total, 20 training sessions on Eudravigilance data submission, 7 training sessions on the xEVMPD and 4 introductory sessions to Eudravigilance were organised in 2015. Additionally, 249 users underwent training on xEVMPD via its e-learning platform.

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, while significant progress was made for users of the systems, particularly with respect to accessing and analysing data, technical improvements of the EudraVigilance system were ongoing in 2015 and will continue through 2016.

[1] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000520.jsp&mid=WC0b01ac05804fa031

5.1. Medicinal product information

In compliance with Article 57 of Regulation (EC) No. 726/2004, the eXtended EudraVigilance Medicinal Product Dictionary (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 for transparency. In order to fully utilise the medicinal product data collected in the xEVMPD, EMA increased its data validation activities to ensure the accuracy of the information and also created and published the Article 57 dashboard, giving competent authorities direct access to a subset of the data held in the xEVMPD for the first time. Details on the collection of submissions are in Annex III and on the data quality activities in Annex IV.

In December 2015 the EMA's Management Board confirmed that the Article 57 database of medicines authorised in the EU can now be 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 where the Pharmacovigilance System Master File (PSMF) of the marketing-authorisation holder of a given medicine is held.

5.2. Medical literature monitoring

To enhance the efficiency of reporting, reduce the duplicate reports in the database and to provide a simplification for the pharmaceutical industry, the EU pharmacovigilance legislation[1] introduced an obligation on EMA to monitor selected medical literature for reports of suspected adverse reactions to medicinal products containing certain active substances and to enter relevant information from the selected medical literature into the EudraVigilance database. The process was designed 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 EMA outsourced the monitoring of scientific and medical literature to a service provider and a contractor was appointed in April 2015.

The service was launched in July 2015, monitoring for 50 pharmaceutical substance groups. In September 2015 the service was extended to the full scope, covering 300 chemical substance groups and 100 herbal substance groups. Since the launch of the medical literature monitoring service, 115,550 literature references were reviewed and the outcome published on a daily basis. 1,464 adverse drug reaction reports, referring to 756 individual cases were entered in EudraVigilance and made available to NCAs and MAHs.

5.3. Extension of publication of adverse drug reaction information

In 2015 EMA worked on increasing the number of languages in which the main pages of the website www.adrreports.eu are available. To provide transparency to stakeholders, this site publishes information on ADRs for the general public and healthcare professionals, allowing reports on these to be reviewed by medicinal product, active substance, reaction, age and gender. Further information on this is provided in section 4.

5.4. EudraVigilance functionalities that will be subject to audit

In preparation for the independent audit foreseen in 2016, EMA has continued developing the EudraVigilance database where many of the IT development activities of the new EudraVigilance system have been completed. These include:

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

- Simplification of the reporting of adverse reaction reports, in particular for MAHs for which EudraVigilance will become a single reporting point in the EEA and the 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).

In 2015 the EMA published key documents for the future of EudraVigilance to support the IT and business changes that will be required for stakeholders. These include the EudraVigilance Stakeholder Change Management Plan[1] and the revised EudraVigilance Access Policy[2]. By the end of 2015 most of the IT enhancements had been delivered and these will go through extensive testing in 2016 prior to the independent audit of the EudraVigilance system.

6. Conclusion

Pharmacovigilance is a collective responsibility with a critical role for the EU Regulatory Network. EudraVigilance has a central role in the safety monitoring of medicines on the EU market, through collecting adverse drug reaction reports, detecting new risks and identifying risks which have changed based on screening ADR reports and in routine support of all pharmacovigilance procedures. EudraVigilance now contains 9.5 million reports referring to 6.2 million cases.

The number of adverse drug reaction reports collected in EudraVigilance continued to increase, including reports submitted directly by patients and consumers. The NCAs and the Agency jointly received in excess of 21,600 statistical outputs for review of newly received ADR reports. The timely detection of signals together with benefit-risk evaluation in periodic safety update reports and risk management planning and their assessment by the PRAC are the cornerstone of EU pharmacovigilance, allowing safe and effective use of medicines and timely access to innovative medicines.

Several projects implementing provisions of the pharmacovigilance legislation reached operation in 2015. The medical literature monitoring has been piloted and launched into full operation in September 2015. The establishment of a comprehensive database of all authorised medicinal products on the EU market and its routine use since July 2015 allows the Agency and the MSs to correctly identify medicinal products and substances in ADR reports, supports the literature monitoring service, informs the scope of pharmacovigilance procedures (PSURs, referrals) and allows the Agency to collect annual pharmacovigilance fees, with the first ‘annual-fee’ invoices issued to MAHs in July 2015. The revised EudraVigilance Access Policy was adopted by the Management Board in Dec 2015, paving the way for enhanced access to adverse drug reaction reports in 2017.

The development of the EudraVigilance database has continued in collaboration with the MSs throughout 2015 in preparation of its independent audit in 2016 and in order for its enhanced functionalities to become fully operational and deliver new tools and simplifications in 2017.

[1] EudraVigilance stakeholder change management plan (EMA/797114/2014)
[2] European Medicines Agency policy on access to EudraVigilance data for medicinal products for human use (EudraVigilance Access Policy) (EMA/759287/2009 Revision 2)

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 2015
Data quality review and duplicate management of adverse reaction reports in EudraVigilance [Legal basis: Regulation (EC) 726/2004, Article 24(3)]	Continued during 2015
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 2015
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 2015
Access to adverse reaction data held in EudraVigilance for CAPs http://www.adrreports.eu/ [Legal basis: Regulation (EC) 726/2004, Article 24]	Continued during 2015
Operation of the Medical Literature Monitoring service [Legal basis: Regulation (EC) 726/2004, Article 27]	Started in 2015

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 reaction reports between the EMA, medicines regulatory authorities and 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.

During 2015, a total of 19,447,374 transactions were successfully performed by the EudraVigilance gateway. Figure 1 presents the total number of transactions performed per month during 2015.

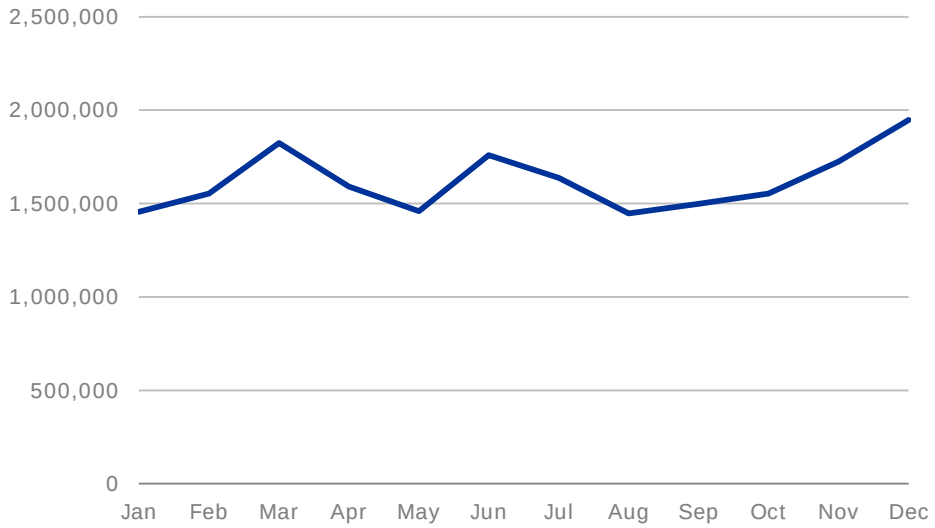


Figure 3. Total number of transactions performed per month at the level of the EudraVigilance Gateway from 1 January 2015 – 31 December 2015

EudraVigilance database

For medicinal products authorised in the EEA, adverse reactions reports are collected from both within and outside the EEA.

The numbers presented in figure 2 refer to the adverse reaction reports received in the post-authorisation module. During 2015, an average of 102,362 adverse reaction reports were received and processed per month and subsequently made available for signal detection and data analysis by EMA and medicines regulatory authorities in the Member States.

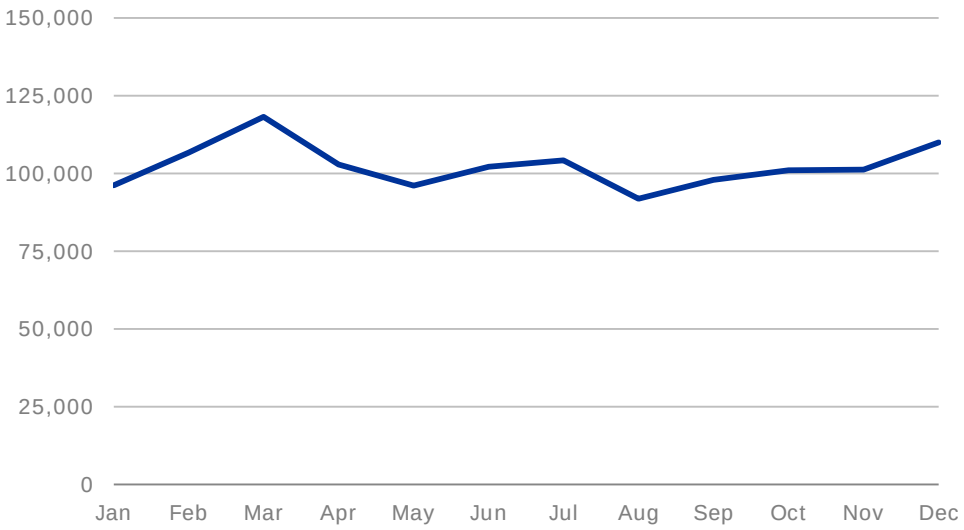


Figure 4. Number of adverse reaction reports processed per month in the EudraVigilance database post-authorisation module in 2015

Figure 3 presents the total number of adverse reaction reports received in the post-authorisation module grouped by EEA and non-EEA for 2015. 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 reaction reports or individual case safety reports (ICSRs).

The total number of ICSRs received in Eudravigilance in 2015 was 1,228,342, which represents an increase of 10% compared to 2014.

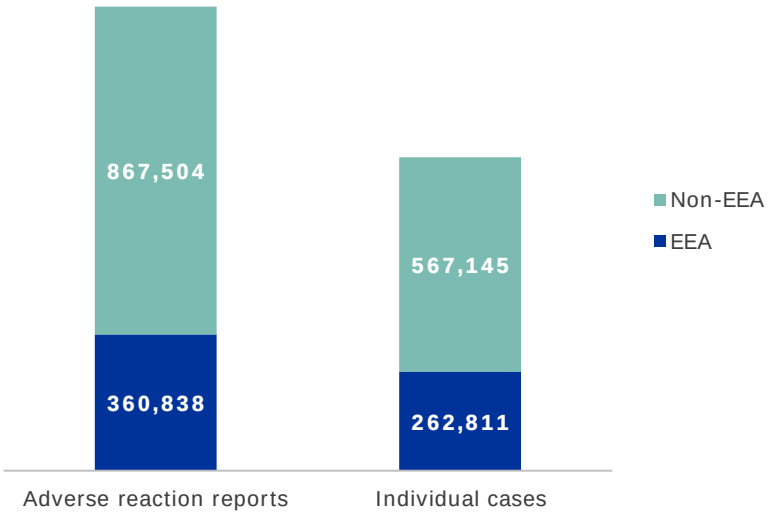


Figure 5. Number of individual cases/adverse reaction reports processed between January and December 2015 in the EudraVigilance database post-authorisation module

By 31 December 2015, the EudraVigilance database (both post-authorisation and clinical trials modules) held a total of 9,530,295 adverse reaction reports, referring to 6,212,064 individual cases (see figure 5).

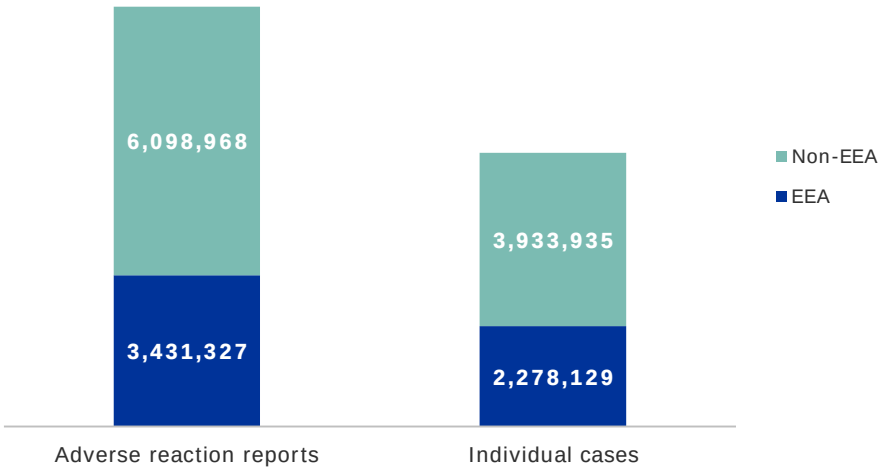


Figure 6. Total number of individual cases/adverse reaction reports received in the EudraVigilance database from its inception in December 2001 until 31 December 2015

In 2015, 48,782 adverse reaction reports were submitted by European patients and consumers through the NCAs and MAHs, referring to 36,483 individual cases. This is an increase of 29 percent over previous year (figure 6).

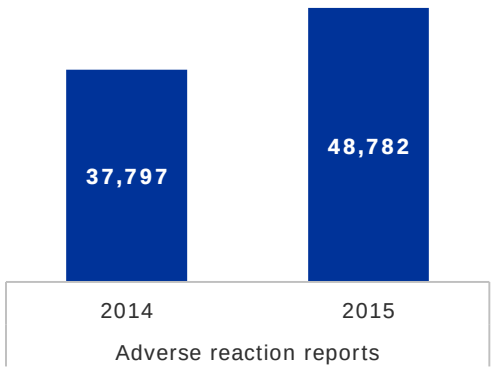


Figure 7. The number of adverse reaction reports by European patients and consumers through the NCAs and MAHs

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

- A total of 886 MAHs (at headquarter level) have sent reports to the EudraVigilance Post-authorisation Module (EVPM) in the period between 1 January 2002 and 31 December 2015.

- A total of 848 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 2015.

Tables 1 and 2 below show the total number of unique cases and ICSRs transmitted by MAHs and sponsors to EVPM and EVCTM and 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 1. Number of adverse reaction reports and individual cases transmitted by MAHs and sponsors to EVPM and EVCTM during 2014

EV Module	Transmission type	Number of transmissions
EVPM	ICSRs	944,822
	Individual cases	618,831
EVCTM	ICSRs	74,193
	Individual cases	29,539

Table 2. Combined 15-day reporting compliance to EVPM for all MAHs and sponsors in 2015

Percentage of ICSRs transmitted to EVPM by MAHs/Sponsors within 15 days:	89.0%

E-reporting status for National Competent Authorities

- All 32 NCAs 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.

Tables 3 and 4 below show the total number of unique cases and ICSRs transmitted by NCAs to EVPM and EVCTM and 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.

The overall NCA 15-day reporting compliance was 90.6%.

Table 3. Number of ICSRs and unique cases transmitted by NCAs to EVPM and EVCTM during 2015

EV Module	Transmission type	Number of transmissions
EVPM	ICSRs	283,520
	Individual cases	212,095
EVCTM	ICSRs	7,098
	Individual cases	2,880

Table 4. Combined 15-day reporting compliance to EVPM for all NCAs in 2015

Percentage of ICSRs transmitted to EVPM by NCAs within 15 days:	90.6%

During 2015, the following 10 NCAs transmitted SUSARs to EVCTM (SUSARs from other countries were received directly from sponsors of clinical trials):

- Belgium (Federal Agency for Medicines and Health Products)
- Denmark (Danish Health and Medicines Authority)
- Estonia (State Agency of Medicines)
- Finland (Finnish Medicines Agency)
- Germany (Federal Institute for Drugs and Medical Devices)
- Germany (Paul-Ehrlich-Institut)
- Hungary (National Institute of Pharmacy and Nutrition OGYEI)
- Ireland (Health Products Regulatory Authority)
- Netherlands (College ter Beoordeling van Geneesmiddelen)
- United Kingdom (Medicines and Healthcare Products Regulatory Agency)

EudraVigilance database and support of signal management process

A total of 21,618 eRMRs were generated in 2015 to facilitate the continuous monitoring of the safety of medicines by the EMA and medicines regulatory authorities in the EEA. Of these, 15,879 were routine eRMRs (produced monthly) and 5,739 were additional eRMRs (produced fortnightly).

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 Period Safety Update Report(s) submissions and Referral procedures;
- supporting literature monitoring activities;
- facilitating NCAs' inspections (e.g. sharing information on Pharmacovigilance Master File location);
- collecting pharmacovigilance fees.

MAHs were required to resubmit their medicinal product information in accordance with the new format between 16 July 2014 and 31 December 2014. These data are being validated by the EMA (see Annex IV for a summary of the validations performed in 2015). Table 5, below, provides a summary of the data resubmitted in the new format as of 1 February 2016.

Table 5. Summary of medicinal product submissions to the xEVMPD

Total number of medicinal product submissions in new format by MAHs by 1 February 2016 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	650,751
Total number of marketing authorisation holders (legal entities) established in the EU (corresponding to EudraVigilance codes)	4,444

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, in collaboration with the EU network, operates procedures to ensure the quality and integrity of the information collected in EudraVigilance. This includes identifying duplicate reports, performing the coding of the reported medicines and reported active substances, and providing feedback on the quality of both adverse reaction reports and medicinal product information sent by NCAs, MAHs and sponsors. Table 6, below refers to the data quality activities performed by the EMA in 2015.

Table 6. Summary of EudraVigilance data quality activities in 2015

Data quality area	Activities performed
Identifying and managing duplicates	Number of duplicate couples assessed: 31,797 (in 2014 this was 133,870)
	Number of 'master' reports generated based on duplicated data: 40,022 (In 2014 this was 48,073)
Coding of reported medicines and active substances	Number of reported medicinal products/active substance terms recoded: 29,424 (In 2014 this was 67,476)
	Number of adverse reaction reports recoded: 54,535 (referring to 30,245 individual cases). In 2014 645,603 adverse reaction reports were recoded, referring to 172,081 individual cases.
Providing feedback on data quality	Total number of organisations subject to ICSR data quality review: 51 (In 2014 this was 104)
	Number of medicinal products in the xEVMPD quality reviewed and, where necessary, corrected: 362,858

The amount of ICSR data quality reviews has decreased from 2014 to 2015 because EMA focussed the quality management budget on medicinal products in the xEVMPD for part of the year. The figure will be greater in 2016.

The coding of reported medicines and active substances has decreased from 2014 because more reported terms are being automatically recoded. This is partly due to the cumulative nature of the recoding work and partly due to the increasing completeness of the xEVMPD, against which all recoding activity is ultimately performed.

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 2015, there were a total of 2,372 potential signals (i.e. drug-event pairs from screening of the EudraVigilance database, medical literature, information received from other regulatory authorities etc.) reviewed in detail by the Agency's Signal Management Team. This represents an increase of 17% compared to the previous year. This increase can most likely be explained by the increased number of ICSRs received in EudraVigilance.

OVERVIEW	2015	2014	2013	2012	2011
Total	2,372	2,030	2,449	2,213	1,586
difference	342	-419	236	627	-468
% compared to previous	17%	-17.1%	10.7%	39.5%	-22.8%

Overall the major source of EMA potential signals in 2015 continues to be EudraVigilance, from which 87.8% of potential signals originated. This result parallels that of the previous year (86.7% in 2014). In addition to EudraVigilance, an increase in potential signals from the scientific literature was also observed (8.7% of potential signals). A further 2.3% originated from communications received from other regulatory authorities (23 from the FDA, 19 from PMDA/MHLW, 7 from Health Canada and 7 from the WHO) and 1.2% from other sources. The overview by action taken is provided below:

Action taken	Number of potential signals Jan-Dec 2015	% of total	Number of potential signals Jan-Dec 2014	% of total
Not validated (closed)	2,045	86.2%	1,657	81.6%
Ongoing	176	7.4%	280	13.8%
Monitored	90	3.8%	59	2.9%
Prioritised and assessed by PRAC	61	2.6%	34	1.7%
Total	2,372	100.0%	2,030	100.0%

In 2015, there was a substantial increase in the number of signals validated by the Agency and assessed by the PRAC, compared with the previous year (61 signals in 2015 and 34 in 2014). The number of potential signals kept under monitoring has increased to 3.8% (2.9% in 2014).

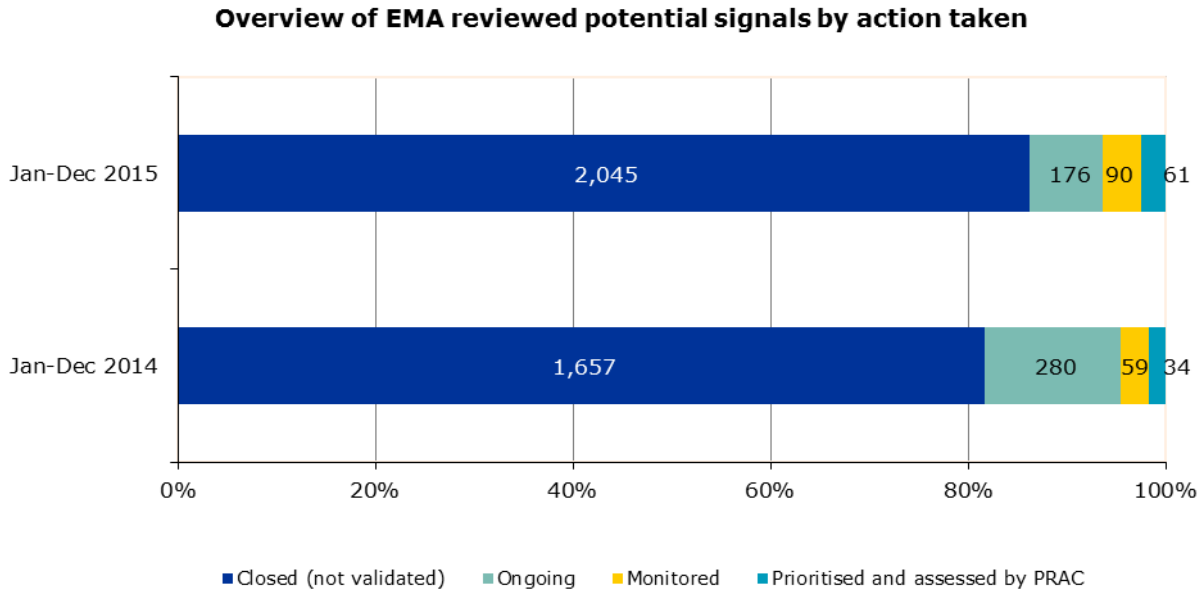


Figure 1: Overview of EMA reviewed potential signals by action taken.

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 2015 was 102, compared with 90 in 2014. Of these 102 signals, 61 were validated by the Agency and 41 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 64% included data from EudraVigilance as their source.

Thirty-four (33%) 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 four of these cases, Direct Healthcare Professional Communications (DHPC) were also recommended by the PRAC to highlight new important safety information. The evaluation of another four signals lead to an update of the RMP, one signal is being accessed through a referral procedure (the PRAC has made recommendations to minimise the risk) and one will be assessed through a Post-Authorisation Safety Study (PASS). Twenty seven (26%) signals were closed and will be subject to routine safety monitoring. The evaluation of 35 signals (35%) is currently ongoing, including 20 via a follow up signal procedure and 15 in the next PSUR/PSUSA.

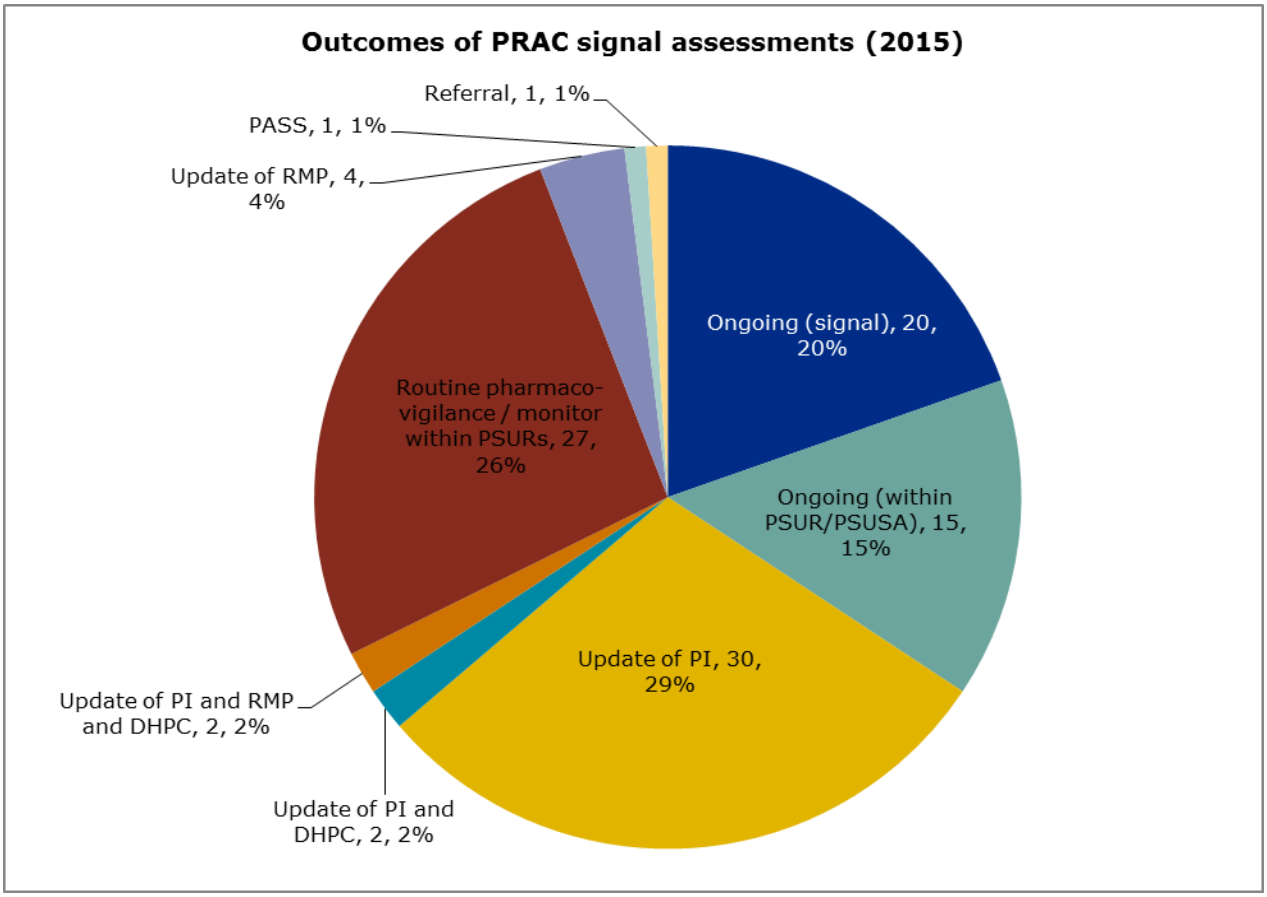


Figure 2: Outcomes of PRAC signal assessments (2015). PI: product information, DHPC: Direct Healthcare Professional Communication, RMP: Risk Management Plan, PASS: Post-Authorisation Safety Study, PSUR: Periodic Safety Update Report, PSUSA: PSUR Single Assessment.

A list of all signals prioritised and assessed by the PRAC in 2015 is provided below, noting the latest status or outcome as of 12 January 2016.

Drug	Issue / Signal	Status or outcome
Adalimumab	Autoimmune haemolytic anaemia (AIHA) and Haemolytic anaemia	ongoing (Signal procedure)
Adalimumab	Convulsion	routine pharmacovigilance / monitor within PSURs
Adalimumab	Glomerulonephritis	ongoing (Signal procedure)
Aflibercept	Higher systemic exposure compared to ranibizumab after intravitreal injection	routine pharmacovigilance / monitor within PSURs
Aliskiren	Severe hyponatraemia leading to neurological symptoms	update of PI
Alogliptin; Linagliptin	Arthralgia	ongoing (Signal procedure)
Amikacin	Drug reaction with eosinophilia and systemic symptoms (DRESS)	routine pharmacovigilance / monitor within PSURs
Amiodarone	Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH)	update of PI
Amiodarone	Pancreatitis	update of PI
Anakinra	Thrombocytopenia	update of PI
Angiotensin-converting enzyme (ACE)-inhibitors: benazepril, captopril, cilazapril, delapril, enalapril, fosinopril, imidapril, lisinopril, moexipril, perindopril, quinapril, ramipril, spirapril, trandolapril, zofenpril	Hallucinations	routine pharmacovigilance / monitor within PSURs
Aripiprazole	Aggression and related events	update of PI
Aripiprazole	Hyperprolactinaemia	update of PI
Atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, simvastatin	Immune-mediated necrotising myopathy (IMNM)	update of PI
Atypical antipsychotics: aripiprazole; asenapine; clozapine; lurasidone; olanzapine; paliperidone; quetiapine; risperidone; sertindole; ziprasidone; zotepine	Acute renal failure	routine pharmacovigilance / monitor within PSURs
Axitinib	Nephrotic syndrome	ongoing (Signal procedure)

Drug	Issue / Signal	Status or outcome
Bcr-abl tyrosine kinase inhibitors	HBV reactivation	ongoing (Signal procedure)
Benzodiazepines	Alzheimer's disease	routine pharmacovigilance / monitor within PSURs
Bevacizumab	Generalised tonic-clonic seizures	ongoing (within PSUR/PSUSA)
Bisphosphonates (alendronic acid; alendronic acid, colecalciferol; clodronic acid; etidronic acid; ibandronic acid; neridronic acid; pamidronic acid; risedronic acid; tiludronic acid; zoledronic acid); Denosumab	Osteonecrosis of the external auditory canal	update of PI[1]
Boceprevir	Hyponatraemia	routine pharmacovigilance / monitor within PSURs
Canagliflozin, canagliflozin, metformin, dapagliflozin, dapagliflozin, metformin empagliflozin, empagliflozin, metformin	Diabetic ketoacidosis	referral
Carbidopa, levodopa	Intussusception	ongoing (Signal procedure)
Clopidogrel	Drug interaction with grapefruit juice leading to potential impairment of therapeutic efficacy	update of PI
Clopidogrel; prasugrel	Safety of dual antiplatelet therapy	routine pharmacovigilance / monitor within PSURs
Clozapine	Myocarditis	ongoing (Signal procedure)
Dabigatran	Pulmonary alveolar haemorrhage	ongoing (within PSUR/PSUSA)
Daclatasvir; Sofosbuvir; sofosbuvir, ledipasvir	Arrhythmia	update of PI and DHPC
Daptomycin	Acute generalised exanthematous pustulosis (AGEP)	ongoing (within PSUR/PSUSA)
Decitabine	Organising pneumonia	ongoing (within PSUR/PSUSA)
Denosumab	Deafness	routine pharmacovigilance / monitor within PSURs
Digoxin	Mortality in patients with atrial fibrillation	routine pharmacovigilance / monitor within PSURs
Donepezil	Rhabdomyolysis	update of PI
Enfuvirtide	Amyloidosis	update of PI

[1] Update of PI applies to bisphosphonates only. For denosumab, the PRAC recommended an update of the RMP.

Drug	Issue / Signal	Status or outcome
Etanercept	Diarrhoea	routine pharmacovigilance / monitor within PSURs
Everolimus	Lymphoedema	update of PI
Fingolimod	Progressive multifocal leukoencephalopathy (PML)	update of PI and DHPC
Flucloxacillin, paracetamol;	Metabolic acidosis following administration of flucloxacillin in association with paracetamol	ongoing (Signal procedure)
Fluoroquinolones ciprofloxacin, enoxacin, flumequine, levofloxacin, lomefloxacin, moxifloxacin, norfloxacin, ofloxacin, pefloxacin, prulifloxacin, rufloxacin	Retinal detachment	ongoing (Signal procedure)
Gadodiamide; Gadopentetic acid; Gadoversetamide	Nephrogenic systemic fibrosis in patients with acute kidney injury	update of PI
HMG-CoA reductase inhibitors: atorvastatin; fluvastatin; lovastatin; pitavastatin; pravastatin; rosuvastatin; simvastatin	Lichenoid drug eruption	routine pharmacovigilance / monitor within PSURs
Hormone replacement therapy (HRT) medicinal products, which are not pharmaceutical forms for vaginal use, containing oestrogens or combined oestrogens-progestagens (tibolone containing products also concerned); bazedoxifene, oestrogens conjugated	Increased risk of ovarian cancer	update of PI
Human fibrinogen / human thrombin	Intestinal obstruction	update of PI and RMP and DHPC
Human normal immunoglobulin	Posterior reversible encephalopathy syndrome (PRES)	ongoing (Signal procedure)
Ibrutinib	Peripheral neuropathy	ongoing (within PSUR/PSUSA)
Infliximab	Rhabdomyolysis	routine pharmacovigilance / monitor within PSURs
Infliximab	Thyroid Gland Disorders	ongoing (Signal procedure)
Interferon alfa-2a; interferon alfa-2b; interferon beta-1a; interferon beta-1b; peginterferon alfa-2a; peginterferon alfa-2b; peginterferon beta-1a	Pulmonary arterial hypertension	update of PI

Drug	Issue / Signal	Status or outcome
Ipilimumab	Vogt-Koyanagi-Harada syndrome (VKH)	update of PI
Latanoprost	Increased reporting of eye disorders, in particular eye irritation, after change of formulation	update of PI
Leflunomide	Colitis	update of PI
Leflunomide	Pulmonary hypertension	update of PI
Lenalidomide	Pulmonary alveolar haemorrhage	ongoing (within PSUR/PSUSA)
Levetiracetam	Encephalopathy	ongoing (within PSUR/PSUSA)
Lithium	Solid renal tumours	update of PI
Long acting GLP-1 agonists: liraglutide, exenatide, albiglutide, dulaglutide	Medullary thyroid cancer	routine pharmacovigilance / monitor within PSURs
Mercaptopurine; azathioprine	Lymphoproliferative disorders	ongoing (Signal procedure)
Methotrexate	Congenital cardiovascular anomaly	ongoing (Signal procedure)
Methotrexate	Progressive Multifocal Leukoencephalopathy (PML), JC Virus Infection	routine pharmacovigilance / monitor within PSURs
Mitotane	Sex hormone disturbances and development of ovarian macrocysts	ongoing (Signal procedure)
Nalmefene	Suicidal ideation	update of RMP
Natalizumab	Anaemia	update of PI
Olanzapine	Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)	ongoing (Signal procedure)
Olanzapine	Angle closure glaucoma	routine pharmacovigilance / monitor within PSURs
Oxybutynin	Psychiatric disorders	update of PI
Palifermin	Increased mortality for unlicensed use in acute lung injury	routine pharmacovigilance / monitor within PSURs
Palifermin	Infection	update of PI and RMP and DHPC
Paliperidone	Accidental exposure of children to oral formulation	update of RMP
Pantoprazole	Subacute cutaneous lupus erythematosus (SCLE)	update of PI
Paracetamol; phenylephrine	Pharmacokinetic Drug Interaction: Increased bioavailability of phenylephrine when co-	routine pharmacovigilance / monitor within PSURs

Drug	Issue / Signal	Status or outcome
	administered with paracetamol	
Paroxetine	Aggression	update of PI
Peginterferon alfa-2a	Acquired haemophilia	ongoing (Signal procedure)
Peginterferon alfa-2a	Guillain-Barré syndrome (GBS)	routine pharmacovigilance / monitor within PSURs
Pemetrexed	Scleroderma	ongoing (within PSUR/PSUSA)
Pertuzumab	Acute renal failure	ongoing (within PSUR/PSUSA)
Pregabalin	Hyponatremia and syndrome of inappropriate antidiuretic hormone (SIADH)	routine pharmacovigilance / monitor within PSURs
Recombinant Factor VIII: Antihemophilic factor (recombinant) Moroctocog alfa Octocog alfa	Inhibitor development in previously untreated patients	ongoing (Signal procedure)
Regorafenib	Acute Pancreatitis	ongoing (within PSUR/PSUSA)
Regorafenib	Haemolysis	ongoing (within PSUR/PSUSA)
Rivaroxaban	Pulmonary alveolar haemorrhage	ongoing (within PSUR/PSUSA)
Saxagliptin; saxagliptin, metformin	Acute kidney injury	PASS
Selective Serotonin Reuptake Inhibitors (SSRIs): citalopoam, escitalopram, fluoxetine, fluvoxamine, mirtazapine, paroxetine, sertraline Serotonin–norepinephrine reuptake inhibitors (SNRIs): duloxetine, venlafaxine	Risk of Autism Spectrum Disorders (ASD) after maternal use of SSRI/SNRI	ongoing (Signal procedure)
Selective Serotonin Reuptake Inhibitors (SSRIs): paroxetine, fluoxetine, fluvoxamine, citalopram, escitalopram, sertraline	New malformative risks in newborn after maternal use of SSRI	routine pharmacovigilance / monitor within PSURs
Sildenafil	Pulmonary haemorrhage in off label paediatric use	update of RMP
Sildenafil	Non-arteritic anterior ischaemic optic neuropathy (NAION)	routine pharmacovigilance / monitor within PSURs
Sitagliptin; vildagliptin	Intestinal obstruction	routine pharmacovigilance

Drug	Issue / Signal	Status or outcome
		/ monitor within PSURs
Sodium containing formulations of effervescent, dispersible and soluble medicines	Cardiovascular events	update of PI
Somatropin	Hypersensitivity reactions	ongoing (within PSUR/PSUSA)
Sorafenib	Acute Generalised Exemanthous Pustulosis (AGEP)	routine pharmacovigilance / monitor within PSURs
Sunitinib	Pneumatosis intestinalis	ongoing (within PSUR/PSUSA)
Tamsulosin	Urinary incontinence	routine pharmacovigilance / monitor within PSURs
Temsirolimus	Myocardial infarction	update of PI
Teriparatide	Angina pectoris	routine pharmacovigilance / monitor within PSURs
Teriparatide	Non-uraemic calciphylaxis	update of RMP
Thioctic Acid	Insulin Autoimmune Syndrome (IAS)	update of PI
Tigecycline	Hypofibrinogenaemia	ongoing (Signal procedure)
Trabectedin	Capillary Leak Syndrome	update of PI
Ustekinumab	Pemphigoid	ongoing (Signal procedure)
Valproate and related substances	Mitochondrial toxicity	update of PI
Vismodegib	Angioedema	ongoing (within PSUR/PSUSA)
Warfarin	Bone density decreased	routine pharmacovigilance / monitor within PSURs
Ziprasidone	Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)	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 2015, the following progress was achieved:

- All PRAC agreed product information changes following signal assessments are now routinely translated into all official EU languages and published on the EMA website. This enhances harmonisation of the product information wording and decreases the workload for the MAHs when submitting variations and for the MSs when assessing them.
- The submission of variations to update the product information was switched from consecutive (i.e. the PI of generic and hybrid products is updated after the conclusion of the update of the PI of the originator product) to concurrent submissions of variations (all MAHs submit PRAC agreed text at the same time). This will lead to faster implementation of new warning and safety information for patients and prescribers in the product information of all medicinal products on the market, and is expected to be up to 10 months quicker in the case of SmPC for generics, than the previous approach.
- Clarifications were agreed regarding the signal confirmation step for signals assessed through other procedures (e.g. ongoing PSUR assessment).
- The list of Designated Medical Events (DMEs) used by the Agency since 2012 has been revised taking into account the experience gained.
- The group was kept updated regarding the progress of the work of the Strengthening Collaborations for Operating Pharmacovigilance in Europe joint action (SCOPE), especially work packages 4 and 5 which deal with ADR collection and signal management from the perspective of MSs.
- Preparatory work on the update of Module IX of the GVP – Signal management was undertaken. This included preparation for signals validated by the MAHs, and amendments to existing processes, refining of the signal confirmation criteria and other process improvements.
- A new eRMR format to widen the scope of EudraVigilance monitoring (i.e. focusing on paediatric and geriatric signal detection, medication error etc.) as well as improving efficiency.
- Completion and assessment of an eRMR pilot phase carried out over 5 months to test new methodology and format changes, with the objectives of efficiency gains, implementation of PROTECT results, enhanced monitoring of special interest groups etc. Results of the pilot were encouraging in all the areas measured (user feedback, workload and capacity to detect signals) and showed both a reduction in the number of highlighted drug-event combinations (reduced workload) and an increase in the number of validated signals.
- Adoption of the draft Addendum to GVP IX which describes components of an effective system for routine screening of spontaneous report data and methodological aspects for detecting potential signals relevant to both MSs and MAHs.

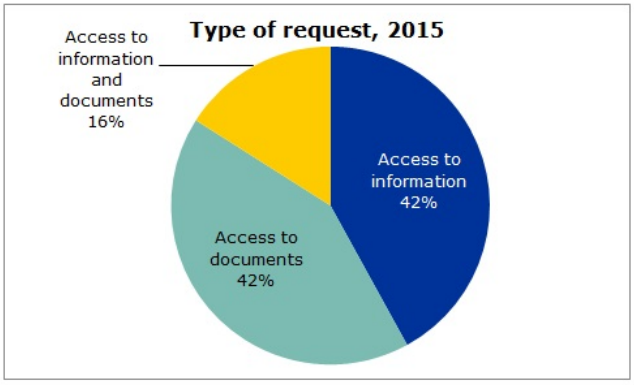
Annex VII - Requests for information and documents

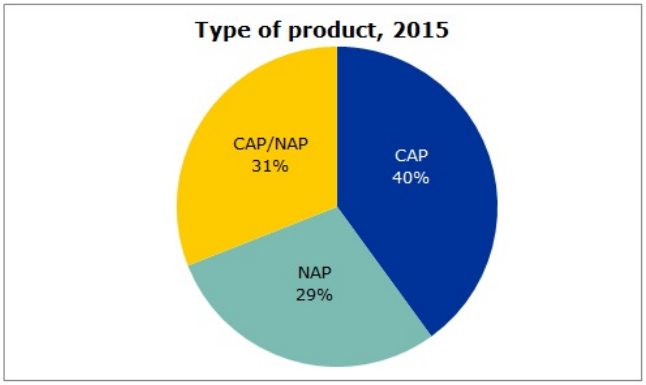
In 2015, 63 requests were answered, which is a decrease compared to 2014 when 82 requests were addressed. Whilst the number of requests may be numerically lower, several involved multiple substances, included whole therapeutic classes or required complex analyses and seven queries received one or more follow-up requests. Nearly half of all requests provided additional information to the EU regulatory network in context of pharmacovigilance assessments including five requests in context of four EU referrals (fusafungine, HPV vaccines, inhaled corticosteroids and Tysabri).

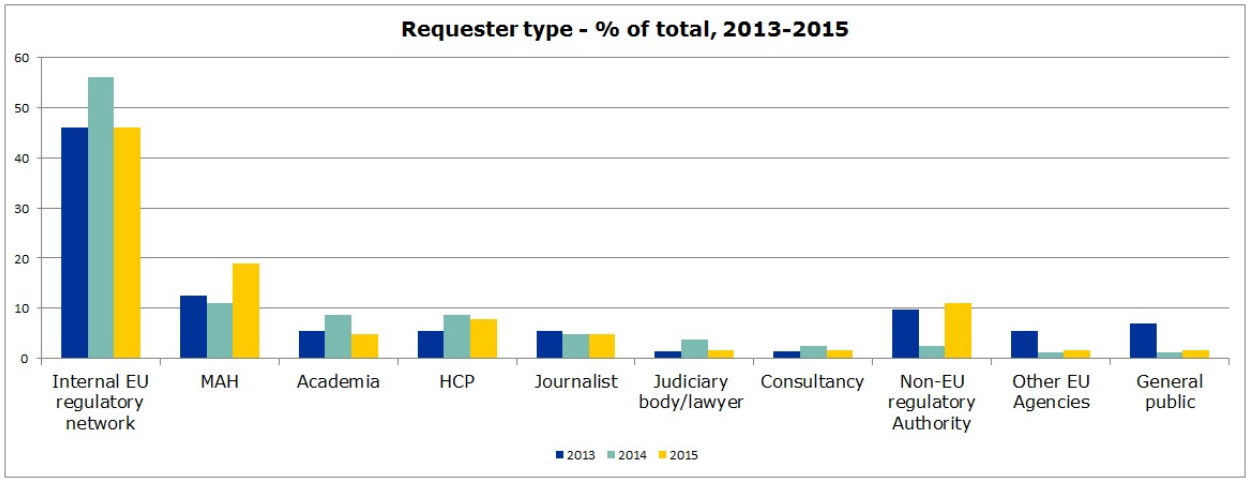
Requests for information and requests for access to documents each accounted for 42% of the requests. 16% of the request concerned both access to information and access to documents. In 2014, 74% of all requests dealt with access to information and 20% dealt with access to documents; 6% were requests for both information and documents. Requests related to nationally authorised products (NAPs) alone accounted for 29% of the total number of requests and 40% of requests were related to centrally authorised products (CAPs) alone, compared to 46% and 44%, respectively, in 2014. An increase was observed in requests from non-EU medicines regulatory authorities and requests from Marketing Authorisation HolderMAHs. The greatest number of requests (26%) was received from the United Kingdom.

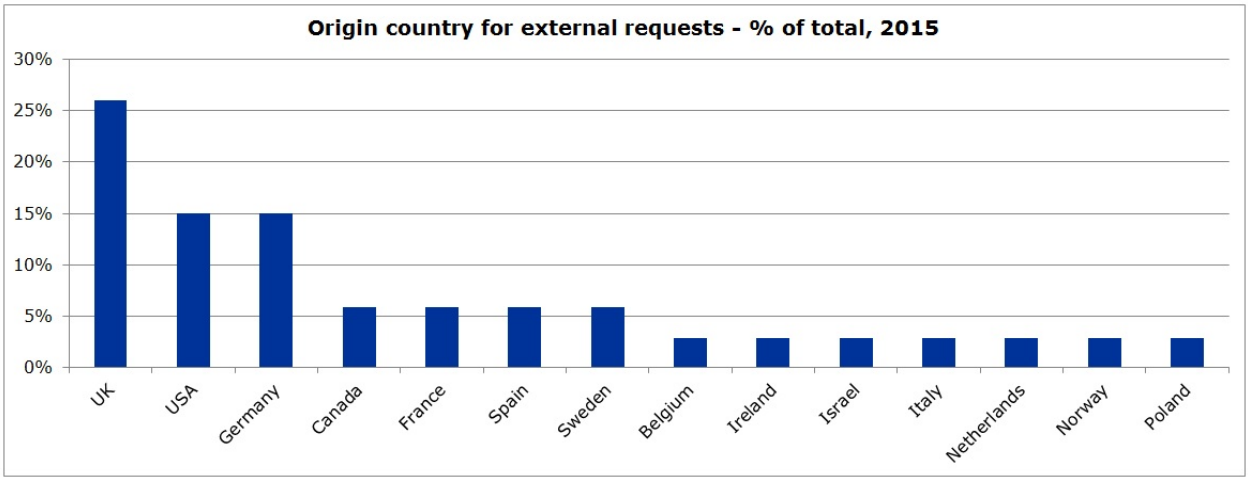
The median response time for the requests was 14 days (range 0-120 days), compared to a median response time of 23 days (range 0-151 days) in 2014. All requests were answered within the timelines as agreed with the requester. More than half of all requests (51%) were answered within 14 days, 76% within 1 month and 95% within two months, which shows an improvement of the response time from 2014 (44%, 61% and 90%, respectively).

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









Overview of requests responded to in 2015

Type of requester	Substance / product	Issue	Type of request
Lawyer	Abilify	Abilify and any kind of thrombosis or formation of blood clots in the veins	Access to documents and information
Non-EU regulatory Authority	Adasuve	All ADRs with Adasuve	Access to information
MAH	All fumaric acid esters	All PML under fumaric acid esters	Access to documents
MAH	All fumaric acid esters	PML and malignomas under fumaric acid esters	Access to documents
MAH	All fumaric acid esters	Update on PML and malignomas under fumaric acid esters	Access to documents
MAH	All fumaric acid esters	All PML under fumaric acid esters and in particular dimethyl fumarate	Access to documents

Type of requester	Substance / product	Issue	Type of request
Academia	All substances	Number of all substances that are suspect or interacting in spontaneous ADR reports from Norway from 2004	Access to information
Internal EU regulatory network	Allergens	All cases in EV	Access to documents
MAH	Almagate	Specific cases with Almagate	Access to documents
MAH	Almogran/Amignul	Specific case related to PSUR assessment	Access to documents
Journalist	Anticoagulants	ADRs with anticoagulants	Access to information
General public	Antidepressants	Reports of withdrawal reactions to antidepressants	Access to documents and information
Non-EU regulatory Authority	Benzatezil	ADRs and cases of quality defect	Access to information
Internal EU regulatory network	Bevacizumab	Cases of eye infections in off label use	Access to documents
Internal EU regulatory network	Bydureon, Trulicity and Eperzan	Cases of Medullary thyroid cancer (MTC) with long-acting GLP-1 agonists	Access to information
Internal EU regulatory network	Corticosteroids (inhaled products)	Inhaled Corticosteroids products and risk of pneumonia in context of referral	Access to information
Internal EU regulatory network	Dextran	All cases in EV	Access to information
Internal EU regulatory network	Dororubicin and Paclitaxel	Medication errors for Caelyx and Abraxane	Access to documents and information
MAH	Eculizumab	ICSR with Eculizumab	Access to documents
Internal EU regulatory network	Eucreas and Galvus	Overview of the ILD in EV	Access to documents
Internal EU regulatory network	Etifoxine	Cases of depression and suicide/self-injury	Access to documents and information
Internal EU regulatory network	Fingolimod	Case narratives of Fingolimod with PML	Access to documents
Internal EU regulatory network	Fusafungine	Serious allergic reactions in children in context of referral	Access to information
Academia	Gabapentinoids	Reports of misuse	Access to documents and information
Internal EU regulatory network	HPV vaccine	EV analysis in preparation of the referral	Access to information

Type of requester	Substance / product	Issue	Type of request
Internal EU regulatory network	HPV vaccine	EV analysis in context of HPV vaccine referral	Access to information
Internal EU regulatory network	HPV vaccine	GI motility	Access to documents and information
Non-EU regulatory Authority	HPV vaccines	Number of non-serious reports relating to HPV vaccines	Access to information
Internal EU regulatory network	HPV vaccines	ADR reports including deaths for HPV vaccines	Access to information
Internal EU regulatory network	Imipenem and Cilastatin	All cases of DRESS in EV with Imipenem-Cilastatin	Access to documents
MAH	Keppra	Polymicrogyria neonatal seizures (off-label use)	Access to documents
MAH	Kineret	Specific cases of thrombocytopenia related to signal assessment	Access to documents
Internal EU regulatory network	Lanthanum	Tables of all ADRs in children vs. adults	Access to documents and information
Internal EU regulatory network	Latanoprost	EV data on comparative trends in reporting	Access to documents and information
Internal EU regulatory network	Lercanidipine and Doxazosin	Reports of hyponatraemia	Access to documents
MAH	Lyrica	Reports of hyponatremia/SIAHD	Access to documents
HCP	Lyrica	Pregabalin (Lyrica) and various ADRs	Access to information
Internal EU regulatory network	Metformin	Number of cases of lactic acidosis related to PSUR assessment	Access to information
Academia	Methylphenidate	Cases of pulmonary arterial hypertension	Access to information
HCP	Migral	Number of cases	Access to information
Internal EU regulatory network	Mysimba	EV extract of ADRs	Access to information
Internal EU regulatory network	N/a	Reports of PML over time	Access to information
Internal EU regulatory network	New antivirals	Chronic hepatitis C	Access to information
MAH	Octenidine	All ADR cases	Access to information
Non-EU regulatory Authority	Olanzapine depot	Number of reports	Access to documents and information
Internal EU regulatory network	Onbrez	Medication errors due to oral consumption	Access to information

Type of requester	Substance / product	Issue	Type of request
Internal EU regulatory network	Opioids	EV analysis on Prescription Opioid Abuse	Access to information
HCP	Pregabalin	Number of cases	Access to information
Internal EU regulatory network	Proton Pump Inhibitors	EV data on pancreatitis	Access to documents
Internal EU regulatory network	Rotavirus vaccines (Rotarix)	Cases of death following administration of rotavirus vaccines	Access to documents
HCP	SGLT-2 inhibitors	Cases of type 2 diabetes with SGLT-2 inhibitors	Access to documents
Internal EU regulatory network	Sodium Oxybate	Spontaneous case reports of intravenous use	Access to information
Non-EU regulatory Authority	Sovaldi	Cases related to assessment of signal of arrhythmia	Access to documents
MAH	Sovaldi and Harvoni	Specific cases related to signal assessment	Access to documents
Internal EU regulatory network	Tramadol	Respiratory depression and death	Access to documents
Non-EU regulatory Authority	Tramadol	Specific case reports	Access to documents
Consultancy	Tranylcypromine	Cases of risk of hypertensive crisis or orthostatic hypotension	Access to documents
Non-EU regulatory Authority	Trastuzumab	Number of reports of medication errors suggestive of name confusion	Access to documents and information
Internal EU regulatory network	Tysabri	PML reports in context of a referral	Access to information
Journalist	Vaccines	Reports of medication errors with vaccines	Access to information
Other EU Agency	Various substances	Information on gums and other substances of natural origin, used as thickening agents	Access to information
HCP	Vioxx	Cases of selected ADRs broken down by year, since 1996	Access to information
Journalist	Zaltrap	Cases of medication errors reported since 04/02/2014	Access to documents