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2014 Annual Report on EudraVigilance for the European Parliament, the Council and the Commission

Reporting period: 1 January to 31 December 2014

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1. Introduction

Pharmacovigilance is defined by the World Health Organization as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem. The European Medicines Agency (EMA), the National Competent Authorities (NCAs) and the European Commission, together, form the EU regulatory network responsible for the pharmacovigilance of medicines for use in the European Union (EU). The revision of the EU pharmacovigilance legislation[1] strengthened the critical public health role of EudraVigilance (EV), the central European data exchange system and database of adverse drug reaction (ADR) reports. It also introduced clearer roles for monitoring ADR reports for new or changing safety issues ('signals') and increased public accessibility to the reports of suspected ADRs. This annual report is prepared in accordance with EU legislation[2]. Given the importance of reporting suspected ADRs in detecting new or changing safety issues, this report presents the 2014 activities on:

- collecting and managing ADR reports, which showed an increase in reporting overall (1,112,988 post-marketing reports received and managed by EudraVigilance in 2014) and continued increase in reporting by European patients, reflecting greater patient engagement in pharmacovigilance.
- data quality activities including training, setting of standards, detecting and managing duplicate reports and reviewing the quality of reports sent by different companies to provide feedback.
- training activities including:
  - 3 information days for stakeholders
  - 6 training sessions on EudraVigilance Data Analysis (83 experts from 23 NCAs);
  - 24 training sessions on Eudravigilance data submission;
  - 11 training sessions on the eXtended EudraVigilance Medicinal Product Dictionary (xEVMPD)
  - 2 introductions to Eudravigilance
  - 250 users followed training on xEVMPD on its e-learning platform.
- provision of data and analyses to NCAs in order to allow them to monitor product safety, including the provision of over 20,000 EV statistical data outputs.
- review of potential signals (i.e. drug-event pairs from screening of the EudraVigilance database, medical literature, information from other regulatory authorities etc.), including more than 2000 potential signals reviewed by EMA, of which approximately 87% originated from analysis of data in the EudraVigilance database, reflecting its central role in European pharmacovigilance.
- key role of the Pharmacovigilance Risk Assessment Committee (PRAC) in prioritising and assessing signals of new or changing safety issues (90 confirmed signals assessed by PRAC in 2014). The safety issues detected and dealt with are notable in public health terms for their breadth and importance. Safety issues include adverse reactions caused by medication errors, adverse reactions in new-born infants and in children and serious or potentially fatal adverse reactions affecting the brain, heart, lungs, liver, muscle, skin, and kidney.
- further increases in transparency with all signals assessed at the PRAC published on the internet and expansion of public access to reports of suspected ADRs via the www.adrreports.eu website.

[1] Regulation (EC) No. 726/2004, Directive 2001/83/EC
[2] Regulation (EC) No. 726/2004, Article 24(2), paragraph 2

- enhancing the EudraVigilance functionalities including preparation for use of the new ISO data standard to improve data quality and searchability, and further technical changes that will, over time, allow industry to report uniquely to EudraVigilance, with individual NCAs then receiving the data via the EudraVigilance system, representing administrative simplification for industry.

2. Data collection and data quality

One of the deliverables[3] of the pharmacovigilance legislation is the electronic submission of a core data set on all medicinal products authorised in the EU by MAHs. In 2012, the Agency published a Legal Notice, and an electronic submission format. Throughout 2012 and 2013, data were collected in this 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. As described in Section 2 and Annex III, in 2014 this format and database were extended in order to maximise utility of the medicinal product data for public health and additional operational objectives. The total number of medicinal product submissions by MAHs in the new format during 2014 was 330,149. Full details on this are presented in Annex III. 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 useful 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, improved communication with and transparency for stakeholders.

Every report of a suspected ADR submitted by a patient or healthcare profession contributes to safety monitoring and thus the safe and effective use of medicines. Additionally, robust research[4] has demonstrated that collating reports 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 2014, 1,112,988 reports related to suspected serious adverse reactions were collected and managed in EudraVigilance, 352,678 of which originate from the EEA. Detailed information relating to these reports is provided in Annex II.

EudraVigilance continues to support the reporting of suspected unexpected serious adverse reactions (SUSARs) in accordance with EU clinical trial legislation[5] and details are provided in Annex II.

Data quality assurance is vital to support pharmacovigilance. In accordance with the pharmacovigilance legislation, EMA operates procedures that ensure the quality and integrity of data collected in EudraVigilance. Specifically, these include the adequate identification of medicinal products associated with reported adverse reactions, removal of duplicate reports, timely submissions of serious adverse reactions, adherence to coding practices and standards as well as adequate case documentation, which form the basis of successful data analysis, scientific assessment and decision making to protect public health.

EMA's efforts in improving data quality include the provision of training to reporters, detecting and merging duplicate reports, performing ICSR data quality reviews, 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] Regulation (EC) No. 726/2004, Article 57(2), second subparagraph
[4] Alvarez Y et al. Validation of statistical signal detection procedures in EudraVigilance post-authorization data: a retrospective evaluation of the potential for earlier signalling. Drug Saf. 2010; 33(6):475-487.
[5] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

3. Data analysis

EudraVigilance data on suspected adverse drug reactions are continuously monitored for the detection of new risks and risks which may have changed in the context of signal management in the EU. EMA staff lead on monitoring centrally authorised products (CAPs) and the NCAs lead on monitoring nationally authorised products (NAPs) as per the List of substances and products subject to worksharing for signal management[6]. The EMA regularly provides appointed Lead Member States with electronic Reaction Monitoring Reports (eRMRs) from EudraVigilance for the substances allocated to them. In 2014, over 20,000 eRMRs (EV statistical data outputs) for EV monitoring were produced and distributed to the EU pharmacovigilance network. For substances with no Lead Member State, all Member States have joint responsibility for monitoring those medicines they have authorised. Among over 2000 potential signals (i.e. drug-event pairs from screening of the EudraVigilance database, medical literature, information from other regulatory authorities etc.) reviewed in detail by the EMA in 2014, approximately 87% originated from EudraVigilance, reflecting its central role in European pharmacovigilance.

In total, the Pharmacovigilance Risk Assessment Committee (PRAC) prioritised and assessed 90 confirmed signals during 2014, including 34 signals validated by the Agency and 56 validated by the Member States based on monitoring of EudraVigilance, national databases, published literature, results of studies, information from other regulatory authorities etc. Approximately 40% of the assessed signals resulted in a recommendation for an update of the product information, including distribution of a Direct Healthcare Professional Communication (DHPC) on seven occasions to highlight important new safety information to prescribers. The evaluation of approximately a third of the signals is ongoing at the time of this report. The assessment of 18 signals (20%) was closed and routine pharmacovigilance recommended as follow-up. One signal resulted in a recommendation to update the Risk Management Plan (RMP), one signal will be further assessed through a Post-Authorization Safety Study (PASS) and two signals were evaluated in a referral procedure. Details on signal detection by EMA and an overview of signals assessed by the PRAC are provided in Annex V. The safety issues detected and dealt with are notable in public health terms for their breadth and importance. Safety issues include adverse reactions caused by medication errors, adverse reactions in new-born infants and in children and serious or potentially fatal adverse reactions affecting the brain, heart, lungs, liver, muscle, skin, and kidney. An overview of achievements in signal management provided in Annex VI.

Additionally, EudraVigilance data is used to support assessment of Periodic Safety Update Reports (PSURs) and referral procedures in the EU. In 2014, various referral procedures required EudraVigilance analysis including ponatinib (measures to minimise the risk of vascular occlusive events were recommended), codeine products for cough or cold in paediatric patients (review ongoing), oral methadone medicines containing povidone (products suspended from the EU market), testosterone (update of product information with latest evidence and warnings about patients at risk) and hydroxyzine (review ongoing).

4. Transparency, communication and training

Access to the general public to aggregated EudraVigilance data on suspected ADRs reported with CAPs was first implemented in May 2012 via creation of the www.adrreports.eu website. This includes data on approximately 720 CAPs containing 527 active substances for which ADR reports were received. In October 2014, an additional 1,724 active substances monitored by the Member States were added,

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

further increasing transparency on received adverse drug reaction data. To allow enhanced future access to EudraVigilance, the EudraVigilance Access Policy is being revised. Public consultation ended in September 2014 with a final Policy to be published in the second half of 2015.

Two 'Pharmacovigilance Programme Updates' primarily aimed at providing Marketing Authorization Holders (MAHs) with information aiding change management activities were published in 2014 (issue 1 in Aug 2014[7] and issue 2 in Dec 2014[8]). Key system and service developments were summarised, with further details on timelines and actions for MAHs.

In terms of the signal management process, two initiatives were implemented in 2014 to strengthen transparency. Since July 2014, MAHs are informed in advance of the list of signals on the agenda of the PRAC prior to its plenary meeting (using the contact details of approximately 3,000 Qualified Persons for Pharmacovigilance (QPPVs) identified from the xEVMPD database). Similarly, MAHs are provided with redacted versions of Rapporteur's preliminary assessment reports of signal procedures within five days of the assessment reports being available. Both of these improvements aim to enable MAHs to better oversee the safety of their products and to be able to keep their product information up to date.

An overview of PRAC recommendations is published after each month's committee meetings. A cumulative list of all signals discussed at the PRAC since September 2012 with links to relevant recommendations is also maintained. The list has proved useful to MAHs and is also of interest to regulators outside the EU (to update patient leaflets for their jurisdictions) and to healthcare professionals, patient organisations and researchers. Starting with the PRAC meeting in January 2015, recommendations for updates of product information are translated in all official EU languages, which will support harmonisation of product information wording in all EU languages, simplification of assessment of variations to update product information and decrease workload for the EU network and MAHs.

EMA continued to respond to requests for EudraVigilance data in line with the EudraVigilance Access Policy in 2014. An increase in requests from the EU pharmacovigilance network was observed, with EV data contributing to scientific assessment and decision making in pharmacovigilance procedures. In 2014, 82 requests for information and documents relating to EudraVigilance data were answered compared to 72 in 2013. An increase was observed in requests from the EU medicines regulatory network, i.e. EMA, NCAs and EC. The total number of external requests remained similar to 2013. An increase was also observed in the number of queries from HCPs, academia, consultancies and lawyers and a slight decrease was observed from other external requesters. A total of 74% of all requests dealt with access to information (versus 60% in 2013). The median response time in 2014 was 23 days. For further details please see Annex VII of this report.

In 2014, the EMA organised three information days for stakeholders in relation to developments in EudraVigilance and international standards in pharmacovigilance. Six training sessions on the EudraVigilance Data Warehouse and Analysis System were delivered by the Agency, training users from the European pharmacovigilance network including 83 experts from 23 NCAs. These training activities enable the users to perform a variety of pharmacovigilance queries in the EudraVigilance system, including disproportionality analyses, supporting PSUR assessments and analysis of the electronic reaction monitoring reports.

In total, 24 training sessions on Eudravigilance data submission, 11 training sessions on the xEVMPD and 2 introductory sessions to Eudravigilance were organised in 2014. Additionally, 250 users followed training on xEVMPD on its e-learning platform.

[7] http://www.ema.europa.eu/docs/en_GB/document_library/Newsletter/2014/08/WC500170851.pdf
[8] http://www.ema.europa.eu/docs/en_GB/document_library/Newsletter/2014/12/WC500178901.pdf

5. Development of EudraVigilance functionalities

To optimise delivery, the EMA Management Board conducted a prioritisation exercise for the implementation of the EU pharmacovigilance legislation. 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 2014 and will continue throughout 2015 and 2016.

5.1. Medicinal product information

In order to fully utilise the medicinal product data collected in the eXtended EudraVigilance Medicinal Product Dictionary (xEVMPD), EMA published a revised format for the xEVMPD, updated the xEVMPD to be able to collect data in this format and commenced data validation activities to ensure the accuracy of the information. 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) and to coordinate pharmacovigilance procedures and transparency. Details on the collection are in Annex III & on the data quality activities in Annex IV.

5.2. Medical literature monitoring

To enhance the efficiency of reporting and to provide a simplification for pharmaceutical industry, the EU pharmacovigilance legislation[9] 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 worldwide regulatory requirements. The EMA has decided to outsource the monitoring of scientific and medical literature to a service provider and a tender was launched in November 2014.

A public consultation of the detailed guide[10] regarding the monitoring of medical literature and the entry of relevant information into the EudraVigilance database was completed in 2014. It is expected that the service will operate in the second half of 2015.

5.3. Extension of publication of adverse drug reaction information

In 2014 EMA extended the scope of the www.adrreports.eu website publishing information on ADRs concerning Nationally Authorised Products (NAPs) for the first time. Information on Centrally Authorised Products (CAPs) has been published since May 2012. This EMA service provides transparency to stakeholders on the suspected ADRs received and allows the reports to be reviewed by medicine, by reaction or by age and gender. Further information on this is provided in section 4.

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

[10] http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2014/06/WC500167985.pdf

5.4. EudraVigilance functionalities that will be subject to audit

In preparation for the foreseen independent audit and to allow direct reporting to EudraVigilance by MAHs and its use by all stakeholders for the conduct of pharmacovigilance in the EU, EMA has continued developing the EudraVigilance database. Developments aim to ensure compliance with the new ISO Individual Case Safety Report standards, enable forwarding of adverse reaction reports to NCAs and include data analysis tools to enhance pharmacovigilance activities. In 2014 the EMA finalised the European Union individual case safety report (ICSR) implementation guide for the ISO ICSR standard. This guide will support stakeholders to prepare for the new data format.

6. Conclusion

EudraVigilance is the cornerstone of European pharmacovigilance activities and is the principle source of reports of suspected adverse drug reactions from which new or changing safety issues can be detected. Detecting such issues allows warnings and restrictions to be introduced for serious safety issues and allows patients to make informed decisions about the medicines they take.

In 2014 the overall increase in reporting of suspected ADRs was maintained as was the increase in reporting by European patients reflecting greater patient engagement in pharmacovigilance. Provision of data and analyses to the NCAs reached new levels with the provision of over 20,000 EV statistical data outputs, to allow them to monitor product safety. In terms of new or changing safety issues more than 2000 potential signals were reviewed by the EMA in 2014, of which approximately 87% originated from analysis of data in the EudraVigilance database, reflecting its central role in European pharmacovigilance. The critical role of PRAC in prioritising and assessing signals of new or changing safety issues was underpinned by the number of signals managed, originating from EMA and the NCAs (90 confirmed signals assessed by PRAC in 2014).

Further increases in transparency were welcomed by stakeholders in 2014 with all signals assessed at the PRAC posted on the web and expansion of the public access to reports of suspected ADRs via the dedicated website (www.adrreports.eu).

Key progress was made in 2014 on enhancing EudraVigilance functionalities including preparation for use of the new ISO data standard to improve data quality and searchability and technical changes that will, over time, allow industry to report to EudraVigilance uniquely, with individual NCAs receiving the data via the EudraVigilance system (administrative simplification for industry). The Agency will continue to work with the Member States to deliver robust safety monitoring for EU public health and future EudraVigilance functionalities will continue to be developed to fully realise the potential for use by all stakeholders in the EU.

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 2014
Data quality review and duplicate management of adverse reaction reports in EudraVigilance [Legal basis: Regulation (EC) 726/2004, Article 24(3)]	Continued during 2014
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]	New format published & implemented during 2014
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 2014
Access to adverse reaction data held in EudraVigilance for CAPs http://www.adrreports.eu/ [Legal basis: Regulation (EC) 726/2004, Article 24]	Continued and extended to NAPs during 2014

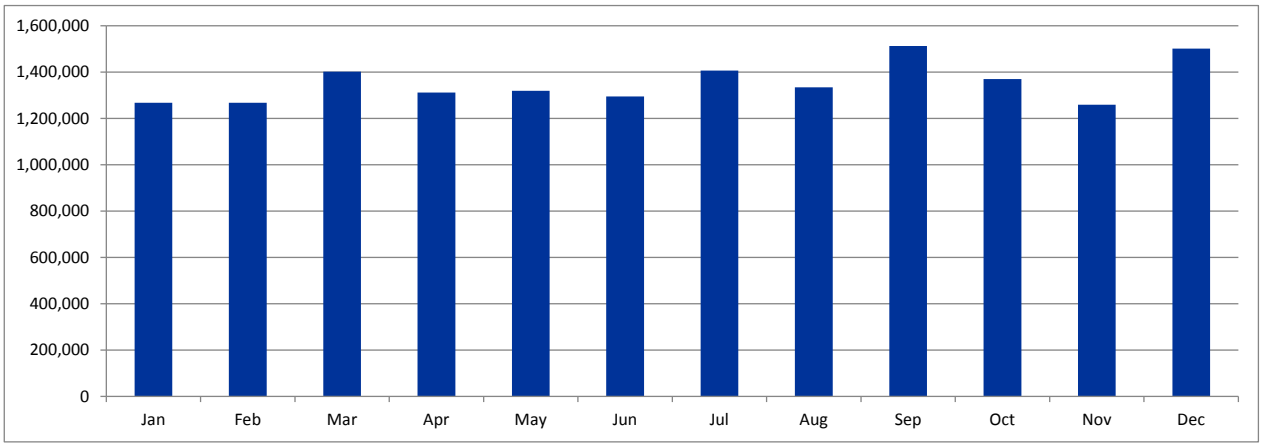
Annex II – EudraVigilance data-processing network and number of suspected adverse reaction reports processed by the EudraVigilance database

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 2014, a total of 16,241,858 transactions were successfully performed by the EudraVigilance gateway. Figure 1 presents the total number of transactions performed per month during 2014.

Figure 1. Total number of transactions performed per month at the level of the EudraVigilance Gateway from 1 January 2014 – 31 December 2014



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 2014, an average of 92,749 expedited 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 2. Number of adverse reaction reports processed per month in the EudraVigilance database post-authorisation module in 2014

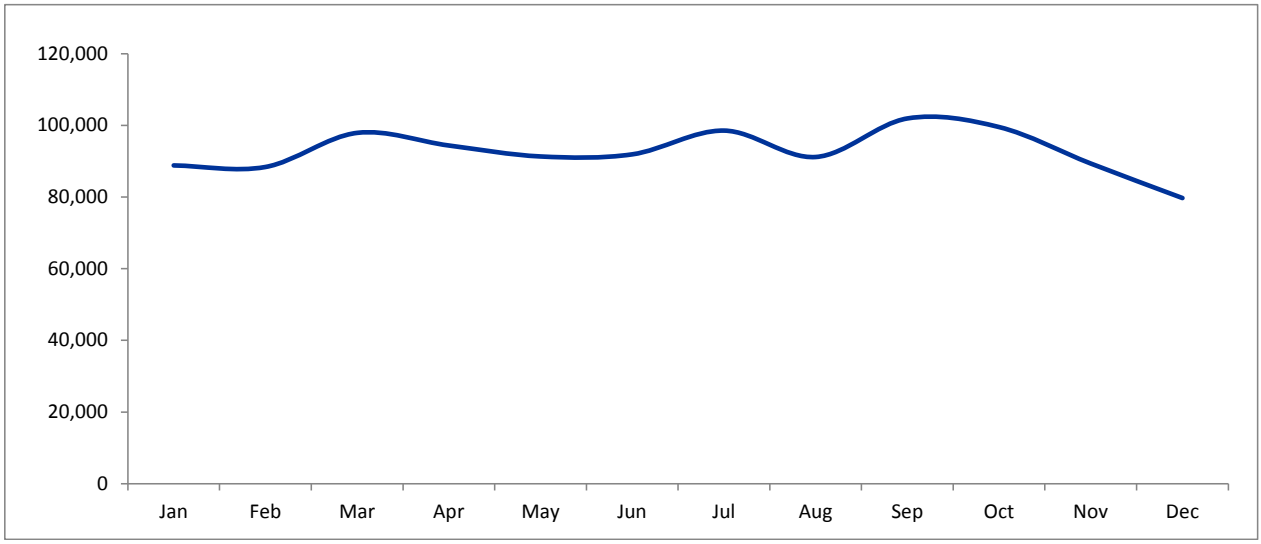
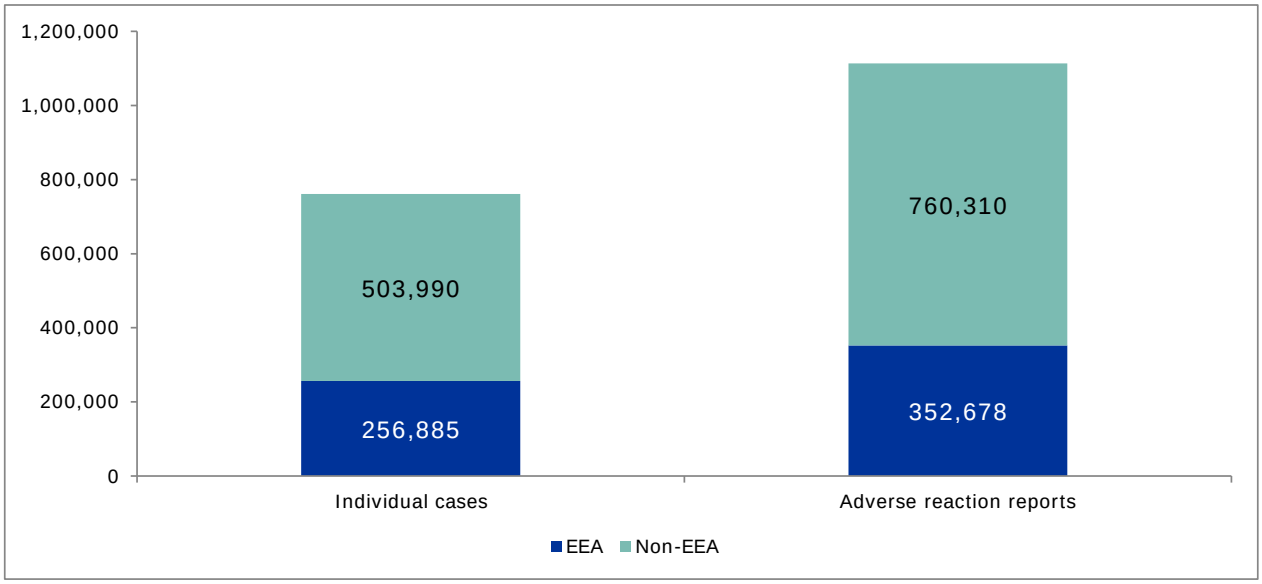


Figure 3 presents the total number of adverse reaction reports received in the post-authorisation module grouped by EEA and non-EEA for 2014. Each individual case in EudraVigilance refers to a single patient; an individual case is composed of at least one report, called the initial report, which might 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).

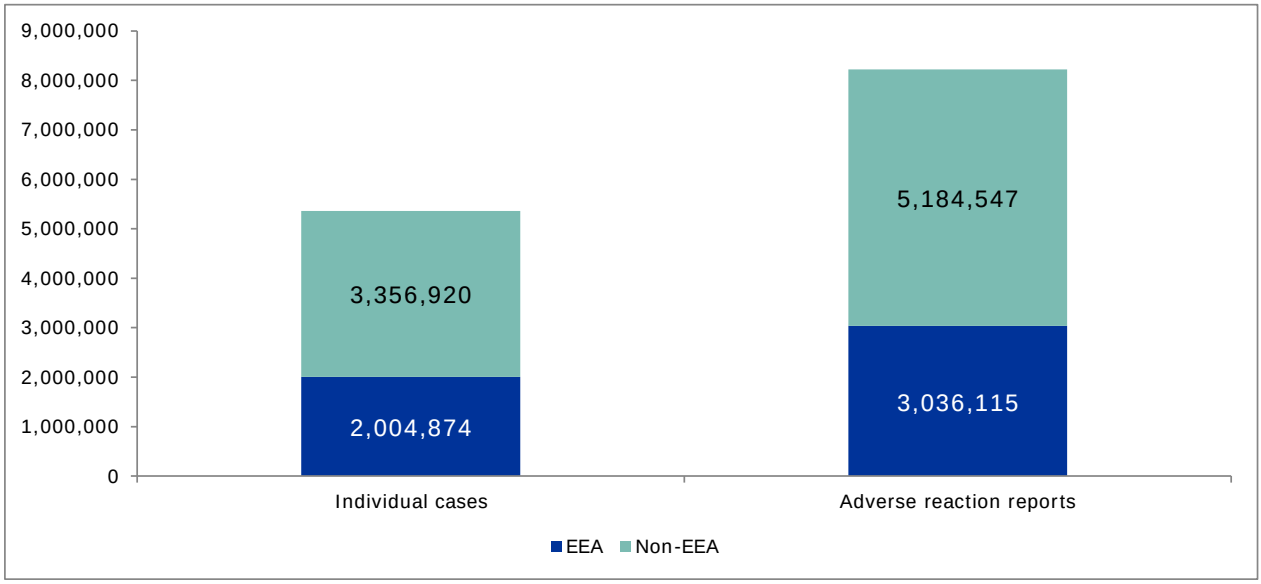
The total number of ICSRs received in Eudravigilance in 2014 was 1,112,988.

Figure 3. Number of individual cases/adverse reaction reports processed between January and December 2014 in the EudraVigilance database post-authorisation module



By 31 December 2014, the EudraVigilance database (both post-authorisation & clinical trials modules) held a total of 8,220,662 adverse reaction reports, referring to 5,361,794 individual cases (see figure 4).

Figure 4. Total number of individual cases/adverse reaction reports received in the EudraVigilance database from its inception in December 2001 until 31 December 2014



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

- A total of 835 MAHs (at headquarter level) have sent reports to the EudraVigilance Post-authorisation Module (EVPM) in the period between 1 January 2002 and 31 December 2014.
- A total of 778 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 2014.

Tables 1 and 2 below show the total (both expedited and non-expedited) 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	833,669
	Individual cases	538,288
EVCTM	ICSRs	74,289
	Individual cases	28,704

Table 2. Combined 15-day reporting compliance to EVPM for all MAHs and sponsors in 2014

Percentage of ICSRs transmitted to EVPM by MAHs/Sponsors within 15 days:	93.4%

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 & 4 below shows the total (both expedited and non-expedited) 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 91%.

Table 3. Number of ICSRs and unique cases transmitted by NCAs to EVPM & EVCTM during 2014

EV Module	Transmission type	Number of transmissions
EVPM	ICSRs	278,719
	Individual cases	203,146
EVCTM	ICSRs	7,201
	Individual cases	2,562

Table 4. Combined 15-day reporting compliance to EVPM for all NCAs in 2014

Percentage of ICSRs transmitted to EVPM by NCAs within 15 days:	91.2%

During 2014, the following 4 NCAs transmitted SUSARs to EVCTM (SUSARs from other countries were received directly from sponsors of clinical trials):

- Denmark (Danish Medicines Agency)
- Germany (Federal Institute for Drugs and Medical Devices)
- Germany (Paul-Ehrlich-Institut)
- Netherlands (College ter Beoordeling van Geneesmiddelen)

EudraVigilance database and support of signal management process

A total of 20,916 e-RMRs were generated in 2014 to facilitate the continuous monitoring of the safety of medicines by the EMA and medicines regulatory authorities in the EEA. Of these, 16,020 were routine eRMRs (produced monthly) and 4,896 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,
- identifying reliably 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 & 31 December 2014. These data are being validated by the EMA (see Annex IV for a summary of the validations performed in 2014). Table 5, below, provides a summary of the data resubmitted in the new format as of 6 January 2015.

Table 5. Summary of medicinal product submissions to the xEVMPD

Total number of medicinal product submissions in new format by MAHs by 6 January 2015 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	330,149
Total number of marketing authorisation holders (legal entities) established in the EU (corresponding to EudraVigilance codes)	4,132

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 medicinal product information sent by NCAs, MAHs and sponsors. Table 6, below refers to the data quality activities performed by the EMA in 2014.

Table 6. Summary of EudraVigilance data quality activities in 2014

Data quality area	Activities performed
Identifying and managing duplicates	Number of duplicate couples assessed: 133,870 (in 2013 this was 122,308)
	Number of 'master' reports generated based on duplicated data: 48,073 (In 2012 this was 65,906)
Coding of reported medicines and active substances	Number of medicinal products/active substances recoded: 67,476 (In 2013 this was 87,660)
	Number of adverse reaction reports recoded: 645,603 (referring to 172,081 individual cases). In 2013 555,798 adverse reaction reports were recoded, referring to 275,852 individual cases.
Providing feedback on data quality	Total number of organisations subject to ICSR data quality review: 104 (In 2012 this was 166)
	Number of medicinal products in the xEVMPD quality reviewed and, where necessary, corrected: 44,656

The amount of ICSR data quality reviews has decreased from 2013 to 2014 because EMA is focussing the quality reviews on those organisations which transmit the greatest number of ICSRs to EudraVigilance. The reviews covered organisations responsible for transmitting over 95% of the ICSRs to EudraVigilance.

The coding of reported medicines and active substances has decreased from 2013 because the backlog was completed during 2013 and the Agency has been performing this coding only on newly-arrived data since then.

Annex V – Signal detection

In 2014, in total 2,030 potential signals, i.e. drug-event pairs from screening of the EudraVigilance database, medical literature, information from other regulatory authorities etc., were reviewed in detail by the Agency's Signal Validation Team. A signal refers to information on one or more observed adverse reactions potentially caused by a medicine and that warrant further investigation. This represents a decrease of approx. 17% compared to 2013 and most likely reflects the experience with EV monitoring as well as improvements to the screening of the electronic reaction monitoring reports (eRMRs), notably the inclusion of hyperlinks to line listings in the EudraVigilance Data Analysis System.

OVERVIEW	2014	2013	2012	2011	2010
Total	2,030	2,449	2,213	1,586	2,054
Difference vs previous year	-419	236	627	-468	Ref.
Difference %	-17.1%	10.7%	39.5%	-22.8%	Ref.

Overall, EudraVigilance continues to be the major source of potential signals with 86.7% of potential signals originating from EudraVigilance. An increase in potential signals from the scientific literature was observed in 2014 (8.6% vs 5% in 2013) after weekly literature alerts were set up from Pubmed. Additionally, 3.2% of potential signals originated from other regulatory authorities and 1.5% from other sources. The overview of signal detection by action taken is provided below:

Action taken	Number of potential signals Jan-Dec 2014	% of total	Number of potential signals Jan-Dec 2013	% of total
Closed (not validated)	1,657	81.6%	2,126	86.8%
Ongoing	280	13.8%	211	8.6%
Monitored	59	2.9%	69	2.8%
Prioritised and analysed by PRAC	34	1.7%	43	1.8%
Total	2,030	100%	2,449	100%

Thirty-four signals which were validated by the Agency have been assessed by the PRAC in 2014. Further 59 potential signals were kept under monitoring, envisaging the review of new cases.

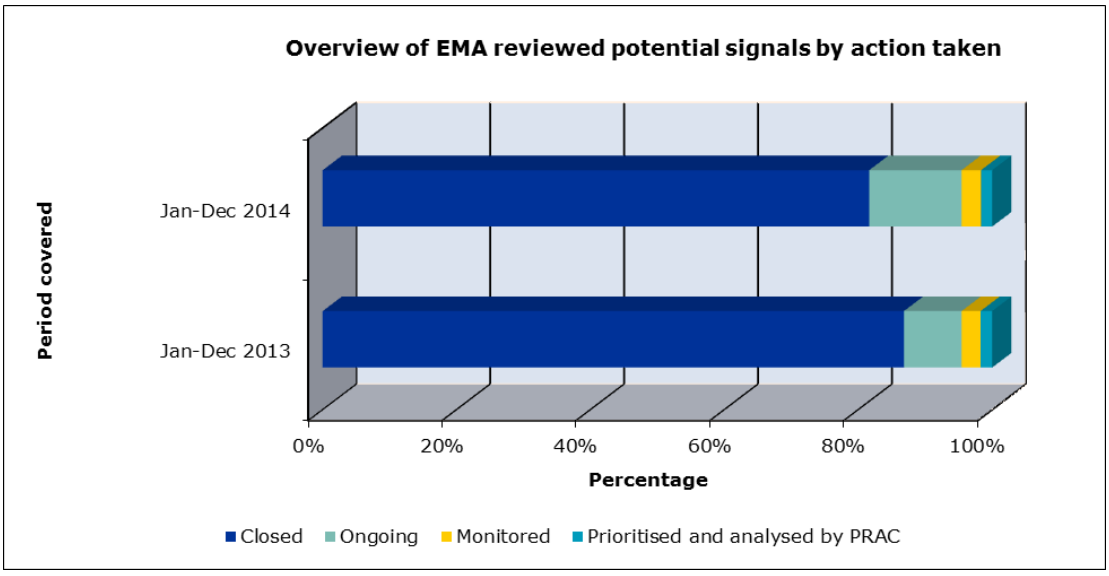


Figure 1: Overview of EMA reviewed potential signals by action taken.

Overview of signals prioritised and assessed by the PRAC

In total, the PRAC prioritised and assessed 90 confirmed signals during 2014, including 34 validated by the Agency and 56 validated by the Member States based on monitoring of EudraVigilance, national databases, published literature, results of studies, information from other regulatory authorities etc. Approximately 40% of the assessed signals resulted in a recommendation for an update of the product information, including the distribution of a Direct Healthcare Professional Communication (DHPC) on seven occasions to highlight important new safety information to prescribers. The evaluation of approximately a third of the signals is ongoing at the time of this report. The assessment of 18 signals (20%) was closed and routine pharmacovigilance recommended as follow-up. One signal resulted in a recommendation to update the Risk Management Plan (RMP), one signal will be further assessed through a Post-Authorization Safety Study (PASS) and two signals were evaluated in a referral procedure.

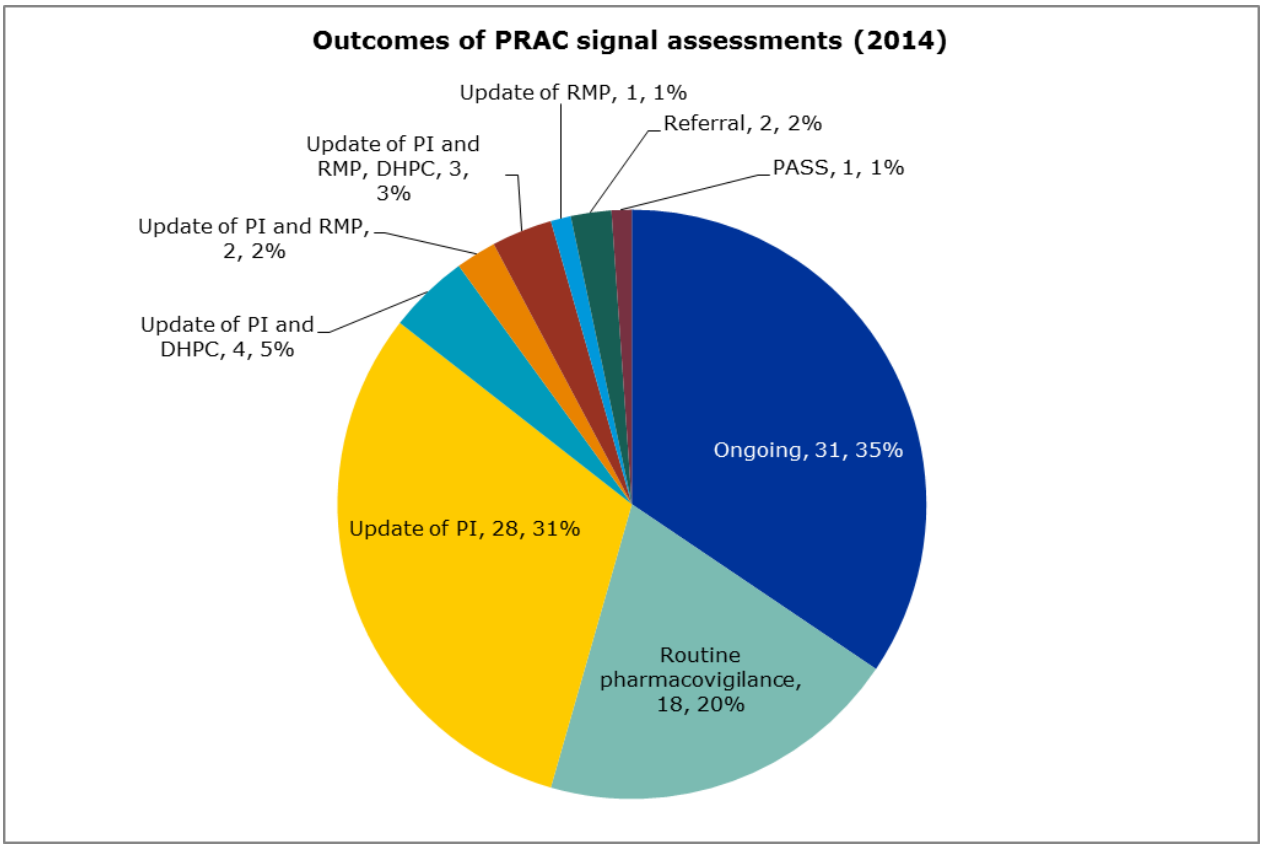


Figure 2: Outcomes of PRAC signal assessments (2014). PI: product information, DHPC: Direct Healthcare Professional Communication, RMP: Risk Management Plan, PASS: Post-Authorization Safety Study.

A list of all signals prioritised and assessed by the PRAC in 2014 is provided below, noting the latest outcome as of 14 January 2015.

Drug	Issue	Status or outcome
Abatacept	Angioedema	routine pharmacovigilance
Adalimumab	Missed dose due to malfunction of the pre-filled pen device	update of PI
Aflibercept	Higher systemic exposure compared to	ongoing

Drug	Issue	Status or outcome
	ranibizumab after intravitreal injection	
Amiodarone	Carcinogenicity	update of PI
Amiodarone	Syndrome of Inappropiate Antidiuretic Hormone secretion (SIADH)	ongoing
Androgen Deprivation Therapy (ADT)	QT interval prolongation due to long-term use	update of PI
Aripiprazole	Aggression and related events	ongoing
Aripiprazole	Diplopia	update of PI
Aripiprazole	Hyperprolactinaemia	ongoing
Atazanavir	Haemolytic anaemia	routine pharmacovigilance
Atorvastatin, simvastatin, pravastatin, fluvastatin, pitavastatin, lovastatin	Immune-mediated necrotizing myopathy (IMNM)	update of PI
Azithromycin	Potentially fatal heart events	PASS
Basiliximab	Cardiovascular instability resulting in fatal outcome following off-label use in heart transplantation	update of PI and RMP, DHPC
Bisphosphonates: alendronate, risedronate, alendronate/colcalciferol; strontium ranelate	Heart valves disorders	routine pharmacovigilance
Buprenorphine, transdermal patches	Skin depigmentation	routine pharmacovigilance
Bupropion	Pancytopenia	update of PI
Calcium channel blockers	Breast cancer risk	routine pharmacovigilance
Cefepime	Convulsions	routine pharmacovigilance
Cefepime	Drug reaction with eosinophilia and systemic symptoms (DRESS)	routine pharmacovigilance
Cetuximab	Increased fatal adverse events in patients with advanced solid tumours – publication from clinical trials	ongoing

Drug	Issue	Status or outcome
Chlorhexidine	Chemical injury including burns when used in skin disinfection in premature infants	update of PI
Clindamycin	Drug interaction with warfarin leading to international normalised ratio (INR) increased	update of PI
Dexmedetomidine	Infantile apnoeic attack	update of PI
Dimethyl fumarate	Progressive multifocal leukoencephalopathy (PML)	update of PI and DHPC
Duloxetine	Vasculitis	ongoing
Enzalutamide	Myalgia	update of PI
Etanercept	Glioblastoma and other brain neoplasms	routine pharmacovigilance
Exenatide	Goitre and worsening, enlargement of goitre	ongoing
Fentanyl, transdermal patch	Accidental exposure	update of PI and DHPC
Fluoroquinolones ciprofloxacin, enoxacin, flumequine, lomefloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin, pefloxacin, prulifloxacin, rufloxacin	Retinal detachment	update of PI
Fluticasone furoate	Oral and upper respiratory fungal infection	routine pharmacovigilance
Gadodiamide; gadopentetic acid; gadoversetamide	Nephrogenic systemic fibrosis in patients with acute kidney injury	update of PI
Goserelin	Long duration flushing and hyperhidrosis	update of PI
Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed)	Complex regional pain syndrome (CRPS) linked to the process of vaccination	routine pharmacovigilance
Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)	Complex regional pain syndrome (CRPS) linked to the process of vaccination	routine pharmacovigilance
Imatinib	Decreased estimated glomerular filtration rate (eGFR)	update of PI

Drug	Issue	Status or outcome
Infliximab	Rhabdomyolysis	ongoing
Interferon alfa-2a; interferon alfa-2b; interferon beta-1a; interferon beta-1b; peginterferon alfa-2a; peginterferon alfa-2b; peginterferon beta-1a	Pulmonary arterial hypertension	ongoing
Interferon beta 1a, interferon beta 1b	Thrombotic microangiopathy (TMA)	update of PI and RMP, DHPC
Ipilimumab	Posterior reversible encephalopathy syndrome (PRES)	ongoing
Ivabradine	Cardiovascular risk	referral
Lansoprazole	Haemolytic anaemia	routine pharmacovigilance
Latanoprost	Increased reporting of eye disorders, in particular eye irritation, after change of formulation	ongoing
Lenalidomide	Parkinson's disease	ongoing
Leuprorelin, suspension for injection	Medication error - wrong technique in drug usage process	update of PI and DHPC
Levonorgestrel-releasing intrauterine device (IUD)	Risk of uterine perforation – Final study results of EURAS-IUD study	update of PI
Lithium	Solid renal tumours	update of PI
Mefloquine	Possibly permanent neurologic (vestibular) side effects	update of PI
Methylprednisolone	Hepatotoxicity after high dose intravenous use	ongoing
Mycophenolate mofetil	Bronchiectasis and hypogammaglobulinaemia - publication from *Boddana et al.*; Clinical Transplantation 2011	update of PI and DHPC
Natalizumab	Anaemia	ongoing
Natalizumab	Neonatal haematological abnormalities (thrombocytopenia/anaemia)	ongoing
Octocog alfa	Inhibitor development in previously untreated patients	ongoing

Drug	Issue	Status or outcome
Orlistat	Pharmacokinetic drug interaction (at absorption) with highly active antiretroviral therapy (HAART) leading to loss of HAART efficacy	update of PI
Paliperidone	Accidental exposure of children to oral formulation	ongoing
Paliperidone and other atypical antipsychotics: olanzapine; aripiprazole; lurasidone; asenapine; clozapine; risperidone; sertindole; quetiapine; ziprasidone; zotepine	Acute renal failure	ongoing
Panitumumab	Increased fatal adverse events in patients with advanced solid tumours – publication from clinical trials	routine pharmacovigilance
Pantoprazole	Subacute Cutaneous Lupus Erythematosus (SCLE)	ongoing
Paracetamol	Drug exposure in pregnancy – publication by *Brandlistuen et al.*; Int. J. Epidemiol., 2013	routine pharmacovigilance
Paracetamol	Drug-induced Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalised exanthematous pustulosis (AGEP)	update of PI
Paroxetine	Aggression	update of PI
Pazopanib	Retinal detachment and retinal tear	ongoing
Quetiapine	Possible misuse and abuse	ongoing
Quetiapine	Suicidality in major depressive disorder (MDD) patients	update of PI
Radium-223 dichloride	Cerebral haemorrhage	ongoing
Regorafenib	Hypersensitivity, drug reaction with eosinophilia and systemic symptoms (DRESS)	update of PI
Rivaroxaban	Spontaneous splenic rupture/haemorrhage	ongoing
Sildenafil	Increased risk of incident melanoma	routine pharmacovigilance

Drug	Issue	Status or outcome
Simvastatin	Risk of myopathy and rhabdomyolysis associated with high doses	update of PI
Sitagliptin, Sitagliptin/metformin, Angiotensin-converting enzyme (ACE) inhibitors	Angioedema due to interaction between sitagliptin and ACE inhibitors	routine pharmacovigilance
Sodium containing formulations of effervescent, dispersible and soluble medicines	Cardiovascular events	ongoing
Sorafenib	Acute Generalised Exemanthous Pustulosis (AGEP)	ongoing
Tacrolimus; Febuxostat	Potential drug-drug interaction between systemic tacrolimus and febuxostat	routine pharmacovigilance
Tapentadol	Suicidal ideation	update of PI
Temozolomide	Dehydration leading to renal failure	ongoing
Temozolomide	Diabetes insipidus	ongoing
Tenofovir disoproxil fumarate; efavirenz, emtricitabine, tenofovir disoproxil fumarate; emtricitabine, rilpivirine, tenofovir disoproxil fumarate; elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate; emtricitabine, tenofovir disoproxil fumarate; NSAIDS	Acute kidney injury caused by co-administration with non-steroidal anti-inflammatory drugs (NSAIDs)	update of PI
Teriparatide	Non-uraemic calciphylaxis	Update of RMP
Testosterone	New publications suggesting the risk of cardiovascular events	referral
Thiotepa	Pulmonary arterial hypertension	update of PI and RMP
Tiotropium bromide	Increased mortality from cardiovascular disease and all-cause mortality – results of TIOSPIR trial	update of PI
Tocilizumab	Cholecystitis	ongoing
Trabectedin	Capillary Leak Syndrome	ongoing
Triamcinolone acetonide	Postmenopausal haemorrhage	update of PI

Drug	Issue	Status or outcome
Ustekinumab	Dermatitis exfoliative	update of PI and RMP, DHPC
Valproate and related substances	Mitochondrial toxicity	update of PI
Vemurafenib	Dupuytren's Contracture	ongoing
Vildagliptin; Vildagliptin, metformin	Interstitial lung disease	routine pharmacovigilance
Vildagliptin; Vildagliptin, metformin	Renal failure	ongoing
Vildagliptin; Vildagliptin, metformin	Rhabdomyolysis/myalgia	update of PI and RMP

Annex VI - Signal management in the EU

Building on experience from previous years, the Signal Management Review Technical Working Group, a subgroup of the PRAC supported by EMA, has contributed to improvements and simplifications in the signal management process in the EU. The highlights of progress from its two work streams, Signal management tools and processes, and the Methodological guidance and signal detection methods are detailed below.

- Several procedural steps in signal management were clarified, including roles for confirmation of signals where no lead MS exists or where several products and substances are concerned and regarding extensions to signal assessment timelines requested by the Rapporteur and the MAHs.
- Improvements were achieved in clarity and consistency of the published PRAC recommendations as an important communication tool for actions on MAHs.
- Following the integration of signal procedures for CAPs into the Agency's tracking systems, a similar output of signal follow-up procedures for nationally authorised products was devised in 2014; it is updated monthly following PRAC meetings and allows the MSs to plan resources for assessments.
- The monitoring frequency for products subject to additional monitoring was adjusted following the agreement on the criteria and the list of medicines under additional monitoring in 2013.
- An updated Assessment report template for signals was agreed, integrating the existing PRAC recommendation form to simplify document flow. The template follows the signal from its validation in the European Pharmacovigilance Issues Tracking Tool (EPITT) up to the final PRAC recommendation, building on previous versions. The EPITT fields were updated accordingly.
- The preliminary and updated versions of the assessment report are now also being shared with MAHs to increase transparency of signal assessments.
- Advanced notification of draft PRAC agenda to MAHs was initiated.
- Establishment of new process for publication by EMA of translation of English text of PRAC recommendations for updates of the product information in all official EU languages. The service will start with the January 2015 PRAC recommendations and aims at supporting harmonisation of product information wording in all EU languages, simplification of assessment of variations to update PI and decrease in workload for network and for MAH.

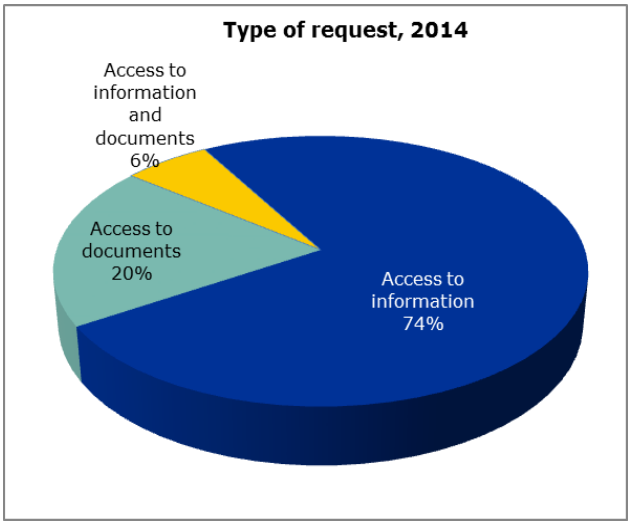
Annex VII - Requests for information and documents

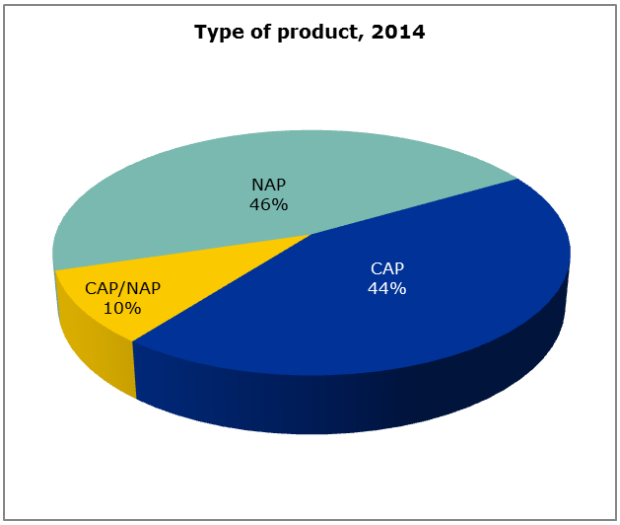
In 2014, 82 requests were answered, compared to 72 in 2013. An increase was observed in requests from the EU medicines regulatory network, i.e. EMA, NCAs and EC (further referred to as "internal EU regulatory network"). The total number of external requests remained similar to 2013. There was an increase observed in the number of queries from HCPs, academia, consultancies and lawyers and a slight drop from other external requesters. 74% of all requests dealt with access to information (versus 60% in 2013).

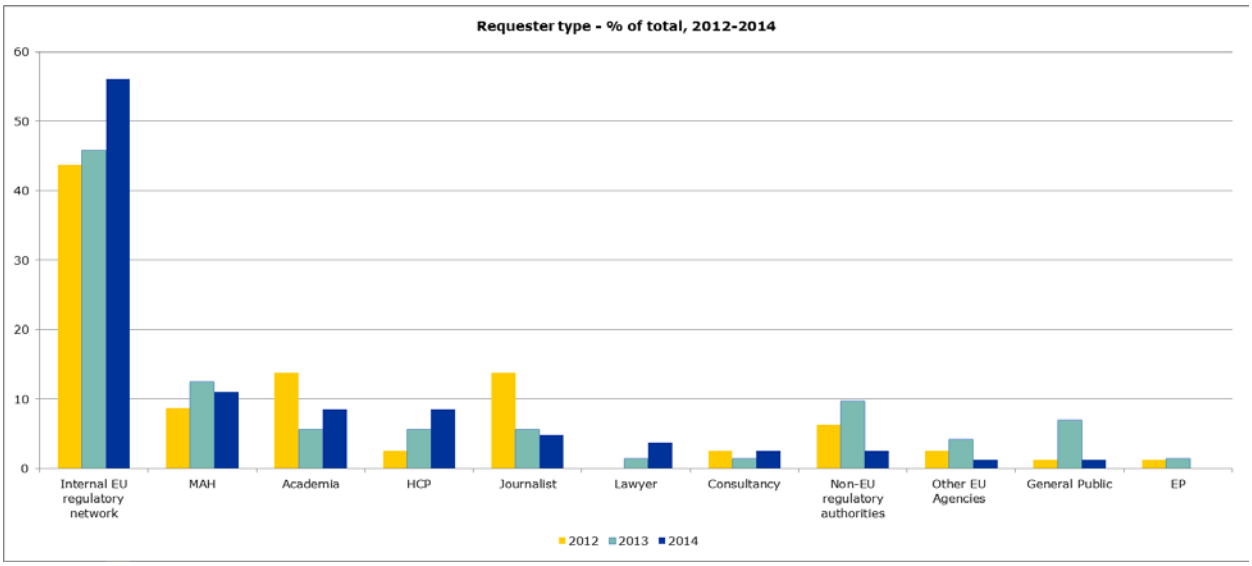
Approximately half of the queries related to nationally authorised products and half to centrally authorised products (as compared to 48% related to NAPs and 35% to CAPs in 2013). Data from five requests were used to support the decision making in the context of major European referral procedures (listed below). For nine queries, one or more follow-up requests were received and answered.

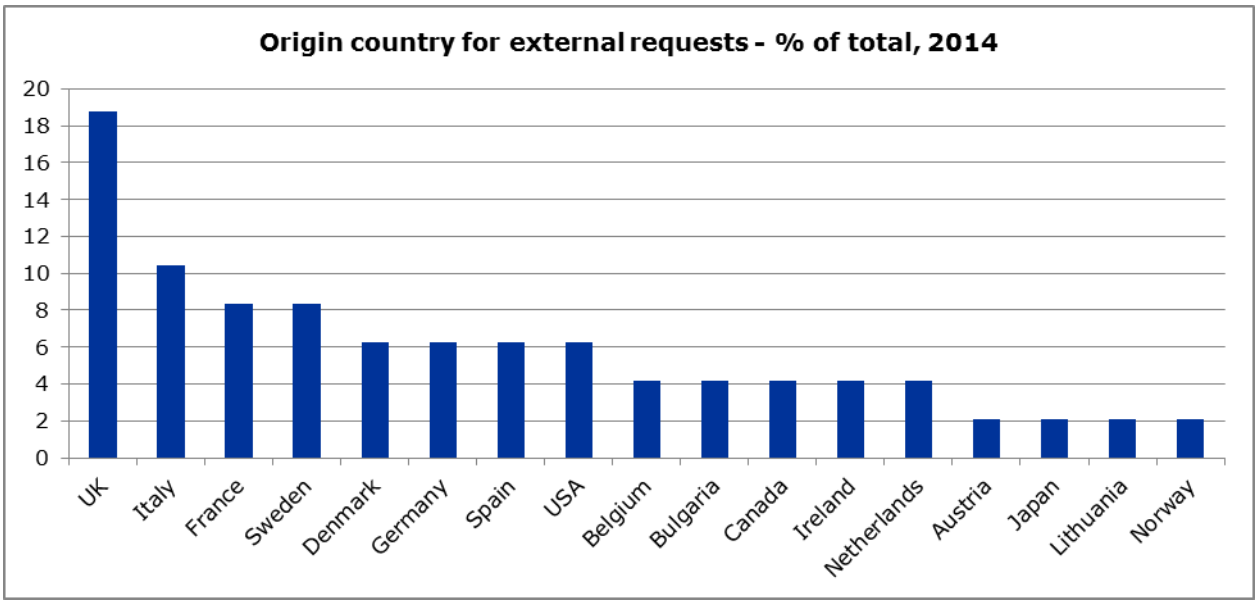
The median response time in 2014 was 23 days (range 0-151 days), the same as in 2013 (range 0-182 days). The time of response varied according to the urgency of the request (especially from the internal EU regulatory network), its volume, the availability of human and technical resources, and the complexity of the required search. 44% of all requests were answered within 14 days, 61% within 1 month and 90% within two months, an improvement compared to 2013 (35%, 61% and 86%, 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 2014

Type of requester	Substance/ product	Issue	Type of request
HCP	Abilify	Abilify use in children and adolescents	Access to documents
Internal EU regulatory network	Actifed	Cases of Actifed 60 mg/2.5 mg tablets when the medication is used off label	Access to information
Academia	All anti-obesity substances	All ADRs	Access to documents
Internal EU regulatory network	All Bisphosphonates	Cases of Bisphosphonate-associated osteonecrosis of the external auditory canal and cases of cholesteatoma	Access to documents

Type of requester	Substance/ product	Issue	Type of request
Academia	All EV	ADRs reported by HCPs, patients, others	Access to information
Academia	All EV	Various ADRs	Access to information
Internal EU regulatory network	All vaccines	Vasculitis SMQ	Access to information
Internal EU regulatory network	Androgen deprivation therapy	QT interval prolongation	Access to information
Non-EU Regulatory Authorities	Angeliq (drospirenone and estradiol) and other products used to treat menopause	Cases of Angeliq, or other products used to treat menopause, being confused as an oral contraceptive	Access to information
Internal EU regulatory network	Atosiban Sun and Tractocile (atosiban)	Comparison of EV records between Atosiban Sun and Tractocile	Access to information
Journalist	Atypical antipsychotics	Various ADRs	Access to information
Internal EU regulatory network	Avastin and Lucentis	All ADRs for ranibizumab and bevacizumab with only intravitreal use	Access to information
Consultancy	Benzathine benzylpenicillin	All ADRs	Access to information
Academia	Berinert, Cinryze, Ruconest, Firazyr, Danazol, tranexamic acid	ADRs reported for C1-inhibitors, conestat-alfa, icatibant, tranexamic acid and Danazol	Access to documents
Academia	Biosimilars: epoetin alfa, epoetin zeta, filgrastim, follitropin alfa, infliximab, somatropin	Various ADRs	Access to documents
Internal EU regulatory network	Biphosphonates	Cases of osteonecrosis of the jaw	Access to information
Journalist	Bismuth	All ADRs with multi- and single ingredient preparations	Access to information
MAH	Botulinum Toxin Type A	Deafness incl. unilateral	Access to documents
Internal EU regulatory network	Bupropion	Drug abuse, dependence and withdrawal	Access to information

Type of requester	Substance/ product	Issue	Type of request
HCP	Celecoxib	Various adverse events	Access to information
Internal EU regulatory network	Cervarix	ICSRs for cases of Postural orthostatic tachycardia syndrome reported by MAH in latest PSUR	Access to documents
Internal EU regulatory network	Cervarix and Gardasil	Leukemia	Access to documents and information
Internal EU regulatory network	Chlorhexidine	Cases of chemical injuries during use in skin disinfection in premature infants - SOCs Skin and Injury researched	Access to information
Internal EU regulatory network	Codeine	Opiate toxicity	Access to information
MAH	Codeine and dihydrocodeine	All ADRs per age group of children and adolescents	Access to information
Internal EU regulatory network	Dabigatran (Pradaxa)	Interactions/medication errors in relation to change from heparin to dabigatran (Pradaxa) leading to bleedings	Access to information
Internal EU regulatory network	Dexamfetamine	Drug dependence in children, developmental disorders cognitive (HLT) and cardiomyopathy	Access to Information
HCP	Diclofenac	More information on spontaneous case reports of suspected Adverse Drug Reactions reported in EV regarding diclofenac and intussusception	Access to information
Internal EU regulatory network	Enalapril, captopril	Renal and cardiac safety	Access to information
Internal EU regulatory network	Fentanyl patches	Medication errors incl. accidental exposure	Access to information
Internal EU regulatory network	Fluad (Influenza vaccine)	All cases of death and of encephalitis	Access to documents and information
Internal EU regulatory network	Fosfodil, Spiriva, Tobi Podhaler and Colobreathe	Various ADRs	Access to documents and information

Type of requester	Substance/ product	Issue	Type of request
Lawyer	Gardasil and Cervarix	All ADRs	Access to documents and information
Lawyer	Gentamicin	Polyneuropathy reactions (human)	Access to information
Internal EU regulatory network	Herceptin, Alimta, Remicade	Adverse events that could be linked to falsified or tampered products related to specific batch numbers	Access to documents
MAH	Hydroxyzine hydrochloride	ADRs pertaining to cardiovascular system, specifically for prolonged QT interval and atrial fibrillation	Access to information
Internal EU regulatory network	Hydroxyzine-containing medicines	Cardiovascular side effects, namely QT prolongation	Access to information
Internal EU regulatory network	Imatinib and all tyrosine kinase inhibitors (TKIs)	Chronic renal failure for all TKIs	Access to Information
Internal EU regulatory network	Inductos	ADRs indicating sterility or contamination problems	Access to information
Lawyer	Infanrix (Diphtheria, tetanus and pertussis)	All ADRs	Access to information
Internal EU regulatory network	Interferon beta products (Interferon beta 1a and 1b)	Reports of TMA, TTP or HUS	Access to information
MAH	Krystexxa (pegloticase)	Specific case and cases not identified by the MAH	Access to documents
Internal EU regulatory network	Lenorgestrel and antiretrovirals	Cases related to pregnancies and drug-drug interaction observed between lenorgestrel and antiretrovirals	Access to information
Internal EU regulatory network	Lidocaine	Referral - Congenital malformations and neoplasms	Access to information
Academia	Lidocaine, articaine	HLTs Paraesthesia and dysaesthesias	Access to information
Internal EU regulatory network	Lucentis	Endophthalmitis	Access to information
HCP	Lyrica	Blindness, visual impairment, attempted suicide, and completed suicides	Access to information

Type of requester	Substance/ product	Issue	Type of request
General public	Lyrica	Blindness, visual impairment, suicide	Access to information
Internal EU regulatory network	Methadone	Fatal cases (in injecting drug abusers) suspected to be related to the excipient povidone	Access to information
Internal EU regulatory network	Methylphenidate	4 specific, redacted narratives	Access to documents
Internal EU regulatory network	Mifepristone, misoprostol, gemeprost	All ADRS	Access to information
Internal EU regulatory network	Mirabegron	Angioedema	Access to information
Internal EU regulatory network	MMR - Vaxpro	Encephalitis after MMR vaccination	Access to information
Internal EU regulatory network	Nevanac	Endophthalmitis	Access to documents
HCP	Nicorandil	Intestinal perforation, fistulation and related terms	Access to information
Non-EU Regulatory Authorities	Oral allergen products	All ADRs	Access to information
Internal EU regulatory network	Oral viscous lidocaine	Serious ADRs in infants and children related to oral viscous lidocaine	Access to information
Internal EU regulatory network	Pandemrix	Narcolepsy cases	Access to information
Internal EU regulatory network	Paracetamol	Cases of paracetamol use associated with PDA closure and paracetamol associated with birth defects	Access to documents and information
HCP	Parecoxib	All ADRs	Access to information
Consultancy	PEG 3350	All ADRs	Access to information
Internal EU regulatory network	Peg-/interferon alfa and beta	Pulmonary arterial hypertension	Access to information
Internal EU regulatory network	Picato	Off label use and medication errors	Access to information

Type of requester	Substance/ product	Issue	Type of request
MAH	Piribedil (Trivastal)	Cases of aggression, abnormal behaviour, oedema and peripheral oedema	Access to documents
Internal EU regulatory network	Privigen	Haemolysis	Access to information
Internal EU regulatory network	Quetiapine	Drug abuse, dependence and withdrawal	Access to information
HCP	Quetiapine	Hypomania	Access to information
Internal EU regulatory network	Rienso (ferumoxytol)	Cases of hypersensitivity incl. fatal cases	Access to information
Internal EU regulatory network	Rienso (ferumoxytol)	Hypersensitivity	Access to information
MAH	Rienso (ferumoxytol)	Hypersensitivity incl. fatal cases	Access to documents
Internal EU regulatory network	Rienso (ferumoxytol)	Hypersensitivity incl. fatal cases	Access to information
Journalist	Rivaroxaban	Reports of liver damage associated with rivaroxaban and relating to liver failure and hepatitis	Access to Information
Internal EU regulatory network	Rivastigmine Actavis Patches	Any information/signal related to Rivastigmine Actavis Patches	Access to information
Other EU Agencies	Rotarix and Rotateq	Intussusception	Access to information
Academia	SSRIs and SRIs	Total number of ADRs retrieved by the SMQ Haemorrhage for various SSRI and SRI drugs	Access to Information
MAH	Stelara (ustekinumab)	Dermatitis exfoliative	Access to documents
MAH	Tacrolimus	Tacrolimus and febuxostat drug-drug interaction	Access to documents
Internal EU regulatory network	Testosterone	Cardiovascular events	Access to information
Journalist	Thiocolchicoside containing products	Various ADRs	Access to information
Internal EU regulatory network	Various oncology products	ADRs in children	Access to information

Type of requester	Substance/ product	Issue	Type of request
MAH	Yellox	Cases of retinal phototoxicity, chorioretinitis, visual field defect and renal failure	Access to documents
Internal EU regulatory network	Zoledronic acid	Osteonecrosis of the jaw for bisphosphonates looking at reporting over time	Access to information