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2013 Annual Report on EudraVigilance for the European Parliament, the Council and the Commission

Reporting period: 1 January to 31 December 2013

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1. Introduction

The European Medicines Agency (EMA) works within the European Regulatory Network to support the monitoring of the safety of medicines. The EMA's main responsibilities in this area include the coordination of the European pharmacovigilance system, the provision of information on the safe and effective use of medicines and operating and maintaining EudraVigilance (EV) and the EudraVigilance Data Analysis System (EVDAS). Both EMA and medicines regulatory authorities in Member States are required by legislation to continuously monitor the adverse reaction data reported to EudraVigilance to determine whether there are new risks or known risks which have changed and whether those risks have an impact on the overall benefit-risk balance of a medicine.

In the context of the implementation of the new pharmacovigilance legislation[1], major emphasis is being been put on further strengthening the role of EudraVigilance as regards simplifying adverse reaction reporting, collecting adverse reactions reported by patients and consumers (as well as those from healthcare professionals), detecting new risks, monitoring known or potential risks, risk assessment by the Pharmacovigilance Risk Assessment Committee (PRAC) and increasing transparency by providing stakeholders with adequate access to adverse reaction data and analysis (via EVDAS and electronic Reaction Monitoring Reports, eRMRs).

In compliance with the EU pharmacovigilance legislation[2], the EMA has prepared this annual report for the European Parliament, the Council and the Commission to provide a summary of the EudraVigilance related activities that the EMA undertook in 2013 within the EU regulatory network and with stakeholders.

2. Development of new functionalities

The revised pharmaceutical legislation foresees further improvements in the functionality of EV. In accordance with Article 24 of Regulation (EC) 726/2004[3], the Agency, in collaboration with the Member States and the Commission, shall draw up the functional specifications for the EudraVigilance database (hereafter referred to as “EudraVigilance functionalities to be audited”) together with a timeframe for their implementation. The EudraVigilance functionalities to be audited focus on the key deliverables which will benefit Member States, pharmaceutical industry and further strengthen the protection of public health. More specifically, they will deliver:

- Simplification of adverse reaction reporting
- High-quality and integrity of pharmacovigilance information held in EudraVigilance
- Adaptation to technical and scientific progress by implementation of the ISO standards for individual case safety reports and identifying medicines (subject to ISO timelines)
- Full implementation of the EudraVigilance Access Policy including access by marketing authorisation holders to the extent necessary to fulfil their pharmacovigilance obligations
- Strengthening of signal detection complemented by statistical analysis

[1] Regulation (EC) No. 726/2004, Directive 2001/83/EC
[2] Regulation (EC) No. 726/2004 Article 24(2), paragraph 2
[3] Regulation (EC) No. 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency

- Electronic reporting of EU cases to the World Health Organisation Uppsala Monitoring Centre.

The EudraVigilance functionalities to be audited have followed the consultation process of the EMA/Member States governance structure for the implementation of the pharmacovigilance legislation including the endorsement by the EU Telematics Management Board, the Pharmacovigilance Risk Assessment Committee and the EMA Management Board.

Following endorsement by the EMA Management Board in December 2013, the EudraVigilance functionalities to be audited will provide a basis for EMA to develop a detailed project plan including the timelines for implementation and the plan for the conduct of an independent audit. Moreover, on the basis of the endorsed functionalities, detailed business requirements will be developed by the EMA in consultation with Member States, which aim to further analyse the end-users' needs. Following completion of the system design and development, user testing with Member States will be performed. The delivery of the agreed functionalities will be accompanied by end-users training. PRAC will be regularly updated on the project milestones and progress made and a PRAC recommendation, as required by legislation, will be sought for the audit that the functionalities have been delivered.

Based on an independent audit report that takes into account the recommendations of the PRAC, the EMA Management Board will confirm and announce when full functionality of the EudraVigilance database has been achieved and the system meets the defined functional specifications. This will bring the new requirements of the Regulation[4] into force.

3. Data collection and data quality

One of the deliverables[5] of the pharmacovigilance legislation focuses on the electronic submission of a core data set on all medicinal products authorised in the EU by marketing authorisation holders (MAHs). Following publication of a Legal Notice,[6] and an electronic submission format, the EMA collected these data as part of the eXtended EudraVigilance Medicinal Product Dictionary (xEVMPD) with the primary objective of facilitating data analysis and signal detection to support better safety monitoring for patients. The total number of medicinal product submissions by MAHs during 2013 is presented in Annex III.

From July 2012, the pharmacovigilance legislation also introduced direct reporting of adverse reactions by patients and consumers in all Member States and enhanced adverse reaction reporting in the context of post-authorisation studies, medication errors, off-label use and occupational exposure. The number of reports related to suspected serious adverse reactions collected and managed in EudraVigilance in 2013 is provided in Annex II. 2013 shows an increase in the level of reporting compared to previous years, and, in particular, a significant increase in the level of direct patient reporting compared to previous years.

EudraVigilance continues to support the reporting of suspected unexpected serious adverse reactions (SUSARs) in accordance with EU clinical trial legislation[7] (see Annex II).

[4] Article 24 of Regulation (EC) No. 726/2004 as amended by Regulation (EU) No. 1235/2010
[5] Regulation (EC) No. 726/2004, Article 57(2), second subparagraph
[6] Legal notice on the implementation of Article 57(2), second subparagraph of Regulation (EC) No. 726/2004 (Doc. Ref. 5 March 2012 EMA/505633/2011)
[7] 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

Quality assurance is key to support pharmacovigilance. In accordance with the pharmacovigilance legislation, the EMA is operating procedures that ensure the quality and integrity of the information collected in EudraVigilance. This refers specifically to 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 for successful data analysis and decision making to protect public health.

The EMA's efforts in improving data quality include training provision, detecting and merging duplicate reports, performing ICSR data quality reviews, providing feedback to individual reporting organisations and conducting recoding of adverse reaction reports utilising the medicinal product data of the XEVMPD. These are summarised in Annex IV.

4. Data analysis

The legislation also introduced clearly defined responsibilities for signal detection and management in the EU for the Agency and the NCAs. A safety signal refers to information on one or more newly observed adverse reactions potentially caused by a medicine and that warrant further investigation. If a safety concern is confirmed or considered likely to be associated with a medicinal product, regulatory action may be necessary and usually takes the form of an update of the summary of product characteristics (SmPC) and the patient leaflet. Sometimes a signal identifies safety concerns requiring action beyond SmPC changes, e.g. restriction of use to populations in which the benefit-risk balance remains positive or the need for gathering further data from additional sources (e.g. observational studies, registries) to better assess the risk.

EudraVigilance is a key tool in operating the new signal management processes in the EU. EMA staff lead on the detection and initial validation of safety signals for centrally authorised medicinal products (CAPs) and the NCAs are leading for non-CAPs. Among safety signals reviewed by the EMA in 2013, more than 90% originated from EudraVigilance. Details of signal detection activities are presented in Annex V and progress in terms of signal management in the EU is described in Annex VI. Additionally, EMA prepares data output reports (electronic reaction monitoring reports, e-RMRs) to support monitoring of data by NCAs in context of the work-sharing of monitoring EV data. Over 19,000 of these e-RMRs were generated and distributed to NCAs and EMA staff in 2013.

In 2013, the PRAC prioritised and assessed 100 signals, totalling 130 signal discussions. This includes 43 signals detected and validated by the EMA and 57 detected and validated by Member States. Among the signals raised by the EMA, the evaluation of 21 signals resulted in changes of the product information (including the distribution of a Direct Healthcare Professional Communication in four cases in order to highlight important new information to prescribers). The evaluation of 14 signals is currently at the stage of an assessment of data provided by MAHs and the evaluation of 7 signals was concluded following the assessment of available data with no further regulatory action. For one signal, a formal review of benefit-risk in the scope of a referral under article 31 of Directive 2001/83/EC was initiated. Overall, the evaluation of signals by the PRAC has led to timely conclusions of safety reviews and appropriate actions for the protection of public health.

In addition to the use of EudraVigilance for signal management, further emphasis has been put on the support of pharmacovigilance referral procedures (incl. urgent union procedures) by providing and analysing safety data for the medicinal products concerned. In 2013, these activities focused on medicinal products containing the active substances almitrine, codeine, combined contraceptives, cyproterone/ ethinylestradiol, diacerin, dihydrocodeine, domperidone, estradiol (topical use), flupirtine,

nicotinic acid and derivatives, strontium ranelate, solutions for infusion containing hydroxyethyl starch, tetrazepam, valproate and related substances, zolpidem.

To support the assessment of PSURs by Member States, EMA is also providing additional data analysis reports from EudraVigilance and providing training to assessors.

5. Transparency, communication and training

A key objective of the new legislation is to enhance transparency and optimise communication in pharmacovigilance. Following the adoption of the EudraVigilance Access Policy in 2011, the EMA launched in 2012 the first phase of the online access to suspected adverse reaction reports[8] in all official languages of the EU on a new public website: www.adrreports.eu. The launch highlights the importance of adverse reaction reporting and EudraVigilance in safeguarding public health. The information currently published relates to over 700 medicines and active substances authorised through the centralised procedure. It is planned to extend this website to substances in nationally authorised medicines subject to worksharing for signal management in 2014. The website, available in all EU languages, was maintained throughout 2013 with 100% availability.

Signals assessed by the PRAC are publicly available in the context of the publication of the PRAC meeting agendas and minutes[9]. In September 2013, the Agency started publishing the adopted PRAC recommendations[10] on signals, in order to facilitate their implementation by the MAHs (e.g. changes to the product information) and to increase transparency.

The Agency published the list of medicinal products subject to additional monitoring[11] in April 2013 and has maintained the list prospectively via monthly updates. Medicines under additional monitoring have a black inverted triangle displayed in their package leaflet and summary of product characteristics, urging healthcare professionals and patients to report any suspected adverse reactions via national reporting systems.

EMA also responds to requests for EudraVigilance data in line with the EudraVigilance Access Policy and EU legislation on access to documents[12], and in compliance with EU personal data protection[13]. Details on requests handled in 2013 are provided in Annex VII.

In 2013 the EMA organised four Information Days for external stakeholders from medicines regulatory authorities and pharmaceutical industry in relation to EudraVigilance and the new international standards in pharmacovigilance.

Finally, twenty nine EudraVigilance and seven xEVMPD hands-on training courses were delivered to stakeholders in 2013 with 228 users following xEVMPD e-learning training. Additionally, EVDAS (EudraVigilance Datawarehouse Analysis System) training was held at the Agency on three occasions, training 44 experts from 10 different NCAs.

[8] http://www.adrreports.eu/EN/index.html
[9] http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/document_listing/document_listing_000353.jsp&mid=WC0b01ac05805a21cf
[10] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000375.jsp&mid=WC0b01ac0580727d1c
[11] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000366.jsp&mid=WC0b01ac058067c852
[12] Regulation (EC) No. 1049/2001 of the European Parliament and of the Council of 30 May 2001 regarding public access to European Parliament, Council and Commission documents
[13] Regulation (EC) No. 45/2001 of the European Parliament and of the Council of 18 December 2000 on the protection of individuals with regard to the processing of personal data by the Community institutions and bodies and on the free movement of such data

6. Conclusion

EudraVigilance continues to be the central pillar to support pharmacovigilance activities and therefore contributes to the protection of public health in the EU. The ever increasing number of reports received in EudraVigilance is used for safety monitoring of medicines by the EMA and the Member States, decision making in signals, PSUR and referral procedures by the Agency's scientific committees and is supported by tools for transparency for the public, healthcare providers, academia and MAHs. In 2013 transparency was strengthened by the publication of adopted PRAC recommendations for signals and by establishing the List of medicinal products subject to additional monitoring.

Further work was carried out in 2013 to improve the data quality in EudraVigilance and a further increase was noted in the number of medicinal product submissions by the MAHs, establishing the most complete resource of authorised medicinal products in the EU.

Following the Management Board endorsement of the functional specifications for the EudraVigilance database ("EudraVigilance functionalities to be audited"), the Agency will continue to work with the Member States in 2014 to further define and develop enhanced functionalities for the benefit of the stakeholders and stronger protection of public health.

Annex I - Summary of EudraVigilance related activities

Implementation activities	Status
Operation and maintenance of EudraVigilance by EMA in collaboration with Member States [Legal basis: Regulation (EC) 726/2004, Article 24]	Continued during 2013
Data quality review and duplicate management of adverse reaction reports in EudraVigilance [Legal basis: Regulation (EC) 726/2004, Article 24(3)]	Continued during 2013
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 2013
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 2013
Access to adverse reaction data held in EudraVigilance for CAPs http://www.adrreports.eu/ [Legal basis: Regulation (EC) 726/2004, Article 24]	Continued during 2013

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 2013, a total of 15,747,644 transactions were successfully performed by the EudraVigilance gateway. Figure 1 presents the total number of transactions performed per month during 2013.

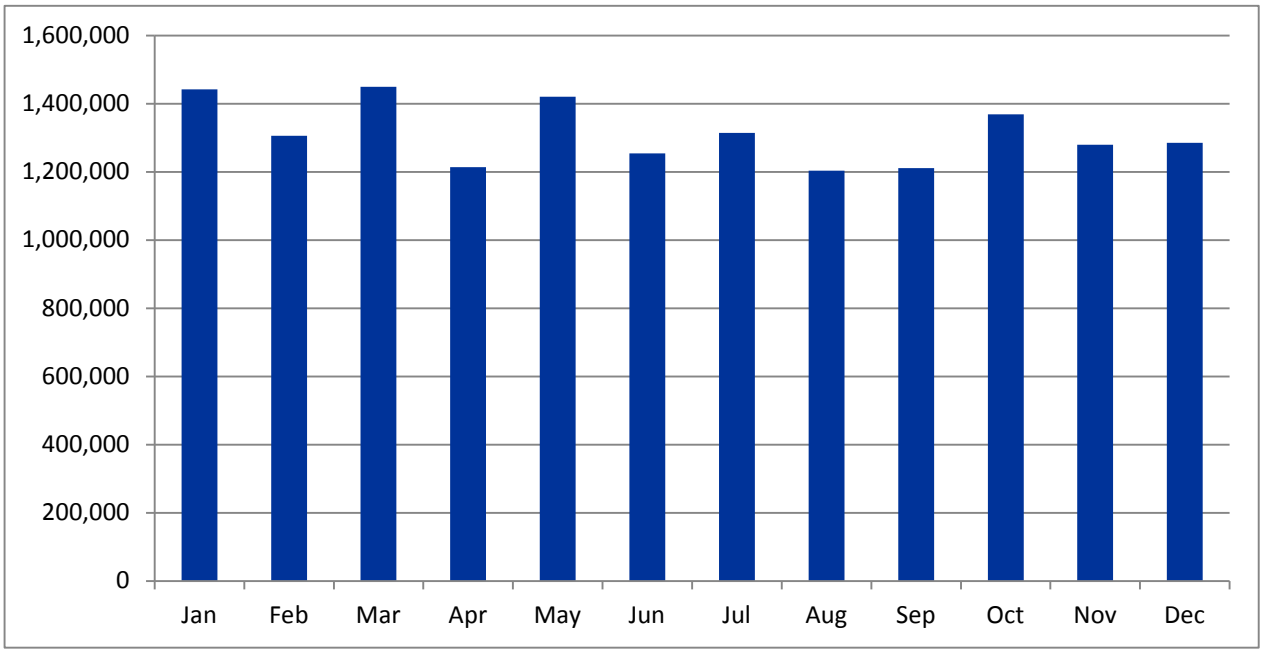


Figure 1. Total number of transactions performed per month at the level of the EudraVigilance Gateway from 1 January 2013 – 31 December 2013

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[14] received in the post-authorisation module. During 2013, an average of 88,474 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.

[14] In the 2012 report, only "expedited" adverse reaction reports were presented. With the new legislation, which has been in force throughout 2013, almost all reports transmitted to EudraVigilance are expedited, so these figures are for all ICSRs/cases transmitted to EV.

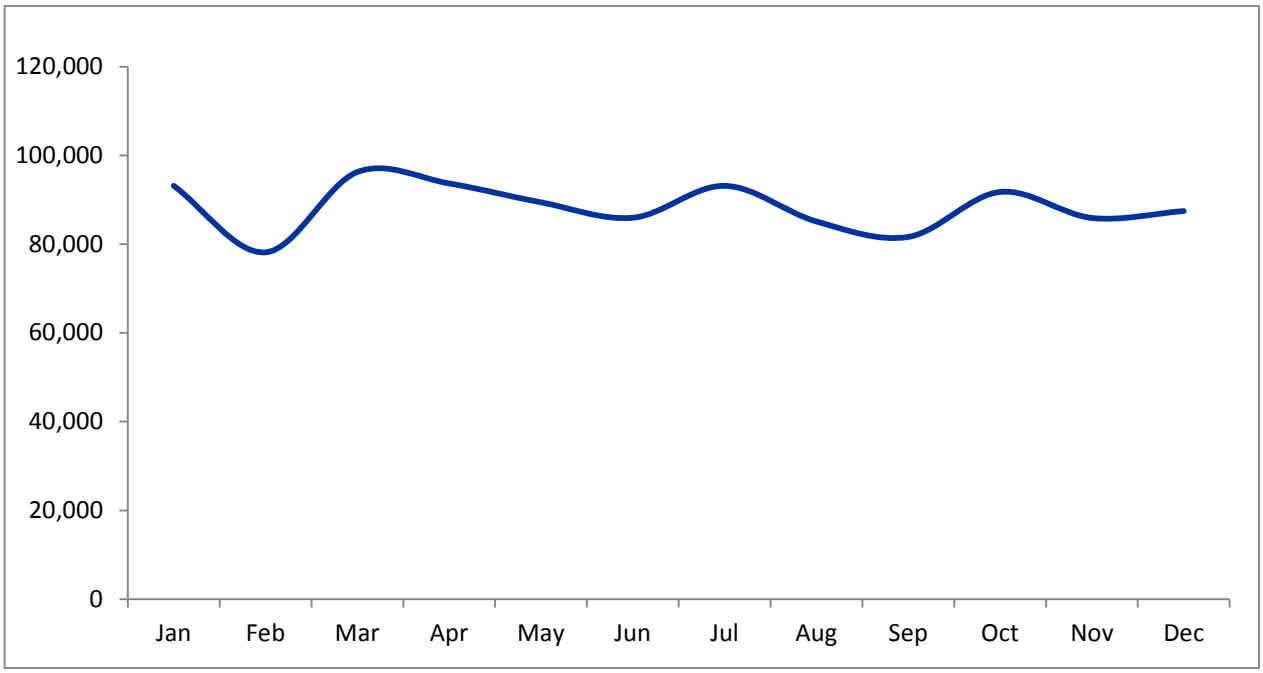


Figure 2. Number of adverse reaction reports processed per month in the EudraVigilance database post-authorisation module in 2013

Figure 3 presents the total number of adverse reaction reports[15] received in the post-authorisation module grouped by EEA and non-EEA for 2013. Each individual case in EudraVigilance refers generally 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.

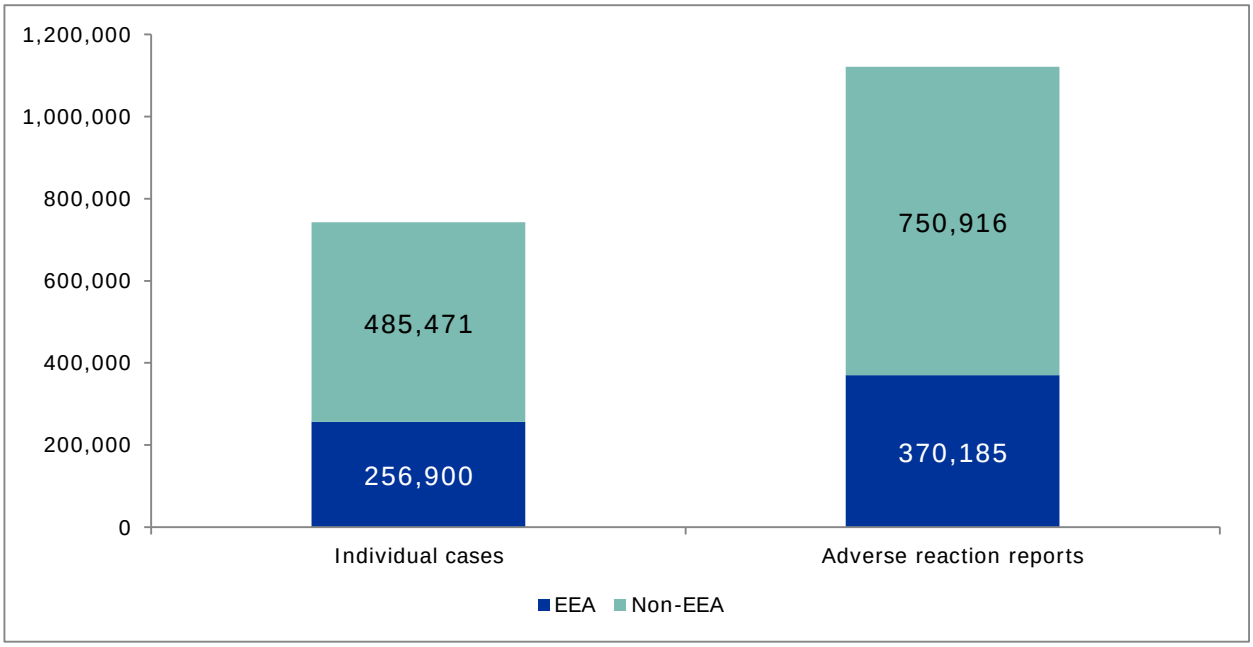


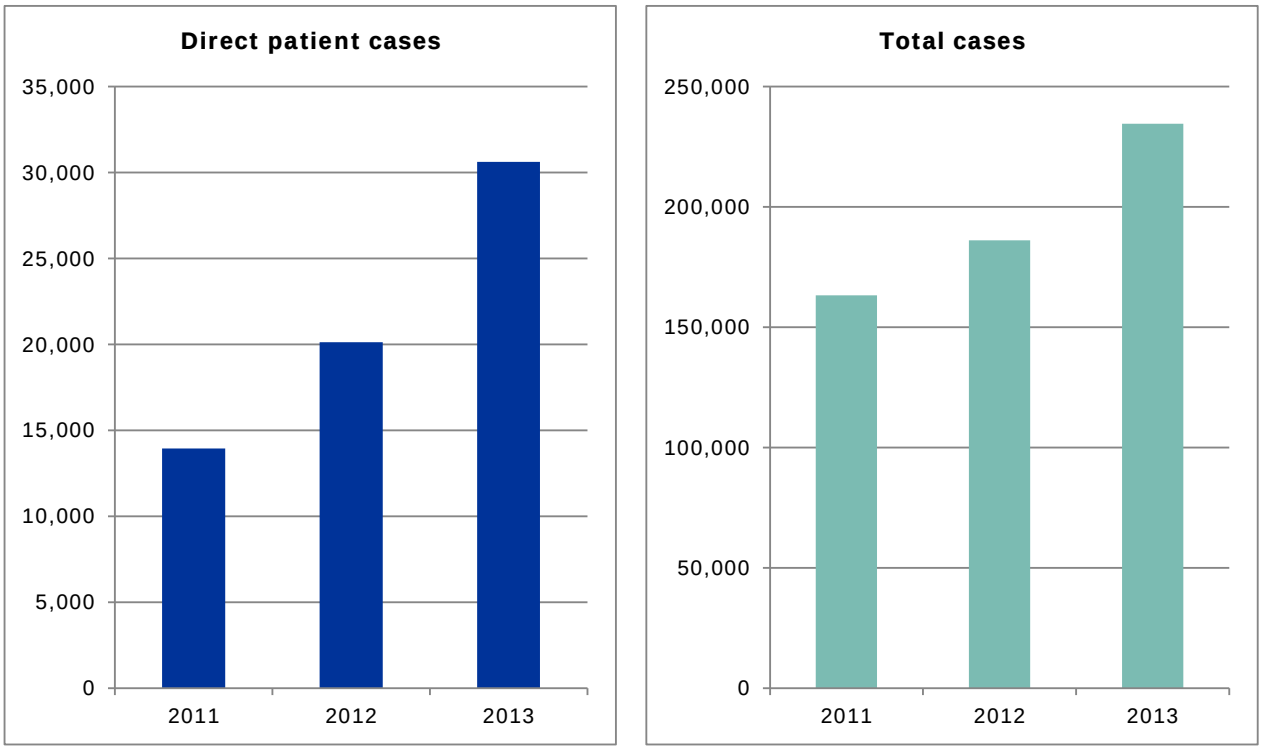
Figure 3. Number of individual cases/adverse reaction reports processed between January and December 2013 in the Eudravigilance database post-authorisation module

[15] In the 2012 report, only "expedited" adverse reaction reports and individual cases were presented. With the new legislation, which has been in force throughout 2013, almost all reports transmitted to Eudravigilance are expedited, so these figures are for all ICSRs/cases transmitted to EV.

One very significant effect of the new pharmacovigilance legislation was to introduce an obligation for MAHs & NCAs to inform the Agency about adverse reactions reports received directly from patients. Within the EEA, this has led to the number of such reports received in EudraVigilance each year increasing significantly (and at a higher rate than the increase in the total number of cases) since the entry into force of the new legislation (13,936 individual cases originating from consumers were transmitted to EV in 2011, and 30,614 were transmitted to EV in 2013).

Figure 4 shows the increase in the number of EEA cases year-on-year and the proportionately greater increase in the number of direct patient reports, from 2011 (the last whole year before the entry into force of the new pharmacovigilance legislation) to 2013. The numbers have been normalised to 2011 values (taking 2011 as 100) to show the comparative rates of increase in direct patient reports versus all reports. Table 1, immediately below Figure 4, gives both the normalised and the true values.

Figure 4. The increase in the rate of direct patient reports compared to the increase in the rate of all reports from the EEA following the entry into force of the new PV legislation



Number of direct patient cases & total cases transmitted to EV each year from 2011 to 2013

Table 1. The rate of direct patient and total EEA case reporting 2011-2013

Year	2011		2012		2013	
Reporter type	**Number of cases**	**% of 2011 rates**	**Number of cases**	**% of 2011 rates**	**Number of cases**	**% of 2011 rates**
Patient	13,936	100	20,115	144	30,614	220
Total	163,275	100	186,136	114	234,546	144

True[16] & normalised values for EEA cases reported to EVPM year-on-year taking 2011 as the baseline for the normalised values

[16] These numbers do not take into account the de-duplication work because they are concerned with the increase in the rate of reporting by primary sources and not the rate of transmission of ICSRs to EV by MAHs or NCAs, and therefore they are not directly comparable to the numbers presented in figures 2 and 3.

By 31 December 2013, the EudraVigilance database (both post-authorisation & clinical trials modules) held a total of 7,026,537 adverse reaction reports, referring to 4,586,491 individual cases (see figure 5).

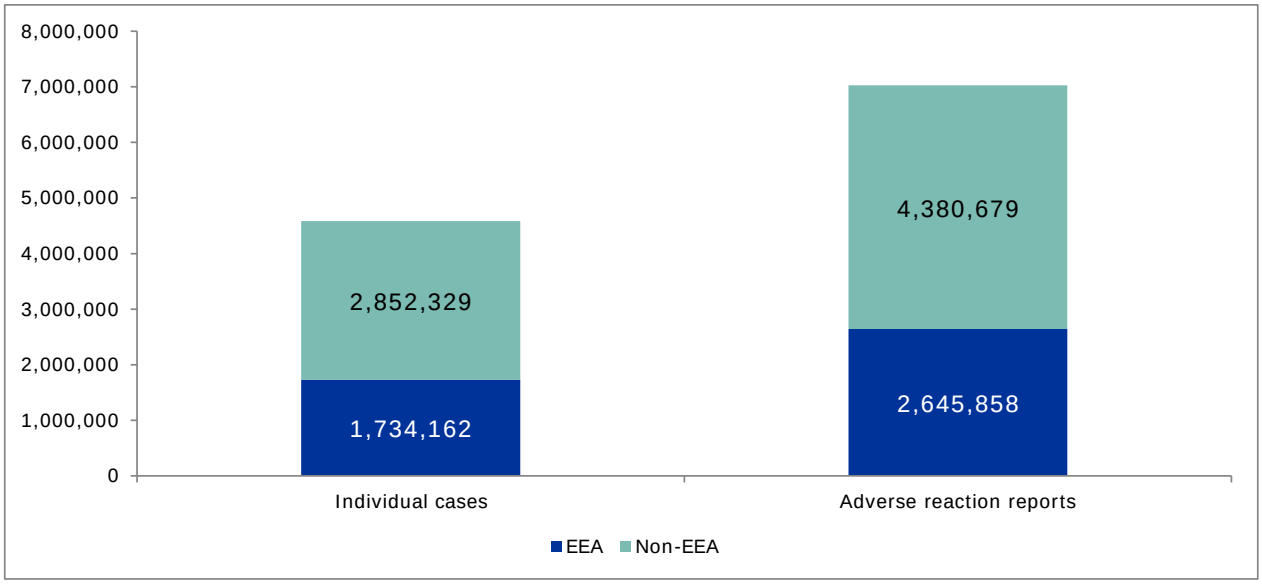


Figure 5. Total number of individual cases/adverse reaction reports received in the EudraVigilance database from its inception in December 2001 until 31 December 2013.

E-reporting status for MAHs and sponsors of clinical trials

- A total of 758 MAHs (at headquarter level) have sent reports to the EudraVigilance Post-authorisation Module (EVPM) in the period between 1 January 2002 and 31 December 2013.
- A total of 713 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 2013.

Tables 2 and 3 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 flagged by the MAHs as serious are included in the calculations.

Table 2. Number of ICSRs and unique cases transmitted by MAHs and sponsors to EVPM and EVCTM during 2013

EV Module	Transmission type	Number of transmissions
EVPM	ICSRs	793,176
	Individual Cases	502,860
EVCTM	ICSRs	75,341
	Individual Cases	28,355

Table 3. Combined 15-day reporting compliance to EVPM for all MAHs and sponsors in 2013.

Percentage of ICSRs transmitted to EVPM by MAHs/Sponsors within 15 days:	**96%**

E-reporting status for NCAs

- All 31 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 4 & 5 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 89%, an increase from 2011 & 2012, when it was 84%.

Table 4. Number of ICSRs and unique cases transmitted by NCAs to EVPM & EVCTM during 2013

EV Module	Transmission type	Number of transmissions
EVPM	ICSRs	327,925
	Individual Cases	239,511
EVCTM	ICSRs	19,557
	Individual Cases	12,161

The figures for “Individual Cases” in the table above include the master cases transmitted by the EMA.

Table 5. Combined 15-day reporting compliance to EVPM for all NCAs in 2013

Percentage of ICSRs transmitted to EVPM by NCAs within 15 days:	89%

During 2013, the following 10 NCAs transmitted SUSARs to EVCTM (SUSARs from other countries were received directly from sponsors of clinical trials):

Member State	National Competent Authority
BELGIUM	FEDERAL AGENCY FOR MEDICINES AND HEALTH PRODUCTS
CZECH REPUBLIC	STATE INSTITUTE FOR DRUG CONTROL
DENMARK	DANISH MEDICINES AGENCY
FINLAND	FINNISH MEDICINES AGENCY
GERMANY	FEDERAL INSTITUTE FOR DRUGS AND MEDICAL DEVICES
GERMANY	PAUL-EHRLICH-INSTITUT
ITALY	AGENZIA ITALIANA DEL FARMACO
NETHERLANDS	COLLEGE TER BEOORDELING VAN GENEESMIDDELEN
SWEDEN	MEDICAL PRODUCTS AGENCY
UNITED KINGDOM	MEDICINES & HEALTHCARE PRODUCTS REGULATORY AGENCY

EudraVigilance database and support of signal management process

A total of 19,330 e-RMRs were generated in 2013 to facilitate the continuous monitoring of the safety of medicines by the EMA and medicines regulatory authorities in the EEA.

Annex III - Total number of medicinal product submissions by MAHs

Total number of medicinal product submissions by MAHs by 3 Feb 2014[17] 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)	459,290
Total number of marketing authorisation holders (legal entities) established in the EU (corresponding to EudraVigilance codes)	3,996

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).

[17] Please note that this figure is as of 3 Feb 2014 and not 31 Dec 2013. This is due to technical changes made to the database which means it is not possible to give a precise figure as of 31 December 2013. The EMA estimates that the number of MAHs and headquarters would have been almost identical as of end-2013 and the number of medicinal products would have been 10-20,000 fewer

Annex IV - EudraVigilance data quality activities

In accordance with Regulation (EC) No 726/2004, Article 24(3), the Agency operates procedures to ensure the quality and integrity of the information collected in EudraVigilance. This includes identifying duplicate reports, performing the coding of the reported medicines and reported active substances, and providing feedback on the quality of information sent by NCAs, MAHs and sponsors. The table below refers to the data quality activities performed by the EMA in 2013.

EudraVigilance data quality activities in 2013		
Identifying and managing duplicates	**Coding of reported medicines and active substances**	**Providing feedback on data quality**
Number of duplicate couples assessed: 122,308 (in 2012 this was 96,298)	Number of medicinal products/active substances recoded: 87,660 (In 2012 this was 82,076)	Total number of organisations subject to data quality review: 166 (In 2012 this was 216)
Number of 'master' reports generated based on duplicated data: 65,906 (In 2012 this was 83,393)	Number of adverse reaction reports recoded: 555,798 (referring to 275,852 individual cases). In 2012 616,001 adverse reaction reports were recoded, referring to 356,000 individual cases.	

The overall rate of duplicates reported to EudraVigilance since its launch is estimated at about 8%. This includes "different-sender" duplicates as well as "same-sender" duplicates. "Same-sender" duplicates are those were all duplicates in the cluster were transmitted to EudraVigilance by the same organisation (NCAs, MAHs, sponsors).

In accordance with Directive 2001/83/EC, Articles 107(5) and 107a(3), the Agency is collaborating with MAHs and NCAs to detect and eliminate duplicate suspect adverse reaction reports. To this end, when suspected duplicate suspect adverse reaction reports are detected in EudraVigilance and both of the suspected duplicates are from the same sender, the Agency will send information on these suspected 'same-sender' duplicates to the organisation which transmitted these cases to EudraVigilance and ask them to manage them appropriately.

Annex V – Signal detection

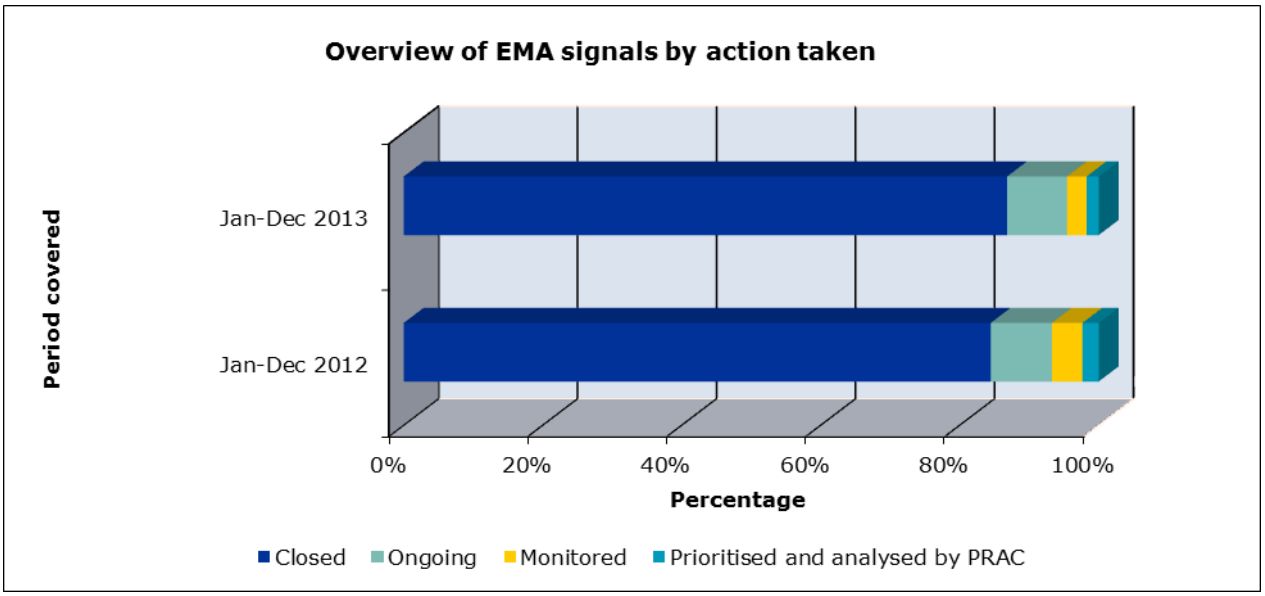
In 2013, the total number of signals reviewed increased by approx. 11% compared to 2012. This parallels the increased number of ICSRs received in EudraVigilance, the increasing use of standardised MedDRA queries (SMQs) for analysis (and subsequently a higher number of preferred terms which are tracked) as well as the implementation of the list of designated medical events (DMEs) in the e-RMR and additional categories which warrant priority screening (i.e. most relevant reactions terms/DMEs, fatal, paediatric reports etc.) in 2012.

OVERVIEW	2013	2012	2011	2010	2009	2008
Total	2,449	2,213	1,586	2,054	1,704	1,327
Difference vs previous year	236	627	-468	350	377	Ref.
Difference %	10.7%	39.5%	-22.8%	20.5%	28.4%	Ref.

Overall, 91% of potential signals originated from EudraVigilance, with other sources accounting for: 5% from the scientific literature, 3% from communications received from other Regulatory Agencies worldwide (52 from MHLW/PMDA, 15 from the FDA, 5 from the WHO and 4 from EMCDDA) and 1% from other sources. The overview of signals validation by action taken is provided below:

Action taken	Number of signals Jan-Dec 2013	% of total	Number of signals Jan-Dec 2012	% of total
Closed	2126	87%	1869	84%
Ongoing	211	9%	195	9%
Monitored	69	3%	97	4%
Prioritised and analysed by PRAC	43	2%	52*	2%
Total	2449	*100%*	2213	*100%*

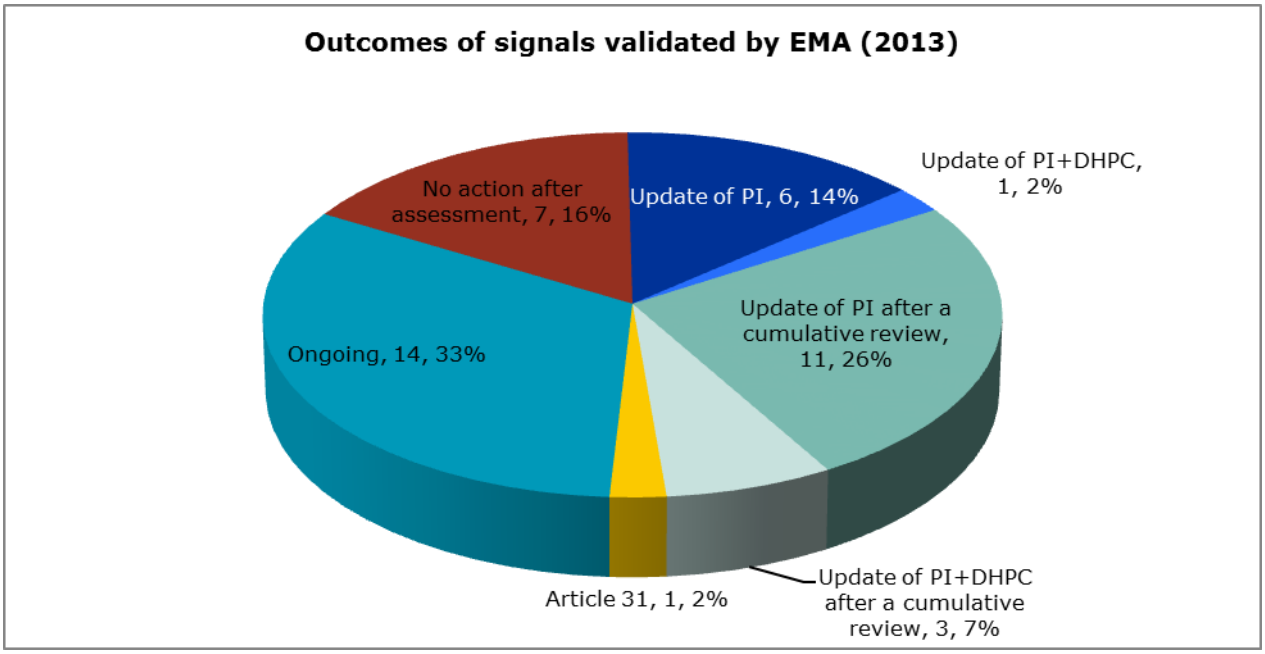
*reflects the number of signals communicated to Rapporteurs by the EMA in 2012 (prior to, and after the inauguration of the PRAC)



In total, 2,449 potential signals were reviewed in 2013 by the Agency. 43 signals validated and communicated to the Rapporteurs by the Agency were prioritised and analysed by the PRAC during

2013. Of note, 2 of these signals had been under monitoring by the signal validation team at the Agency in 2012, 8 were prompted by the scientific literature and 5 by information received from other regulatory authorities (3, 5 and 6, respectively in 2012).

At the time of this report, approximately half of the 43 signals handled by the PRAC (n=21) led to recommendation for changes to the product information, either directly (n=7) or following a cumulative review (n=14), providing information to patients and healthcare professionals on the safe use of these products. For four signals, this also included the distribution of Direct Healthcare Professional Communications (DHPC) to increase awareness about the new safety information. The evaluation of 14 signals following the recommendation for a cumulative review is currently on-going. The evaluation of seven signals was closed with no further regulatory action required, with the routine pharmacovigilance activities deemed satisfactory for further follow-up of these signals. One signal led to a formal evaluation of the benefit-risk balance via an Article 31 referral.



Additionally, 69 signals (approx. 3%) were kept under monitoring (as of end of Dec 2013). If a signal is monitored, in principle all new cases of that reaction sent to EudraVigilance are reviewed.

Overview of signals validated by the Agency prioritised and assessed by the PRAC

Since the establishment of the PRAC in July 2012, a new signal management process has been in place. Signals are communicated to PRAC members who confirm the validity of the signals in line with the new legislation and the Guideline on good pharmacovigilance practices: Module IX – Signal management. Confirmed signals are transmitted to the PRAC for prioritisation and analysis. In line with the new legislation's aim of increasing transparency and communication in pharmacovigilance, agendas and minutes of the PRAC are being made public. Since September 2013 this also includes the recommendations on signals as adopted by the Committee, and can be found here.

An overview of validated signals is provided in the following tables, including the latest regulatory status as of 21 January 2014. When the outcome of an initial recommendation is already known, both are noted sequentially.

Drug	Issue	Latest status or outcome
Adalimumab	Dermatomyositis	cumulative review: update of product information
Adalimumab	Immune Reconstitution Inflammatory Syndrome (IRIS)	cumulative review
Aflibercept	Blindness	cumulative review
Agents acting on the renin-angiotensin system	Efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomised trials	Article 31 referral: evaluation ongoing
Agomelatine	QT prolongation	cumulative review: no regulatory action (routine pharmacovigilance)
Bevacizumab	Anaphylactic shock	cumulative review: no regulatory action (routine pharmacovigilance)
Brentuximab Vedotin	Pulmonary toxicity	cumulative review: update of product information
Capecitabine	Acute renal failure	cumulative review: update of product information
Capecitabine	Convulsion	cumulative review
Cinacalcet	Fatal case with severe hypocalcemia in a pediatric clinical study	update of product information and DHPC
Clopidogrel	Acquired haemophilia A	cumulative review: update of product information
Clopidogrel	Cross-reactivity between clopidogrel and ticlopidine among patients with previous allergic and/or haematologic reactions to one of these products	update of product information
Clopidogrel	Eosinophilic pneumonia	cumulative review: update of product information
Denosumab	Vasculitis	cumulative review
Dexmedetomidine	Infantile apnoeic attack	cumulative review
Docetaxel	Serious and fatal drug interactions involving CYP3A4 (grapefruit juice and dronedarone)	cumulative review: update of product information
Docetaxel	Thrombotic microangiopathy	cumulative review: no regulatory action (routine pharmacovigilance)
Duloxetine	Interaction with aripiprazole - serotonin syndrome	cumulative review: no regulatory action (routine pharmacovigilance)

Drug	Issue	Latest status or outcome
Duloxetine	Interaction with linezolid leading to serotonin syndrome	update of product information
Efavirenz; Emtricitabine, efavirenz, tenofovir	Interaction with *Ginkgo biloba*	update of product information
Etanercept	Dermatomyositis	cumulative review: update of product information
Exenatide	Injection site abscess and cellultis	cumulative review
Exenatide, Liraglutide	Cholecystitis and cholelithiasis	cumulative review
Exenatide, Liraglutide	Gastrointestinal stenosis and obstruction	cumulative review: update of product information
Filgrastim, Pegfilgrastim	Capillary leak syndrome, cytokine release syndrome	cumulative review: update of product information and DHPC
Fondaparinux	Heparin-induced thrombocytopenia	cumulative review: no regulatory action (routine pharmacovigilance)
Glycopyrronium	Angioedema	cumulative review
Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed)	Complex regional pain syndrome	cumulative review
Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)	Complex regional pain syndrome	cumulative review
Infliximab	Immune Reconstitution Inflammatory Syndrome (IRIS)	cumulative review
Leflunomide	Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)	update of product information
Leflunomide	Myositis	cumulative review: no regulatory action (routine pharmacovigilance)
Lenograstim	(Systemic) capillary leak syndrome (CLS)	cumulative review: update of product information and DHPC
Levetiracetam	Hyponatraemia and inappropriate antidiuretic hormone secretion (SIADH)	cumulative review: update of product information
Mirabegron	Urinary retention	cumulative review
Orlistat	Pharmacokinetic drug interaction (at absorption) with highly active antiretroviral therapy(HAART) leading to loss of HAART efficacy	cumulative review: update of product information

Drug	Issue	Latest status or outcome
Sitagliptin, Sitagliptin/metformin	Angioedema due to interaction between sitagliptin and ACE inhibitors	cumulative review
Somatropin	Convulsions	cumulative review: no regulatory action (routine pharmacovigilance)
Temozolomide	Hepatic failure	cumulative review: update of product information and DHPC
Teriparatide	Anaphylactic shock	update of product information
Thalidomide	Posterior Reversible Encephalopathy Syndrome (PRES)	cumulative review: update of product information
Ticagrelor	Food interaction with grapefruit juice	update of product information
Vemurafenib	Renal failure	cumulative review

Annex VI - Signal management in the EU

Signal management is the procedure which covers all the steps from the detection of a new signal to its evaluation by the appropriate scientific committee, including the signal validation, signal confirmation, signal analysis and prioritization, signal assessment, recommendation for action and the exchange of information between the relevant parties.

Following the experience from the Pilot of signal management in the EU, further progress in signal management has been made through the Signal Management Review Technical Working Group, a collaboration group for continuous process improvement between the EMA and the MSs in the European Medicines Regulatory Network. Three areas were identified for facilitation of signal management in the EU: Signal management tools and processes, Methodological guidance and Signal detection methods. The following actions were completed in 2013:

- Standardised templates for assessment of signal data and the corresponding form for the PRAC recommendation were developed for the use by the network.
- A Questions & answers on signal management document (EMA/261758/2013) was published on the EMA website to provide procedural guidance for MAHs regarding handling of signals discussed at PRAC and any follow-up actions that may arise.
- The Agency started publishing the signal recommendations adopted by the PRAC on a dedicated section of the EMA website[18] to facilitate implementation of the PRAC recommendations by the MAHs and to increase transparency.
- The European Pharmacovigilance Issues Tracking Tool database was amended following the implementation of the new pharmacovigilance legislation, to accommodate the new steps in signal management process in line with the new legislation and to allow for a more complete tracking of the signal life cycle. The user guide was updated accordingly.
- Integration of signal procedures into the Agency's tracking systems was achieved, to allow for tracking of signal procedures and their corresponding timetables. Further work for nationally authorised products is foreseen in the future.
- Further research into statistical signal detection methods was carried out, with a view to update the existing Guideline on the use of statistical signal detection methods in EVDAS (Doc. Ref. EMEA/106464/2006).

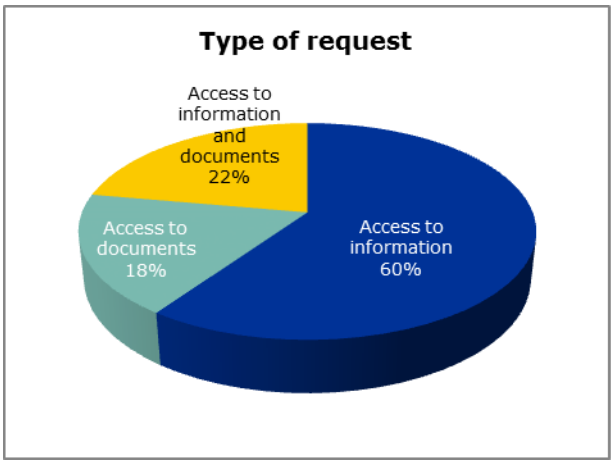
[18] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000375.jsp&mid=WC0b01ac0580727d1c

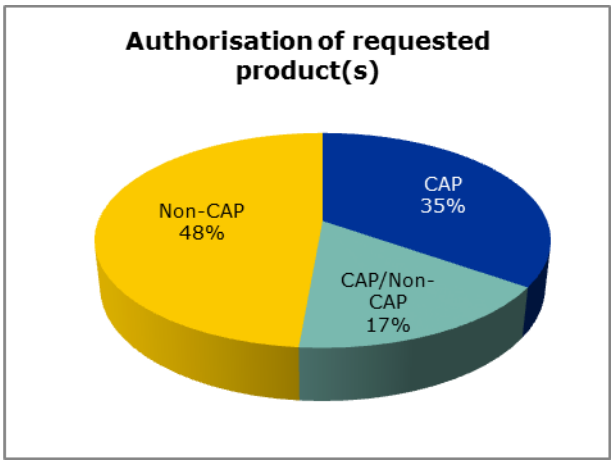
Annex VII - Requests for information and documents

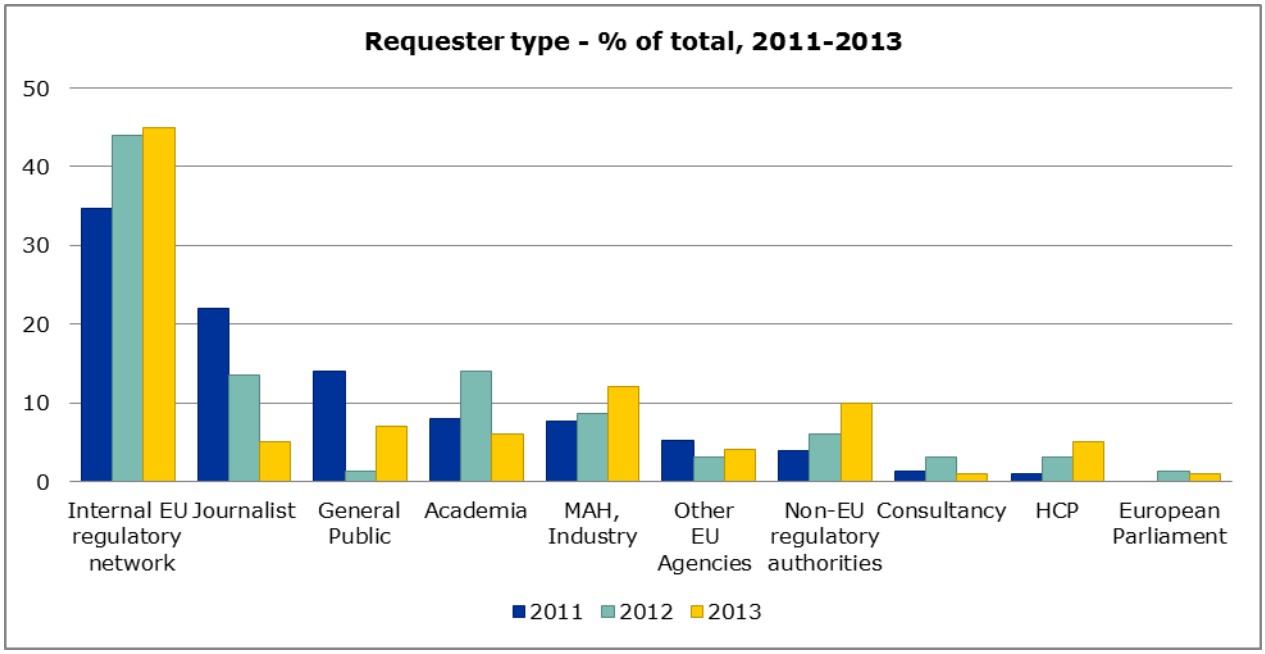
Seventy-two requests were answered in 2013, compared to 80 in 2012. Whereas the total number has remained similar, an increase was observed for requests from the general public, HCPs, the MAHs and non-EU regulatory authorities. The drop in requests from journalists was observed already in 2012 and continued throughout 2013. This may be due to the proactive publication of adverse drug reaction data for CAPs at www.adrreports.eu, which started on 31 May 2012. Data from seven requests were used to support the decision making in the context of European referral procedures (listed below).

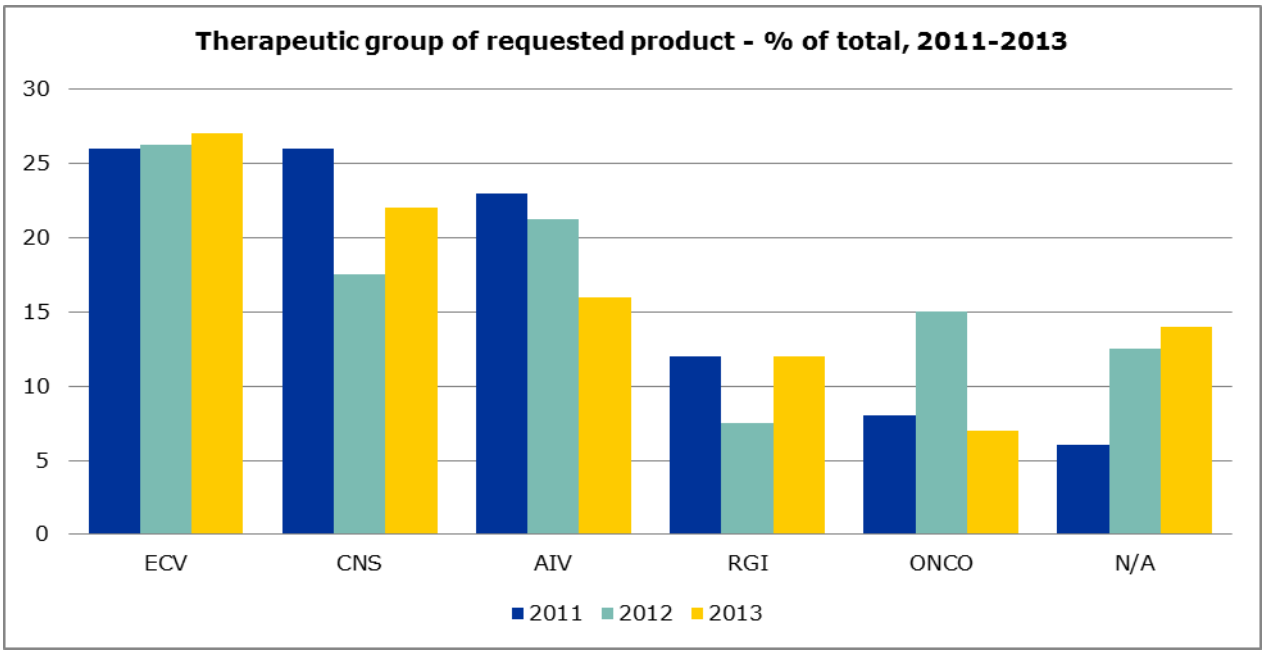
The median response time in 2013 was 23 days (range 0-182 days) compared to 18 days in 2012 (range 0-100 days). The time of response is subject to different factors such as the urgency of the request, the complexity of the search needed and the agreed timeliness especially for internal EU requests. 35% of the requests were answered within 14 days, 61% within 1 month and 86% within two months which is a decrease compared with 2012 (49%, 68% and 95%, respectively) and reflects the increase in complexity of requests and number of products/reactions requested.

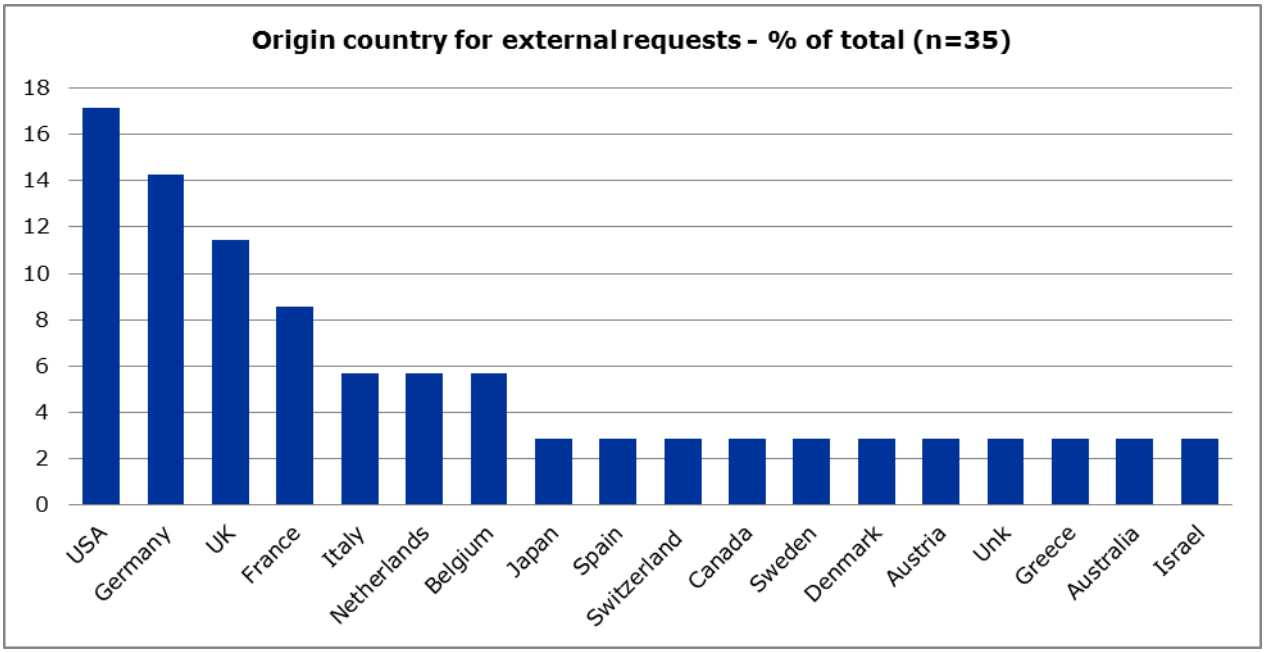
An overview is provided below by type of request, authorisation type of requested product(s), requester type, therapeutic group of requested product(s) and origin country (external requests only).








Therapeutic group of requested product - % of total, 2011-2013
30
25
20
15
10
5
0
ECV
CNS
AIV
RGI
ONCO
N/A
2011
2012
2013


Origin country for external requests - % of total (n=35)
18
16
14
12
10
8
6
4
2
0
USA
Germany
UK
France
Italy
Netherlands
Belgium
Japan
Spain
Switzerland
Canada
Sweden
Denmark
Austria
Unk
Greece
Australia
Israel

Overview of requests handled in 2013

Type of requester	Drug/substance	Issue	Type of request
Internal EU Regulatory Network	Acetylsalicylic acid	ADRs for acetylsalicylic acid in low dose	Access to information and documents
MAH	Agomelatine	Angioedema	Access to documents
Law firm	Alendronate Flutamide Omeprazole Rimonabant	Alendronate - ONJ Flutamide - Death Omeprazole - Hepatitis and Hepatotoxicity Rimonabant - Depression, manic depression and mental disorders	Access to information
Internal EU Regulatory Network	Aliskiren	Data of use in paediatric population	Access to information and documents
Internal EU Regulatory Network	All substances in the database	PML	Access to information
General Public	Allopurinol	ICSRs submitted within the Skin SOC	Access to information
Non-EU Regulatory Authorities	Andrographis paniculata (Burm.f.) Nees.	All ICSR submitted to the database	Access to information
Internal EU Regulatory Network	Antidiabetic medicines	Pancreatitis and pancreatic cancer	Access to information
Non-EU Regulatory Authorities	Arcoxia - etoricoxib	- Fatal outcomes - Cardiac disorders - Central nervous system - Vascular disorders	Access to information and documents
Academia	Asthma medications in children	All ADRs reported in children submitted from 2007 to 2011	Access to documents
Internal EU Regulatory Network	Atosiban	Contamination issues	Access to information
MAH	Avastin - bevacizumab	Anaphylactic shock	Access to documents
Internal EU Regulatory Network	Avastin - Bevacizumab	Ocular use	Access to information
Internal EU Regulatory Network	Azithromycin	Fatal arrhythmias	Access to documents
Journalist	Bedaquiline	All ADRs reported to the database	Access to information
Internal EU Regulatory Network	Benzyl Alcohol	Gasping syndrome	Access to information
Internal EU Regulatory Network	Biphasic insulin aspart	Homogeneity issue	Access to information
Journalist	Cabazitaxel	Medication errors	Access to information
Non-EU Regulatory Authorities	Clopidogrel	Acquired haemophilia A	Access to documents

Type of requester	Drug/substance	Issue	Type of request
Internal EU Regulatory Network	Codeine	Data to support the Referral procedure	Access to information
General Public	Colchicine and methotrexate	All ICSRs submitted to the database	Access to information
Internal EU Regulatory Network	Combined oral contraceptives	Data to support the Referral procedure	Access to information
Internal EU Regulatory Network	Contraceptives	Embolic and thrombotic events	Access to documents
Internal EU Regulatory Network	Cyproterone	Data to support the Referral procedure	Access to information
Internal EU Regulatory Network	Dextromethorphan	ADRs reported in the EU	Access to information
Academia	Diabetic medicines	Research Protocol	Access to information
Internal EU Regulatory Network	Diacerein	Data to support the Referral procedure	Access to information
MAH	Digoxin Amitriptyline	Details of all the ICSRs submitted	Access to documents
Academia	Domperidone	All ICSRs submitted to the database	Access to information and documents
Internal EU Regulatory Network	Domperidone	Data to support the Referral procedure	Access to information
Journalist	Drospirenone	All ADRs reported to the database	Access to information and documents
Internal EU Regulatory Network	Efavirenz	Cancer reports and birth defects	Access to information
General Public	Enoxaparin	Cardiovascular disorders	Access to information
Journalist	Exenatide Liraglutide Lixisenatide Sitagliptin Saxagliptin Linagliptin Vildagliptin	Cancer of the thyroid and pancreatic glands	Access to information
Internal EU Regulatory Network	Fluenz and Fluariz	Medication errors	Access to information
Internal EU Regulatory Network	Flupirtine	Data to support the Referral procedure	Access to information
European Parliament	Gardasil	Multiple Sclerosis	Access to information and documents
Internal EU Regulatory Network	Gilenya - fingolimoid	PML	Access to information
Internal EU Regulatory Network	Gilenya - fingolimoid	PML	Access to information and documents
General Public	Havrix, Engerix and Twinrix	Multiple sclerosis	Access to documents

Type of requester	Drug/substance	Issue	Type of request
Internal EU Regulatory Network	Heparins	Trend analysis of ADRs	Access to information
Internal EU Regulatory Network	Hexoprenaline	All ICSRs submitted to the database	Access to information and documents
Non-EU Regulatory Authorities	HPV Vaccines	Complex regional pain syndrome	Access to information
MAH	Hydroxyethyl starch	Total of ICSRs and cases reports with fatal outcome	Access to information
Internal EU Regulatory Network	Inotuzumab ozogamicin	Veno-occlusive disease and hepatotoxicity	Access to information and documents
Internal EU Regulatory Network	Interferon beta	Risk of collapsing focal segmental glomerulosclerosis	Access to information
Non-EU Regulatory Authorities	Intralipid	Reports of ADRs submitted for an specific formulation	Access to information and documents
MAH	Lopinavir/ritonavir and quetiapine	Drug interaction between protease inhibitors and quetiapine	Access to documents
HCP	Magnesium sulfate, thiamine and procaine	All ADRs reported to the database	Access to information and documents
MAH	Mirtazapine	Pancreatitis	Access to documents
Other EU Agencies	MMR Vaccines	Information on ADRs of MMR vaccines in adults.	Access to information
Academia	Multiple substances	Research protocol	Access to information
General Public	Natalizumab	PML	Access to documents
Internal EU Regulatory Network	Nicotinic acid	Data to support the Referral procedure	Access to information
Internal EU Regulatory Network	Numeta G13%E	Hypermagnesaemia in preterm infants	Access to information
HCP	Paracetamol	Allergic reactions	Access to information and documents
Other EU Agencies	Phenibut	All ICSRs submitted to the database	Access to information
Internal EU Regulatory Network	Privigen	Haemolysis	Access to information
Internal EU Regulatory Network	Ranbaxy products	Quality issues	Access to information
Consultancy	Resorcinol	Endocrine, skin and subcutaneous disorders	Access to information and documents
MAH	Sertraline	Growth retardation in children and adolescents	Access to documents
HCP	Sodium picosulphate + magnesium citrate Polyethylene glycol	Convulsions, seizures and epilepsy	Access to information and documents

Type of requester	Drug/substance	Issue	Type of request
	(macrogol) + ascorbic acid/ascorbate Oral polyethylene glycol (macrogol)		
MAH	Strontium ranelate	Atypical femur fracture	Access to information and documents
Internal EU Regulatory Network	Synflorix	Information on case reports from clinical trials	Access to information
Non-EU Regulatory Authorities	Tacrolimus	Medication errors	Access to information
Internal EU Regulatory Network	Thiocolchicoside	Genotoxicity	Access to information and documents
Internal EU Regulatory Network	Tolcapone, natalizumab and alosetron	Tolcapone - Hepatic disorders Natalizumab - PML Alosetron - Gastrointestinal disorders	Access to information
Internal EU Regulatory Network	Tredaptive (laropiprant, nicotinic acid)	All ADRs reported	Access to information
Other EU Agencies	Tropicamide	Misuse and abuse	Access to information
HCP	Valproate	Middle or/and inner ear malformation	Access to information
Non-EU Regulatory Authorities	Xaluprine - mercaptopurine	Medication errors	Access to Information
MAH	Yellox - bromfenac	Cardiac failure	Access to documents