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from:	General Secretariat of the Council
to:	Delegations
Subject:	First Annual Report on EudraVigilance for the European Parliament, the Council and the Commission - Reporting period: 1 January to 31 December 2012

Delegations will find attached a note from European Medicines Agency on the above subject.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

Reporting period: 1 January to 31 December 2012

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1. Introduction

A major revision of the pharmacovigilance legislation[1] came into force in the European Union (EU) in 2010 and applies from July 2012. This new legislation aims to promote and protect public health by strengthening the European system for monitoring the safety and benefit-risk balance of medicines while enhancing transparency and enabling simplification where possible. It builds on existing pharmacovigilance processes and tools such as EudraVigilance, the database and data-processing network specifically designed to facilitate reporting, monitoring and the evaluation of suspected adverse reactions for all medicinal products authorised in the EU.

The European Medicines Agency (EMA) plays a key role in 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. 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 have changed and whether those risks have an impact on the overall benefit-risk balance of a medicine.

In compliance with the new legislation[2], the EMA has prepared this first 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 2012, in collaboration with the EU regulatory network and with stakeholders.

2. Background

EudraVigilance is a web-based information system designed to manage information on suspected adverse reaction reports also known as Individual Case Safety Reports (ICSRs). It was launched by the EMA in December 2001 in accordance with Article 24 of Council Regulation (EEC) No 2309/93. The database and data-processing network was developed in full compliance with the specifications of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and currently holds a total of 3.9 million ICSRs related to medicinal products for human use authorised in the EU. It receives data from National Competent Authorities (NCAs) and marketing authorisation holders (MAHs), who first receive the reports from healthcare professionals, patients and consumers.

It provides the newly established Pharmacovigilance Risk Assessment Committee (PRAC), which is responsible for assessing and monitoring safety issues for human medicines, the EMA and medicines regulatory authorities in Member States with a unique tool to continuously monitor the safety profile of medicines and to rapidly initiate actions where necessary to protect public health.

In the context of the new pharmacovigilance legislation, major emphasis has 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 and providing stakeholders with adequate access to adverse reaction data. A technical implementing regulation and detailed guidance have been issued in 2012 to facilitate this enhancement of EudraVigilance. These refer specifically to the Commission Implementing Regulation (EU) No 520/2012 and the Good

[1] Regulation (EU) No 1235/2010 of 15 December 2010 amending Regulation (EC) No 726/2004 and Regulation (EC) No 1394/2007
Directive 2010/84/EU of 15 December 2010 amending Directive 2001/83/EC
[2] Regulation (EC) 726/2004 Article 24(2), paragraph 2

Pharmacovigilance Practices (GVP) published in June 2012 to facilitate the performance of pharmacovigilance in the EU.

3. Development of new functionalities

The EudraVigilance related activities provided for in the new legislation require the addition of new functionalities. These new functionalities refer in particular to the implementation and use of internationally agreed formats, standards and terminology, improved data quality management, enhanced data analysis and signal detection, electronic communication and re-routing of ICSRs to medicines regulatory authorities in the Member States and regular provision of the reports to the World Health Organisation (WHO), increased access of stakeholders of the data held[3] in EudraVigilance and simplified literature monitoring while fully respecting EU legislation on personal data protection.

At the request of the Commission, the EMA has been leading from an EU regulatory perspective on standards development, relevant to medicinal products, resulting in the recent adoption of the new ISO ICSR standard and five ISO Identification of Medicinal Products (IDMP) standards, which will be a key building block for the further development of EudraVigilance.

A further technical enhancement of EudraVigilance including new functionalities is currently deferred. This will also defer the conduct of an independent audit to confirm that the new functionalities of EudraVigilance have been achieved. According to the new legislation, a successful audit is the prerequisite for the EMA Management Board to announce centralised reporting by MAHs to EMA only (i.e. no longer to the NCAs).

4. Data collection and data quality

One of the deliverables[4] of the new legislation focused on the electronic submission of a core data set for all medicinal products authorised in the EU by marketing authorisation holders (MAHs). Following publication of a Legal Notice,[5] 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. The total number of medicinal product submissions by MAHs during 2012 is presented in Annex III.

For the first time, the new legislation also introduces 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 in EudraVigilance in 2012 is provided in Annex II. Reporting of non-serious adverse reactions will be initiated following the successful outcome of the independent audit as referred to in chapter 3.

EudraVigilance further supports the reporting of suspected unexpected serious adverse reactions (SUSARs) in accordance with EU clinical trial legislation[6] (see Annex II).

Quality assurance is key to support pharmacovigilance. In accordance with the new pharmacovigilance legislation, the EMA is operating procedures that ensure the quality and integrity of the information

[3] http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/07/WC500108538.pdf
[4] Regulation (EC) 726/2004, Article 57(2), second subparagraph
[5] 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)
[6] 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

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.

EMA's efforts in improving data quality including 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 are summarised in Annex IV.

5. Data analysis

The new legislation introduces clearly defined responsibilities for signal detection and management in the EU. Within the context of the operation of the EU regulatory network, the Agency and the NCAs continuously monitor the data available in EudraVigilance and other data sources to determine whether there are new risks or whether risks have changed and whether those risks have an impact on the benefit-risk balance of medicines. A safety signal refers to information on one or more newly observed adverse reactions potentially caused by a medicine and that warrant further investigation. EudraVigilance data is an important data source for detecting new safety signals. Other data sources include clinical trial data, periodic safety update reports (PSURs), risk management plans (RMPs), other health data and the scientific literature.

If a safety concern is confirmed or considered likely to be associated with a medicinal product, regulatory action may be necessary. This 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 (CAP) and the NCAs are leading for non-CAPs. 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.

To support monitoring of data by NCAs in the EudraVigilance database the EMA prepares data outputs and statistical reports called electronic reaction monitoring reports (e-RMRs). In July 2012 EMA started the provision of e-RMRs for non-CAPs to Member States appointed to monitor data in EudraVigilance for specific active substances with the aim to detect and validate safety signals on behalf of the EU Regulatory Network (work-sharing concept).

The overall goal of this work-sharing for signals, whereby one Member State is responsible for monitoring a single active substance contained in a medicine authorised through a national, mutual-recognition or decentralised procedure is to further strengthen the signal detection system and optimise use of resources across the EU network for the benefit of public health.

The newly established PRAC is responsible for assessing all aspects of the risk management of medicines for human use. This includes initial analysis and prioritisation of signals, assessment, minimisation and communication relating to the risk of adverse reactions. It also has responsibility for the design and evaluation of post-authorisation safety studies and pharmacovigilance audits.

Following the inaugural meeting of the PRAC in July 2012, the committee discussed thirty six new signals, including twenty one detected and validated by the EMA and fifteen detected and validated by Member States, up to and including its December 2012 meeting. For twelve of the discussed signals the assessment concluded that a variation to update the product information was required to ensure warnings and improved advice on safe and effective use reach patients and healthcare professionals. The assessment of twenty two signals was on-going at the time of preparation of this report (for thirteen signals a cumulative review by the MAH was requested, eight will be assessed as part of the current/next PSUR and for one signal the MAH is to answer a list of questions posed by the PRAC). One signal was closed requiring no further action. For one signal, a referral under article 31 of Directive 2001/83/EC was initiated.

Signals assessed by the PRAC are publically available in the context of the publication of the meeting agendas and minutes of the PRAC.[7]

In addition to the use of EudraVigilance for signal management, further emphasis has been put on the support of referral procedures (incl. urgent union procedures) by providing and analysing safety data for the medicinal products concerned. In 2012, these activities focused on medicinal products containing the active substances meprobamate, cilostazol and metoclopramide.

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

6. 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 approximately 650 medicines and active substances authorised through the centralised procedure. It is planned to extend this website to substances in nationally authorised medicines.

EMA also responds to requests for EudraVigilance data in line with the EudraVigilance Access Policy and EU legislation on access to documents[9], and in compliance with EU personal data protection[10]. Details on requests handled in 2012 are provided in Annex VII.

In 2012 the EMA organised six 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 two EudraVigilance and thirty seven XEVMPD hands-on training courses were delivered to stakeholders in 2012 with 825 users following XEVMPD e-learning training. Additionally, EVDAS (EudraVigilance Datawarehouse Analysis System) training was held at the Agency on four occasions,

[7] http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/document_listing/document_listing_000353.jsp&mid=WC0b01ac05805a21cf
[8] http://www.adrreports.eu/EN/index.html
[9] 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
[10] Regulation (EC) 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

training 56 experts from 17 different NCAs and the Agency also delivered one training session at the offices of a NCA.

7. Conclusion

EudraVigilance is a central pillar to support pharmacovigilance activities and the protection of public health in the EU. The data held in EudraVigilance are specifically used for the following activities:

- Continuous safety monitoring of medicines by the EMA and the Member States.
- Support of referral procedures including the urgent union procedures.
- Facilitation of decision making by the PRAC and other scientific committees of the EMA based on best evidence.
- Increasing transparency and communication on adverse reaction reports.
- Establishing a comprehensive inventory of all medicinal products authorised in the EU, core to the conduct of pharmacovigilance by the EMA and the EU regulatory network.

In the context of the new pharmacovigilance legislation, the EMA in collaboration with the NCAs has significantly progressed with the data collection and management activities. Transparency and communication has been strengthened. A new signal management process has been implemented. All these activities have assisted the newly established PRAC in assessing the various aspects of safety monitoring and the risk management of medicines. A summary of activities completed in 2012 is presented in Annex I.

Whilst functional specifications have been reviewed and international standardisation work has been completed, a further technical enhancement of EudraVigilance including new functionalities is currently deferred. The EMA will continue to work closely with stakeholders to ensure that all EudraVigilance activities set out in the new pharmacovigilance legislation can be successfully supported and that the safety of medicines and the protection of public health will be further strengthened in the EU.

Annex I - Summary of EudraVigilance related activities

Preparatory work	Status
Updated data entry tool for marketing authorisation holders [Legal basis: Regulation (EC) 726/2004, Article 57(2), second subparagraph]	Completed (published/ released March 2012)
Input to the drafting of the Commission Implementing Regulation (EU) 520/2012 to facilitate the performance of pharmacovigilance in the EU	Completed (published June 2012)
Good Pharmacovigilance Practices (GVP) • Module VI – Management and reporting of adverse reactions to medicinal products • Module IX – Signal management	Completed (published June 2012)
ISO Individual Case Safety Report (ICSR) international standard complemented by an ICH ICSR Implementation Guide [Legal basis: Commission Implementing Regulation (EU) 520/2012, Article 25 and Article 26]	Completed (published by ISO in December 2011/finalised by ICH in November 2012)
ISO Identification of Medicinal Products (IDMP) international standards [Legal basis: Commission Implementing Regulation (EU) 520/2012, Article 25 and Article 26]	Completed (published by ISO in October 2012)
Publication of list of active substances that are subject to work-sharing [Legal basis: Commission Implementing Regulation (EU) 520/212, Article 22]	Completed (first list published in October 2012)
Agreement with Member States on utilisation of standard reporting forms for patients and consumers [Legal basis: Regulation (EC) 726/2004, Article 25]	Completed (July 2012)

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 2012
Data quality review and duplicate management of adverse reaction reports in EudraVigilance [Legal basis: Regulation (EC) 726/2004, Article 24(3)]	Continued during 2012

Implementation activities	Status
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 2012
Operation of the new 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]	Started in July 2012 and continued during 2012
Access to adverse reaction data held in EudraVigilance for CAPs http://www.adrreports.eu/ [Legal basis: Regulation (EC) 726/2004, Article 24]	Completed (started in May 2012)

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) 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 2012, a total of 16,262,470 transactions were performed by the EudraVigilance gateway. Figure 1 presents the total number of transactions performed per month during 2012.

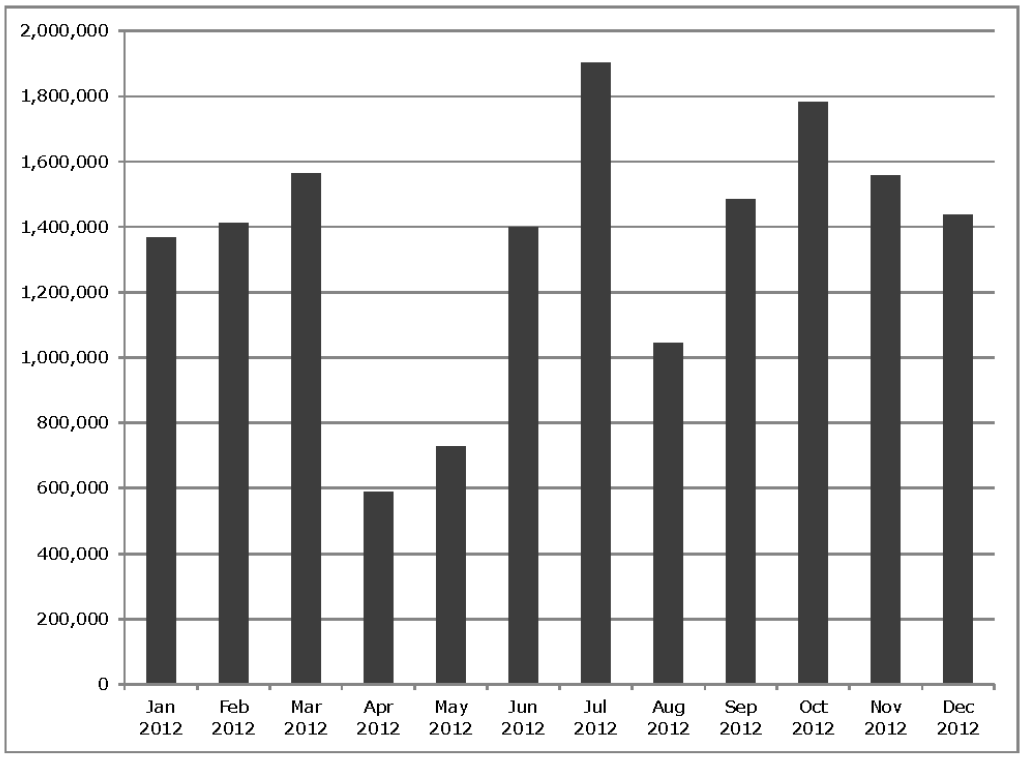


Figure 1. Total number of transactions performed per month at the level of the EudraVigilance Gateway from 1 January 2012 – 31 December 2012

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 expedited adverse reaction reports received in the post-authorisation module. During 2012, an average of 70,150 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.

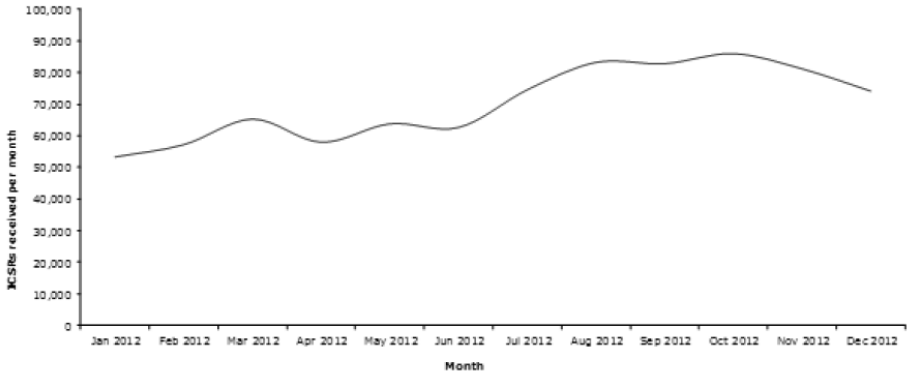


Figure 2. Number of expedited adverse reaction reports processed per month in the EudraVigilance database

Figure 3 presents the total number of expedited adverse reaction reports grouped by EEA and non-EEA for 2012.

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.

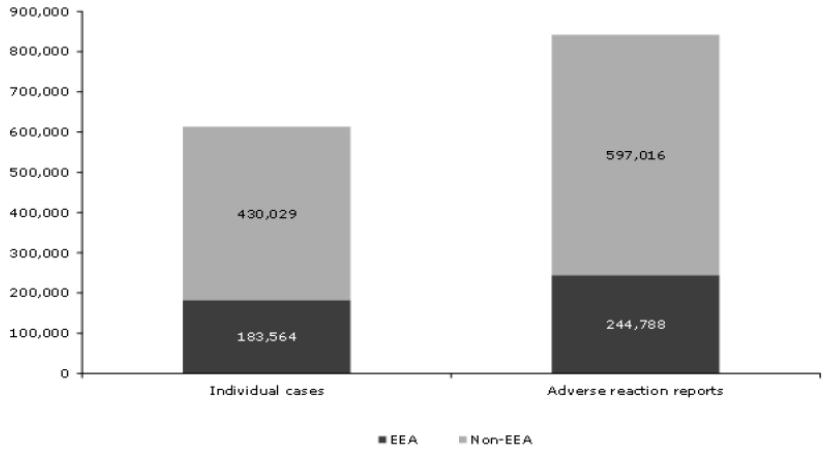


Figure 3. Number of expedited individual cases/adverse reaction reports processed in 2012 in the EudraVigilance database

By 31 December 2012, the EudraVigilance database held a total of 3,867,243 adverse reaction reports, referring to 2,224,670 individual cases (see figure 4).

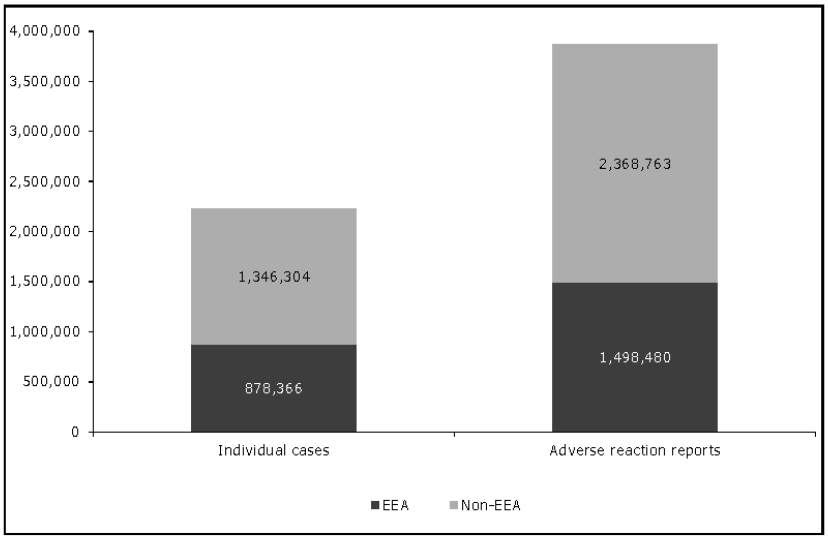


Figure 4. Total number of individual cases/adverse reaction reports held in the EudraVigilance database as of 31st December 2012

E-reporting status for MAHs and sponsors of clinical trials

- A total of 628 MAHs (at headquarter level) have sent reports to the EudraVigilance Post-authorisation Module (EVPM) in the period between 1 January 2002 and 31 December 2012.
- A total of 641 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 2012.

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.

Table 1. Number of ICSRs and unique cases transmitted by MAHs and sponsors to EVPM and EVCTM during 2012

EV Module	Transmission type	Number of transmissions
EVPM	ICSRs	757,545
	Individual Cases	536,228
	Backlog Cases	10,161
EVCTM	ICSRs	74,685
	Individual Cases	34,174
	Backlog Cases	19

Table 2. Combined 15-day reporting compliance to EVPM for all MAHs and sponsors in 2012.

Percentage of ICSRs transmitted to EVPM within 15 days:	92%

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 3 and 4 below show 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 each NCA when reporting serious cases to EVPM.

Compliance is calculated by subtracting the date the ICSR was sent to EudraVigilance (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 NCA 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 remained at 84% in 2012, the same as in 2011.

Table 3. Number of ICSRs and unique cases transmitted by NCAs to EVPM & EVCTM during 2012

EV Module	Transmission type	Number of transmissions
EVPM	ICSRs	241,009
	Individual Cases	179,313
	Backlog Cases	8,341
EVCTM	ICSRs	7,516
	Individual Cases	3,682
	Backlog Cases	50

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

During 2012, the following 9 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
Germany	Federal Institute for Drugs and Medical Devices
Germany	Paul-Ehrlich-Institut

Member State	National Competent Authority
Malta	Medicines Authority
Netherlands	College ter beoordeling van geneesmiddelen
Sweden	Medical Products Agency
United Kingdom	Medicines and Healthcare Products Regulatory Agency

EudraVigilance database and support of signal management process

Since the implementation of the new signal management process in July 2012 and based on the adverse reaction reports held in EudraVigilance, a total of 7,412 e-RMRs were generated 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 during 2012 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)	352,117
Total number of marketing authorisation holders (legal entities) established in the EU (corresponding to EudraVigilance codes)	2,885
Total number of headquarters[11] (corresponding to EudraVigilance codes)	1,255

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).

[11] The count by headquarters corresponds more closely to the Commission definition of a mother company or group of companies in accordance with the Commission Communication 98/C 229/03, (footnote 27) than the count by legal entities

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 2012.

EudraVigilance data quality activities in 2012		
Identifying and managing duplicates	**Coding of reported medicines and active substances**	**Providing feedback on data quality**
Number of duplicate couples assessed: 96,298	Number of medicinal products/active substances recoded: 82,076	Total number of organisations subject to data quality review: 216
Number of 'master' reports generated based on duplicated data: 83,393	Number of adverse reaction reports recoded: 616,001 (referring to 356,000 individual cases)	

The overall rate of duplicates reported to EudraVigilance since its launch is established 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 2001/8/3EC, 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.

A total of 3,197 suspect "same-sender" duplicate cases transmitted by MAHs and sponsors had been detected by the Agency by 31 December 2012. The number of suspected "same-sender" duplicate cases transmitted by the NCAs by 31 December 2012 since they have been in production with EudraVigilance amounts to 9,081. Information per NCA is provided in the table below.

Member State	National Competent Authority	No. "same sender" suspected duplicate cases	No. post-marketing cases transmitted to EudraVigilance
Austria	Agentur fuer Gesundheit und Ernaehrungssicherheit	451	11,985
Belgium	Federal Agency for Medicines and Health Products	247	10,083
Bulgaria	Bulgarian Drug Agency	12	714
Czech Republic	State Institute for Drug Control	91	12,604
Denmark	Danish Medicines Agency	653	15,218

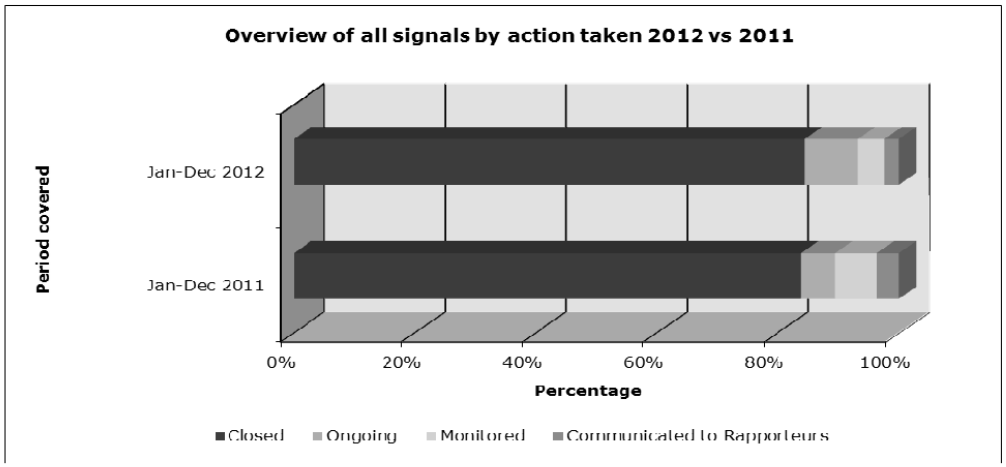
Member State	National Competent Authority	No. "same sender" suspected duplicate cases	No. post-marketing cases transmitted to EudraVigilance
Estonia	State Agency of Medicines	5	598
Finland	Finnish Medicines Agency	36	6,659
France	AFSSAPS	81	115,953
Germany	Federal Institute for Drugs and Medical Devices	1,563	150,978
Germany	Paul-Ehrlich-Institut	678	39,079
Greece	National Organisation for Medicines	535	7,561
Hungary	National Institute of Pharmacy	22	3,852
Ireland	Irish Medicines Board	309	15,417
Italy	Agenzia Italiana del Farmaco	792	91,865
Latvia	Pharmacovigilance Department of SAM	7	610
Lithuania	State Medicines Control Agency	11	1,065
Malta	Medicines Authority	2	589
Netherlands	College ter beoordeling van geneesmiddelen	1,061	70,035
Norway	Norwegian Medicines Agency	103	10,435
Poland	OFR of Med Products Med Devices and Bio Prod	497	7,685
Portugal	Infarmed	321	9,800
Romania	Agentia Nationala A Medicamentului	55	2,236
Slovakia	State Institute for Drug Control	13	1,135
Slovenia	Agency for Medicinal Products and Medical Devices	19	1,303
Spain	Agencia Esp de Medicamentos y Prod Sanitarios	183	38,073
Sweden	Medical Products Agency	64	45,660
United Kingdom	Medicines and Healthcare Products Regulatory Agency	1,270	104,958
	Total	**9,081**	**776,150**

Annex V – Signal detection

A new tool for periodic signal detection (the e-RMR) was piloted in 2011 and was further enhanced in 2012 to include information on seriousness, age stratification, route of administration, medically confirmed reports, solicited reports, literature reports, medical errors and drug abuse. The e-RMR was also cross-linked with the PROTECT ADR database (coded SmPC 4.8. information). Finally, a list of designated medical events (DMEs) was implemented and categories for priority screening were created.

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

In 2012, the total number of signals reviewed increased by approx. 40% compared to 2011. This parallels the increased number of ICSRs received in EudraVigilance, 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 DMEs in the e-RMR and additional categories which warrant priority screening (i.e. most relevant reactions terms/DMEs, fatal, paediatric reports etc.).



Overall, 96.3% of potential signals originated from EudraVigilance, with other sources accounting for: 2.3% from bibliography and 1.4% from communications received from other Regulatory Agencies worldwide (1 from the FDA, 1 from Health Canada and 30 from MHLW/PMDA).

Of the 2213 potential signals, 52 were validated and communicated to the Rapporteurs. Of note, 3 of these signals had been under monitoring by the signal validation team at the Agency in 2011, 5 were prompted by the scientific literature and 6 by information received from other regulatory authorities (8, 9 and 3, respectively in 2011).

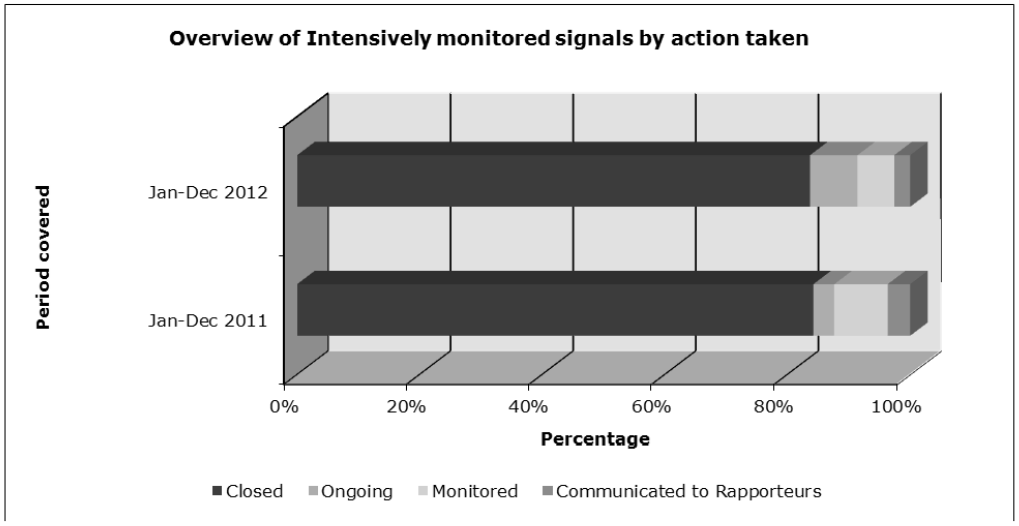
In line with SOP/H/3065, products authorised within the last two years (new active substances, biosimilars and hybrids), products where the marketing authorisation was varied within the last two years to include a new population, route of administration etc. which may impact the safety profile, or products with low patient exposure or with important safety concerns, are monitored intensively, i.e.

reaction monitoring reports are produced and screened every two weeks. All other products are monitored routinely, i.e. with a monthly frequency.

The 2012 number of potential signals for intensively monitored products was 1,205 and the number for routinely monitored products was 1,008 giving a total 2012 figure of 2,213 potential signals.

Intensively monitored products

Action taken	Number of signals Jan-Dec 2012	% of total	Number of signals Jan-Dec 2011	% of total
Closed	1,008	84%	720	84%
Ongoing	93	8%	29	3%
Monitored	73	6%	75	9%
Communicated to Rapporteurs	31	3%	31	4%
Total	1,205	100%	855	100%



In total, 1205 potential signals were evaluated during the period of this report for intensively monitored products, an increase of approx. 41% vs 2011.

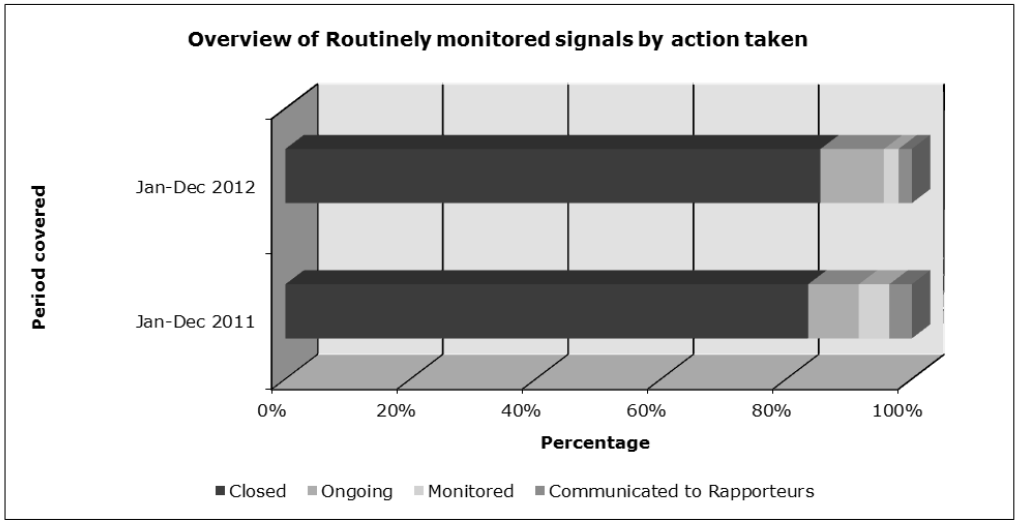
31 signals (approx. 3%) were validated and communicated to Rapporteurs. Labelling changes were recommended in 13 instances, a cumulative review was recommended as a first step in 15 instances; 1 signal was handled within an ongoing procedure (addition of information to DHPC) and in 2 cases the signal was not confirmed by the Rapporteur where a review of the topic was foreseen in the PSUR.

Additionally, 73 signals (approx. 6%) were kept under monitoring[12] (as of end of Dec 2012).

[12] If a signal is monitored, in principle new cases of that reaction sent to EudraVigilance should be reviewed

Routinely monitored products

Action taken	Number of signals Jan-Dec 2012	% of total	Number of signals Jan-Dec 2011	% of total
Closed	861	85%	610	83%
Ongoing	102	10%	59	8%
Monitored	24	2%	36	5%
Communicated to Rapporteurs	21	2%	26	4%
Total	1,008	100%	731	100%



In total, 1008 potential signals were evaluated during the period of this report for routinely monitored products, an increase of approx. 38% vs 2011. It has to be noted that 35 intensively monitored products (counted at substance level) were switched to routine monitoring in accordance with SOP/H/3065; for additional 18 products due for switching the IM status was maintained and 14 routinely monitored products were switched back to IM.

21 signals (approx. 2%) were validated and communicated to Rapporteurs. 1 signal was not confirmed by the Rapporteur; labelling changes were recommended in 8 instances and a cumulative review (as a PAM or in a PSUR) was recommended in 11 instances . Of note, 1 issue led to an Art. 31 referral (codeine).

Additionally, 24 signals (approx. 2%) were kept under monitoring.

Overview of new signals communicated to the Rapporteurs by the Agency

Until July 2012, signals were communicated to CHMP Rapporteurs via EPITT (European Pharmacovigilance Issues Tracking Tool) and direct email and the following categories were used to classify their feedback/recommendation:

- Signal not validated by the Rapporteur/no immediate action required.

- Signal to be monitored in the next appropriate regulatory procedure (e.g. in the next PSUR).
- Signal to be reviewed by the MAH in the next appropriate regulatory procedure (e.g. in the next PSUR).
- Cumulative review requested to MAH.
- Labelling change requested.
- Urgent evaluation of the signal required (possible impact on risk/benefit).

With the establishment of the PRAC in July 2012, a new signal management process was implemented. Signals are now 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, including recommendations on signals as adopted by the Committee.

An overview of validated signals is provided in the following tables, including the latest regulatory status as of 31 January 2013. When the outcome of an initial recommendation is already known, both are noted sequentially.

Intensively monitored products

Drug	Issue	Latest status or outcome
Adalimumab – Humira	Dermatomyositis[13]	Labelling change recommended
Atazanavir - Reyataz	Angioedema	Cumulative review recommended, in context of a variation to product information
Dabigatran - Pradaxa	Angioedema	Cumulative review in next PSUR: labelling change
Dabigatran - Pradaxa	Drug-drug interaction with dronedarone and amiodarone	Labelling change (concurrent use contraindicated)
Dabigatran - Pradaxa	Splenic embolism and infarction	Cumulative review in next PSUR
Denosumab - Prolia, Xgeva	Prolonged/delayed severe sometimes life-threatening risk of hypocalcaemia; convulsion, QT prolongation	Information included in DHPC in context of an ongoing variation
Docetaxel - Taxotere	Serious and fatal drug interactions involving CYP3A4	Labelling change
Docetaxel - Taxotere	Thrombotic microangiopathy	Cumulative review

[13] Signal of adalimumab-dermatomyositis was also extended to infliximab (labelling change recommended) and etanercept (cumulative review recommended as post-authorisation measure); no cases were identified in EudraVigilance with golimumab or certolizumab

Drug	Issue	Latest status or outcome
Dronedarone - Multaq	Drug-drug interaction with statins (simvastatin)	Labelling change
Dronedarone - Multaq	Pharmacokinetic drug-drug interaction with immunosuppressants (tacrolimus, sirolimus, everolimus and ciclosporin)	Labelling change
Duloxetine - Cymbalta	Interaction with aripiprazole - serotonin syndrome	Cumulative review: routine pharmacovigilance to continue
Erlotinib - Tarceva	Cerebrovascular accident	Cumulative review
Erlotinib - Tarceva	Vasculitis	Cumulative review recommended in the next PSUR: routine pharmacovigilance to continue
Exenatide - Byetta, Bydureon and liraglutide - Victoza	Gastrointestinal stenosis and obstruction	Cumulative review recommended, in context of a variation to product information
Fingolimod - Gilenya	Convulsion	Cumulative review: routine pharmacovigilance to continue
Fingolimod - Gilenya	Uveitis	Signal not confirmed - review will be performed in next PSUR
Human papillomavirus vaccine [types 6,11, 16, 18] - Gardasil	Brachial plexopathy, neuralgic amyotrophy, radiculitis brachial	Cumulative review: routine pharmacovigilance to continue
Ipilimumab - Yervoy	Anaphylactic reaction	Cumulative review recommended in current PSUR: routine pharmacovigilance to continue
Meningococcal group A, C, W-135 and Y conjugate vaccine - Menveo	Cellulitis	Labelling change
Pantoprazole - Controloc Control	Interaction with methotrexate	Labelling change
Pioglitazone - Actos	Pancytopenia	Signal not confirmed - issue to be addressed in the current PSUR
Rituximab - Mabthera	Capillary leak syndrome	Cumulative review: routine pharmacovigilance to continue
Rituximab - Mabthera	Reproductive toxicity	Labelling change recommended
Sitagliptin - Januvia	Rhabdomyolysis	Cumulative review recommended in current PSUR: addition to RMP as potential risk

Drug	Issue	Latest status or outcome
Sirolimus - Rapamune	Reactivation of hepatitis B or hepatitis C viruses	Cumulative review in next PSUR
Sunitinib - Sutent	Cholecystitis	Cumulative review recommended as post-authorisation measure: labelling change
Sunitinib - Sutent	Oesophagitis	Labelling change
Telaprevir - Incivo	Renal failure acute	Cumulative review in next PSUR
Ticagrelor - Brilique, Possia	Food interaction with grapefruit juice	Labelling change recommended
Tolvaptan - Samsca	Severe dehydration involving a possible interaction with diuretics	Cumulative review: labelling change
Vemurafenib - Zelboraf	Pancreatitis	Cumulative review recommended in the next PSUR

Routinely monitored products

Drug	Issue	Latest outcome
Agomelatine - Valdoxan	Angioedema	Cumulative review recommended, in context of a variation to product information
Aripiprazole - Abilify	Serotonin syndrome	Cumulative review recommended in current PSUR: labelling change
Busulfan - Busilvex	Endocrine late effects	Signal not confirmed
Busulfan - Busilvex	Hypogonadism	Cumulative review: labelling change
Capecitabine - Xeloda	Interstitial lung disease	Cumulative review
Capsaicin - Qutenza	Severe burns	Labelling change recommended within an ongoing PSUR procedure
Cetuximab - Erbitux	Cytokine Release Syndrome	Cumulative review recommended
Cinacalcet - Mimpara	QT prolongation and ventricular arrhythmias	Labelling change recommended: PRAC advice on variation provided - positive CHMP opinion
Clopidogrel - Plavix	Eosinophilic Pneumonia	Labelling change recommended
Codeine - n/a	Fatal or life-threatening drug toxicity in CYP2D6 ultra-rapid metabolisers	Art. 31 referral initiated (outcome expected in Apr 2013)

Drug	Issue	Latest outcome
Filgrastim - Neupogen and pegfilgrastim - Neulasta	Capillary leak syndrome, cytokine release syndrome	Cumulative review recommended as post-authorisation measure
Leflunomide - Arava	Myositis	Cumulative review recommended as post-authorisation measure
Paclitaxel - Abraxane	Anaphylactic reaction	Labelling change
Palivizumab - Synagis	RSV diagnostic test interference and Immunogenicity	Labelling change
Somatropin - NutropinAq, Omnitrope, Valtropin	Convulsions	Cumulative review recommended as post-authorisation measure
Somatropin - NutropinAq, Omnitrope, Valtropin	Hypertrophic cardiomyopathy	Cumulative review: routine pharmacovigilance to continue
Sugammadex - Bridion	Bradycardia and cardiac arrest	Cumulative review recommended: variation for labelling change was submitted by MAH
Temozolomide - Temodal	Hepatic failure	Cumulative review recommended as post-authorisation measure
Thalidomide - Thalidomide Celgene	Posterior Reversible Encephalopathy Syndrome	Cumulative review recommended in current PSUR
Varicella-zoster virus vaccine (live, attenuated) - Zostavax	Pemphigoid	Cumulative review in next PSUR
Voriconazole - Vfend	Drug level decreased, drug level below therapeutic	Cumulative review in current PSUR

Annex VI - Signal management in the EU

The new pharmacovigilance legislation contributes to the promotion and protection of public health through continuous monitoring of the benefit risk balance, optimising the safe and effective use of medicines and reducing the burden of adverse drug reactions. It includes the concept of signal detection and signal management to allow the reinforcement of the key product surveillance and public health principle of monitoring medicinal products' benefit risk profile throughout the product lifecycle.

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 analysis and prioritisation, signal assessment, recommendation for action and the exchange of information between the relevant parties.

The new legal obligations concerning data monitoring and signal management require the assessors in the NCAs to have appropriate (scientific) expertise, and the capacity to collaborate with the Agency and the other Member States. In order to develop common working methodologies and to identify potential challenges, the Pharmacovigilance Working Party (PhVWP) decided in May 2011 to start a two steps pilot phase on the signal management in the EU governed and monitored by the signal management drafting group (SMDG). Based on the experiences gained with this exercise, the needs, challenges and possible adaptations were highlighted and proposals made to succeed in the implementation of the new legislation.

The pilot phase 1 started in May 2011 and ended in January 2012. Its objectives were to:

- Evaluate whether the guidance on signal management[14] was sufficiently clear from a Member State perspective and implementable at national level.
- Collect feedback from the Member States when working in line with the guidance in order to potentially update/improve the existing process (as described in the guidance document), and to round off the roles and responsibilities of the stakeholders involved.
- Define Key Performance Indicators (KPIs) to be used at the end of Phase 2 to assess the effectiveness of the EU regulatory network in managing signals.

This pilot phase (see final progress report[15] of phase 1) allowed collecting further experience in managing signals identified by the EMA and the Member States at an EU level using EPITT, and constituted a basis to draft the GVP module IX on Signal Management[16].

The pilot phase 2[17] lasted from February 2012 to June 2012 and aimed at evaluating the performance of the system using the KPIs agreed during phase 1. During this part of the pilot, the list of signals circulated through EPITT was sent to the NCAs on a monthly basis. Some of them were also reviewed by the PhVWP.

The experience gained during the signal management pilot exercise was key to the finalisation of the GVP module IX. It also confirmed that EPITT is user friendly and should be considered by all the NCAs and the EMA as the tool to use for the sharing of information related to signals identified in the EU. The

[14] Final guideline - Roles, responsibilities and tools for exchange of information relating to signals between EU competent authorities - Dated June 2011 - EMA/731847/2010
[15] Final Progress report on a Pilot Phase 1 for the Signal Management in the EU - Jan 2012 - EMA/48215/2012
[16] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/02/WC500123209.pdf
[17] Final Progress report on a Pilot Phase 2 for the Signal Management in the EU - July 2012 - EMA/67997/2013

need to revise the Signal template of EPITT to ensure tracking of various characteristics and sources of the signals was identified.

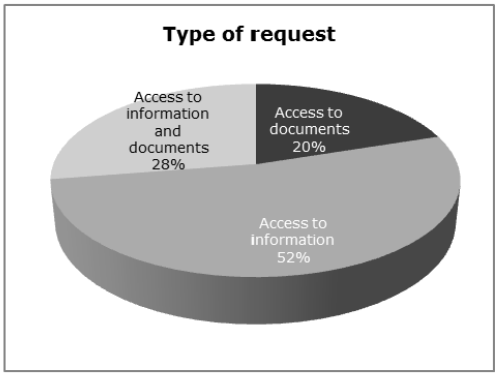
Annex VII - Requests for information and documents

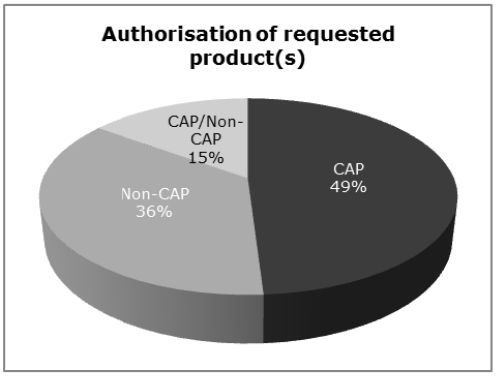
Eighty requests were answered in 2012, compared to 78 in 2011. Whereas the total number has remained constant, there was a significant increase in the complexity of requests from the EU regulatory network and from academia, often spanning across dozens of substances or classes of products and both requiring complex, time and resource intensive analysis.

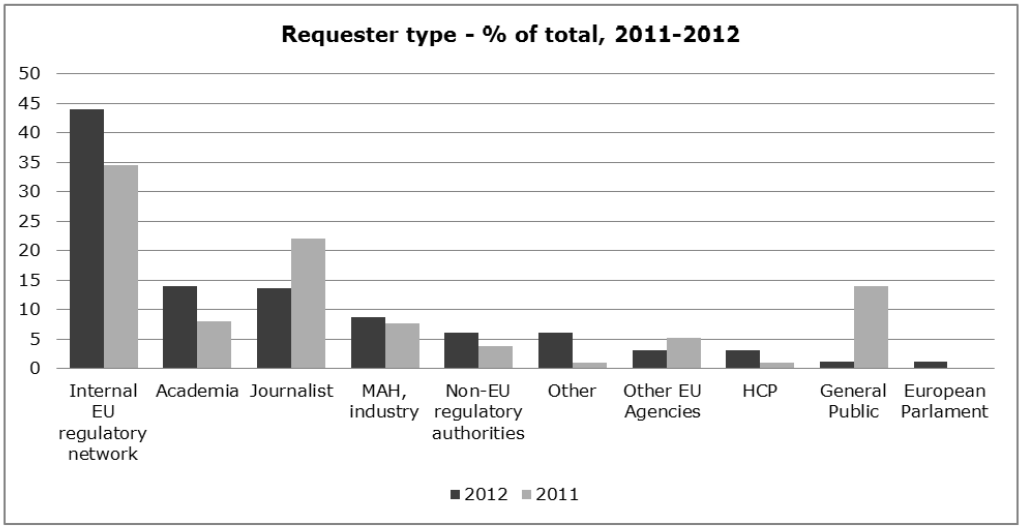
Despite the above, the timeliness of the responses was maintained. The median response time in 2012 was 18 days (range 0-100 days; 1 extreme value excluded) compared to 21 days in 2011 (range 0-98 days). 49% of the requests were answered within 14 days, 68% within 1 month and 95% within two months which also represents an improvement compared to 2011 (39%, 60% and 94%, respectively).

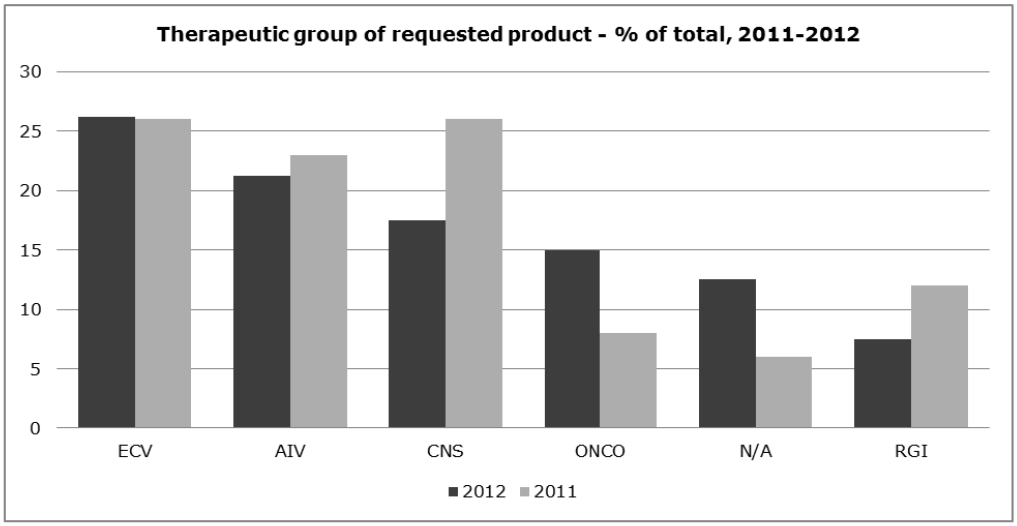
Of note, a drop was observed in requests from both journalists and the general public, which may be partly due to the proactive publication of adverse drug reaction data for CAPs at www.adrreports.eu, which started on 31 May 2012.

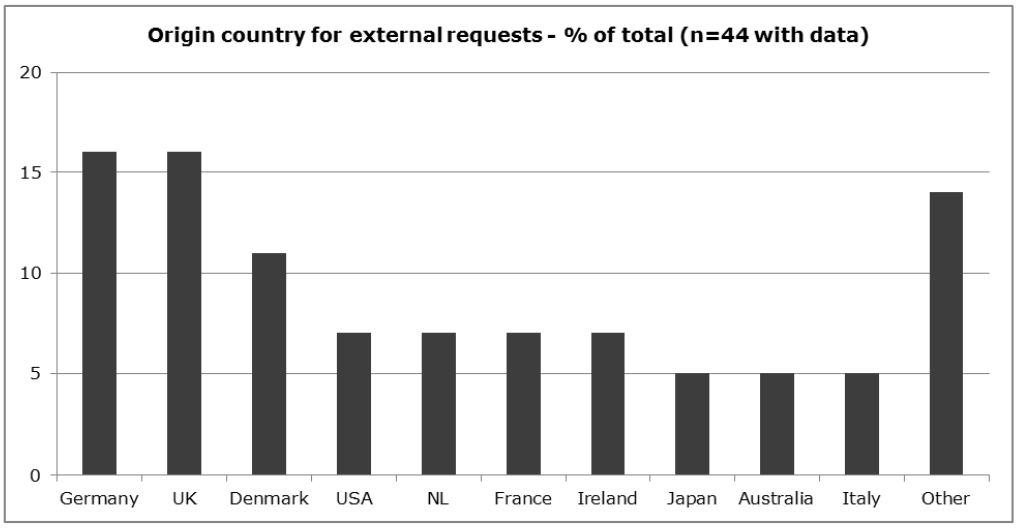
An overview of the requests is provided below by type of request, authorisation type of requested product(s), requester type, therapeutic group of requested product(s) and origin country.











Overview of requests handled in 2012

Type of requester	Drug/substance	Issue	Type of request
EU regulatory network	Acetylcysteine	All ADRs - intravenous and unknown route of administration	Access to information and documents
MAH	Agomelatine - Valdoxan	Differencies in data in a PSUR and in EudraVigilance	Access to information and documents
Information centre	Anti-malarials: atovaquone, doxycycline, mefloquine, proguanil	All ADRs	Access to documents

Type of requester	Drug/substance	Issue	Type of request
EU regulatory network	Aspirin, ibuprofen, diclofenac, naproxen, phenazon, propyphenazon, incl. combinations	EU ADRs from 2000 onwards for terms from the SMQ Gastrointestinal perforation, ulceration, haemorrhage or obstruction	Access to information and documents
EU regulatory network	Atazanavir - Reyataz	Spontaneus abortion	Access to information and documents
EU regulatory network	BCG vaccine SSI	Lymphadenitis, lymphadenitis suppurative, lymph node abscess, adenitis, BCG related lymphadenitis, axillary abscess since authorization in EU up to April 2012	Access to information and documents
Academia	Benfluorex	Heart valve disease and pulmonary arterial hypertension	Access to information
Other regulatory authorities	Bevacizumab - Avastin	All ADRs	Access to information
EU regulatory network	Bevacizumab - Avastin	ADRs due to intraocular use; PRR	Access to information and documents
EU regulatory network	Bevacizumab - Avastin	ADRs due to intraocular use; PRR	Access to information and documents
Academia	Biosimilars	All ADRs	Access to information
Journalist	Bisphosphonates	Eye inflammation - scleritis, uveitis, iritis, iridocyclitis	Access to information
Other regulatory authorities	Bortezomib - Velcade	Intrathecal administration	Access to information and documents
HCP	Bortezomib - Velcade	Intrathecal administration	Access to documents
National health service	Bortezomib - Velcade	Intrathecal administration	Access to documents
Academia	Botulinum toxin type B - Neurobloc and dibotermin alfa - Inductos	All ADRs	Access to documents
Other regulatory authorities	Burprenorphine, naloxone	Medication errors	Access to information
MAH	Calcitonin	ADRs from SOC Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Access to information and documents
EU regulatory network	Celpavan and Pandemrix	Klein-Levin syndrome (sleep disorder, somnolence, fatigue or a similar related terms)	Access to information and documents

Type of requester	Drug/substance	Issue	Type of request
EU regulatory network	Clopidogrel - Plavix and ticlopidine - Ticlid	Angioedema; Thrombocytopenia; Hypersensitivity and Drug Hypersensitivity - where both drugs have been taken by a patient	Access to information and documents
MAH	Co-trimoxazole - Septrin	ADRs during 1997-2007	Access to documents
EU regulatory network	Cytarabine - Depocyte	Infection (especially meningitis) - reports from the recent three years	Access to information
Journalist	Dabigatran - Pradaxa	Bleeding resulting in death worldwide and in the EU; myocardial infarction and acute coronary syndrome both fatal and non-fatal worldwide and in the EU; case reports of death according to indication, age group (older than 75 and the rest), gender and body weight	Access to information
EU regulatory network	Dabigatran - Pradaxa and clopidogrel - Plavix	Name confusion between Pradaxa-Plavix	Access to documents
Journalist	Dabigatran and rivaroxaban	Bleeding resulting in death with either drug, major/severe bleeding (incl. fatal) with both drugs	Access to information
HCP	Denosumab – Prolia, Xgeva	ADRs for specified SOCs; ONJ; atypical femoral shaft fractures	Access to information and documents
Other regulatory authorities	Echinacea	All ADRs	Access to information
Journalist	Eribulin	Medication errors related to expression of the strength (active moiety and salt)	Access to information
EU regulatory network	Fenofibrate	Risk of rhabdomylyosis associated with fenofibrate when administered in children	Access to information
EU regulatory network	Fentanyl	Accidental exposure in children	Access to information and documents
EU regulatory network	Fentanyl	Overdose, accidental overdose, death, accidental death, sudden death, multiple drug overdose – incl. route of administration	Access to information
EU regulatory network	Fibrin sealents - Tisseel, Tissucol, Quixil, Beriplast, Artiss	Air embolism	Access to information
Academia	Filgrastim - Ratiograstim	All ADRs	Access to documents
Consultancy	Fingolimod - Gilenya	Reports of sudden or unexplained death	Access to documents

Type of requester	Drug/substance	Issue	Type of request
EU regulatory network	Gelatin polysuccinate with electrolytes - Gelaspan	Quality Defect (class II)	Access to information
General public	GnRH agonists - buserelin, goserelin, histrelin, leuprorelin, nafarelin and triptorelin	ADRs from specified SOCs	Access to information and documents
EU regulatory network	Heparins	Pattern of deaths or (serious) adverse reactions linked to heparins; review of EudraVigilance data	Access to information
EU regulatory network	Hepatitis A Vaccine - Havrix	Juvenile arthritis and arthritis	Access to information
EU regulatory network	Human papilloma virus vaccine - Gardasil	Asthma, asthma deteriorated, bronchospasm	Access to information
European Parliament	Human papillomavirus vaccine - Cervarix	Chronic fatigue syndrome	Access to documents
EU regulatory network	Infanrix IPV, Infanrix Hexa and Tetravac	Oedema peripheral, extensive swelling of vaccinated limb	Access to information and documents
EU regulatory network	Infliximab - Remicade, adalimumab - Humira, etanercept - Enbrel	Hepatosplenic T-cell lymphoma (HSTCL)	Access to information and documents
Other EU Agencies	Influenza vaccine (H1N1)v (split virion, inactivated, adjuvanted) - Pandemrix	Narcolepsy cases per country	Access to information
EU regulatory network	Influenza vaccines	Reaction monitoring report	Access to information and documents
National agency for patient rights	Iodixanol - Visipaque	Guilain-Barré syndrome and/or chronic inflammatory demyelinating polyradiculoneuropathy	Access to information
MAH	Ipilimumab - Yervoy	Numbers of reports of pulmonary embolism, polymyositis and myositis for a PSUR period	Access to documents
Journalist	Isotretinoin	Documents released to a previous requester	Access to documents
Journalist	Ivabradine	QT-prolongation, ventricular tachycardia, TdP	Access to information
EU regulatory network	Macrolides	Hearing disorders and rhabdomyolysis	Access to information
EU regulatory network	Measles, mumps and rubella vaccine (live) - M-M-RVAXPRO	Reports with a particular batch	Access to information

Type of requester	Drug/substance	Issue	Type of request
EU regulatory network	Meprobamate	Review of the data available in the EudraVigilance database	Access to information and documents
Academia	Mesalazine	Hepatitis/liver dysfunction/elevated liver enzymes as a result of treatment with mesalazine	Access to documents
Journalist	Misoprostol	All ADRs; ADRs in use for abortions, missed abortions and labour induction	Access to information
Academia	Multiple drugs - antipsychotics, anti-infectives and H1-antihistamines (total cca 40)	Arrhythmic potential of drugs - QTc prolongation, Torsade de Pointes (TdP), ventricular fibrillation and sudden death	Access to documents
Academia	Multiple drugs - biosimilars	ADRs due to switching between innovator and similar biological products	Access to documents
Academia	N/A	Consumer reports submitted to the Danish medicines agency between 2007 - 2011	Access to information and documents
Academia	N/A	Number of the following reacitons per year – inflammatory bowel disease	Access to information
EU regulatory network	N/A	Top ten active substances for which medication errors have been reported as serious ADRs (paediatric)	Access to information
Journalist	Natalizumab - Tysabri	Number of reports of lymphoma and leukemia including Non-Hodgkin's lymphoma or B-cell-lymphoma	Access to information
EU regulatory network	Olanzapine - Zyprexa	Post-Injection Syndrome	Access to information
MAH	Palivizumab - Synagis	False negative tests result	Access to documents
Consultancy	Phentermine	Reaction monitoring report	Access to information
EU regulatory network	Phentermine/ topiramate	Safety data for combination of substances	Access to information
EU regulatory network	Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) -Prevenar 13 and hexavalent vaccine - Infanrix Hexa	Fatal cases	Access to information and documents
EU regulatory network	Ranolazine - Ranexa	Medication errors	Access to information
MAH	Rivaroxaban - Xarelto	Serious bleeding events incl. fatal	Access to information

Type of requester	Drug/substance	Issue	Type of request
Academia	Rosuvastatin - Crestor	Neuropsychiatric ADRs	Access to information
EU regulatory network	Rotavirus vaccine, live, oral - Rotateq and pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) -Prevenar 13	Sudden death, sudden infant death syndrome	Access to information
Academia	Several drugs	Number of ADRs per targeted SOC	Access to information
EU regulatory network	Sitagliptin - Januvia	Rhabdomyolysis	Access to information
Journalist	SSRIs	All ADRs and ADRs for past 5 years	Access to information
Journalist	SSRIs	Question on how EMA calculates numbers of cases of death	Access to information
EU regulatory network	Telaprevir - Incivo	Death and sudden death	Access to information
MAH	Temoporfin – Foscan	All ADRs (including SUSARs)	Access to documents
EU regulatory network	Terbinafine	Haematopoietic cytopenias (paediatric request)	Access to information
EU regulatory network	Terbutaline	Maternal and offspring safety in connection with use of short acting beta agonists (SABA) in tocolysis	Access to information and documents
Other regulatory authorities	Thalidomide - Thalidomide Celgene and lenalidomide - Revlimid	Reports of pregnancy	Access to information and documents
EU regulatory network	Tissue sealents - Tisseel, Tissucol, Quixil, Beriplast, Artiss	Air embolism	Access to information
Journalist	Varenicline – Champix	Completed suicide	Access to information
Other EU Agencies	Zopiclone	Reports of misuse	Access to information