12 June 2013
EMA/733372/2012

2011 EudraVigilance-Human Annual Report

1 January 2011 – 31 January 2011

Key messages

- This report presents a summary of routine and ad-hoc activities covering the period 1 January to 31 December 2011. The report consists of 2 main parts. The 1st part describes the signal detection and management activities whilst the 2nd part provides an update on the collection and management of data in EudraVigilance-Human.
- In terms of signal detection and management activities:
  - A new tool for signal detection was developed and implemented in 2011 in order to increase efficiency and to further enhance the process through provision of additional functionalities.
  - A total of 1,586 potential signals related to Centrally Authorised Products (CAPs) were evaluated by the EMA.
  - Of the 1,586 potential signals 57 were validated and communicated to the respective rapporteurs (compared to 39 in 2010). Of these 57, a number of 31 were raised on products belonging to the intensively monitored group, and 26 belonging to the routinely monitored group.
  - A 150% increase was observed in requests for data from EudraVigilance in 2011 compared to 2010. 54% of the requests for analysis of EudraVigilance data related to CAPs. Of all requests 39% were replied to within 14 calendar days, 60% within 31 days and 94% within 2 months.
- In terms of the collection and management of EudraVigilance data:
  - Progress was made during 2011 as regards the use of EudraVigilance, illustrated by a significant increase of Member States working with the EudraVigilance Data Analysis System (EVDAS): the amount of queries run by Member States' users each month increased by 14% compared with 2010.
  - Compliance with the legal timeframes for the transmission of Individual Case Safety Reports (ICSRs) has improved overall by 5% compared to 2010 and NCAs, overall, now have a 15-day reporting compliance of 84%.
  - The EMA has been working closely with Sponsors, Marketing Authorisation Holders (MAHs) and Member States to improve the quality of the data submitted to EudraVigilance. Major steps of

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this initiative include the entry into force of the new EudraVigilance Business Rules, the data cleaning activities performed on the EudraVigilance data by the EMA's service provider (Kinapse), and the introduction of a process of cooperation with the pharmacovigilance inspectors of the Member States to provide them with the results of the EMA's analyses of the quality of data in EudraVigilance submitted by MAHs.

- Significant milestones were reached during 2011 in the context of international harmonisation and standardisation activities. The Final ISO Individual Case Safety Report (ICSR) standard was published in December 2011 and ISO Identification of Medicinal Products (IDMP) documents were agreed for Final Draft International Standard (FDIS) ballot.

Table of contents

Introduction

This report consists of two main parts. The first part describes the signal detection and management activities and the second part provides an update on the status of data collection and management in EudraVigilance-Human.

This report provides a summary of routine and ad-hoc activities covering the period 1 January to 31 December 2011, and focuses on activities related to Centrally Authorised Products (CAPs). A mid-year report covering the period 1 January to 30 June 2011 was presented to the Management Board in December 2011.

The report on signal detection, signal management and data analysis activities is prepared by the staff of the Signal Detection and Data Analysis Section (P-PV-SDA) of the Pharmacovigilance and Risk Management Sector within the Patient Health Protection Unit of the European Medicines Agency. The status of data collection and management in EudraVigilance-Human is prepared by the Section of Data Collection and Management (P-PV-CDM), also within the Pharmacovigilance and Risk Management Sector of the Patient Health Protection Unit.

1. Signal detection

A new tool for signal detection was developed and implemented in 2011 in order to increase efficiency and to further enhance the process through provision of additional functionalities. A total of 1586 potential signals were evaluated between January – December 2011. The evaluation, supported by the new tool for signal detection, focused on a lower number of potential signals compared to 2010 (approx. 22.8% less compared to 2010). These are presented below according to the frequency of monitoring for the respective medicinal products. Of the 1586 potential signals, 57 signals[1] were validated and communicated to the rapporteurs, an increase of approx. 46% (39 signals in 2010). Details of these signals are also provided by action taken in respective parts of this section – for signals communicated to rapporteurs, frequency of monitoring is indicated as of the date when the signal was validated. Of note, 8 out of these 57 signals had been under monitoring by the EMA Signal validation team in 2010, 9 were prompted by scientific literature and 3 by information received from other Regulatory Authorities.

Overall, approx. 92.6% of potential signals presented above originated from EudraVigilance, with other sources accounting for: 3.7% from bibliography and 3.7% from communications received from other Regulatory Agencies worldwide (18 from the FDA, 25 from MHLW/PMDA, 1 from Health Canada, 2 from Swissmedic and 13 from WHO).

Overview	Jan – Dec 2011	Jan – Dec 2010
Weekly monitoring[2]	0	21
Intensive monitoring	855	903
Routine monitoring	731	1130
Total	**1586**	**2054**

[1] A signal is "information that arises from one or multiple sources (including observation and experiments), which suggests a new potentially causal association or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action" ((*source: Report of the CIOMS working group VIII, Practical Aspects of Signal Detection in Pharmacovigilance, Geneva 2010*)).

[2] Weekly monitoring is only undertaken in special circumstances. In 2009 and 2010 this included pandemic influenza vaccines and antivirals. For further details, please refer to SOP/H/3317 – Specific signal detection for situations including a pandemic.

As described in the relevant SOPs (SOP/H/3065 and SOP/H/3317), products are classified according to the periodicity of their safety monitoring, as follows:

Intensively monitored (IM) products - line listings of all reported serious adverse drug reactions (ADRs) are produced and reviewed at least every 2 weeks by the EMA Signal Validation Team (SVT). The criteria for assigning a product to intensive monitoring are the following:

- CAPs with a new active substance, biosimilars and hybrids, authorised for less than two years.
- CAPs containing active substances of well-established medicinal products, which have been authorised within the last two years to a new patient population or with a new route of administration.
- CAPs for which the marketing authorisation has been varied or extended within the last two years, leading to changes in the strength, pharmaceutical form or route of administration which may modify the original patient population or the safety profile of the medicinal product.
- Generic and informed consent CAPs for which the originator is under intensive monitoring.
- Any CAP for which the safety information is limited due to low patient exposure, including products authorised under conditional approval or under exceptional circumstances (e.g. Orphan medicinal products).
- Any CAPs with a potential safety concern, i.e. a potential risk that could impact on the risk-benefit balance of the product or have implications for public health, therefore justifying a more frequent monitoring. This may include risks associated with an important misuse, abuse or off-label use.
- A signal arising from the signal detection activities does not necessarily mean that the product has to be included in the list of intensively monitored products.

Routinely monitored (RM) products – these are made up of CAPs not included in the list of intensively monitored products. Line listings of all reported serious ADRs are produced and reviewed monthly.

Following review of Reaction Monitoring Reports (RMRs) and Individual Case Safety Reports (ICSRs), signals are discussed by the EMA SVT resulting in one of the following actions:

- Close (further investigation is not required).
- Ongoing (evaluations are still ongoing).
- Monitor (not enough evidence to validate: every new case needs to be reviewed).
- If a signal is validated by the EMA SVT, communicate to rapporteurs via EPITT (European Pharmacovigilance Issues Tracking Tool) and direct email.

1.1. Intensively monitored products

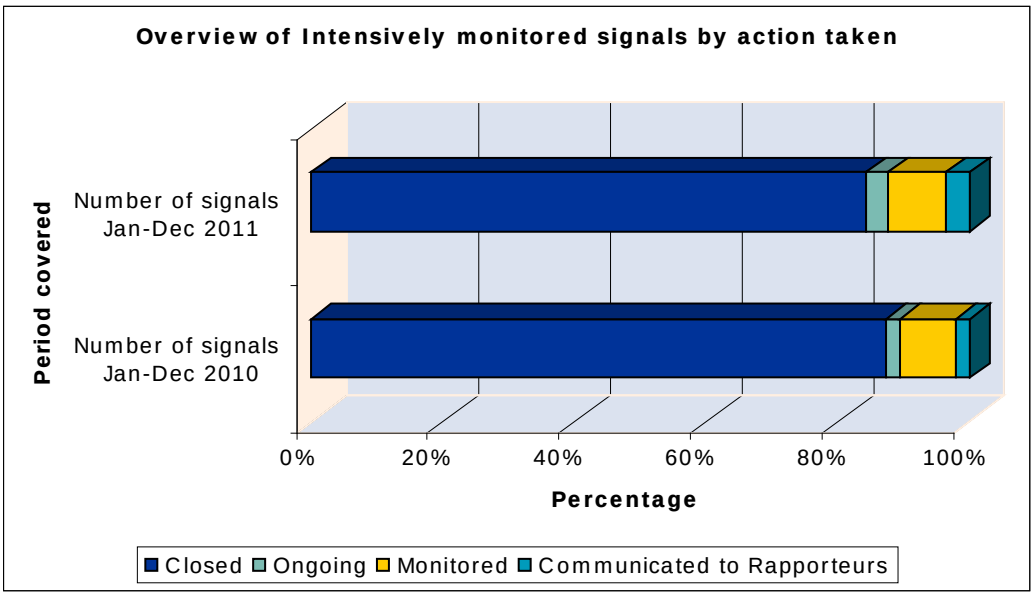
Action taken	Number of signals Jan-Dec 2011	% of total	Number of signals Jan-Dec 2010	% of total
Closed	720	84.2%	787	87.2%
Ongoing	29	3.4%	21	2.3%
Monitored	75	8.8%	76	8.4%
Communicated to rapporteurs	31	3.6%	19	2.1%
Total	**855**	*100.0%*	**903**	*100.0%*

The evaluation, supported by the new tool for signal detection, focused on a lower number of potential signals compared to 2010 (a decrease of approx. 5.3%). In total, 855 potential signals were evaluated during the period of this report for intensively monitored products.

31 signals (approx. 3.6%) were validated and communicated to rapporteurs. Labelling changes were requested in 4 instances, a cumulative review was requested in 6 instances, two signals were escalated to the PhVWP and in 18 cases the signal was recommended for monitoring/review in the next regulatory procedure (including one in the context of an ongoing Art. 20 referral). One signal was not validated by the rapporteur during this analysis period.

Of note, 23 weekly RMRs for pandemic influenza vaccines were produced by P-PV-DCM, distributed to network stakeholders and reviewed internally by P-PV-SDA (RMR distribution ceased on 15 June 2011); this led to the identification and assessment of 7 potential signals: 3 for Arepanrix, 1 for Focetria and 3 for Pandemrix.

Additionally, 75 signals (approx. 8.8%) were kept under monitoring (as of end of Dec 2011).



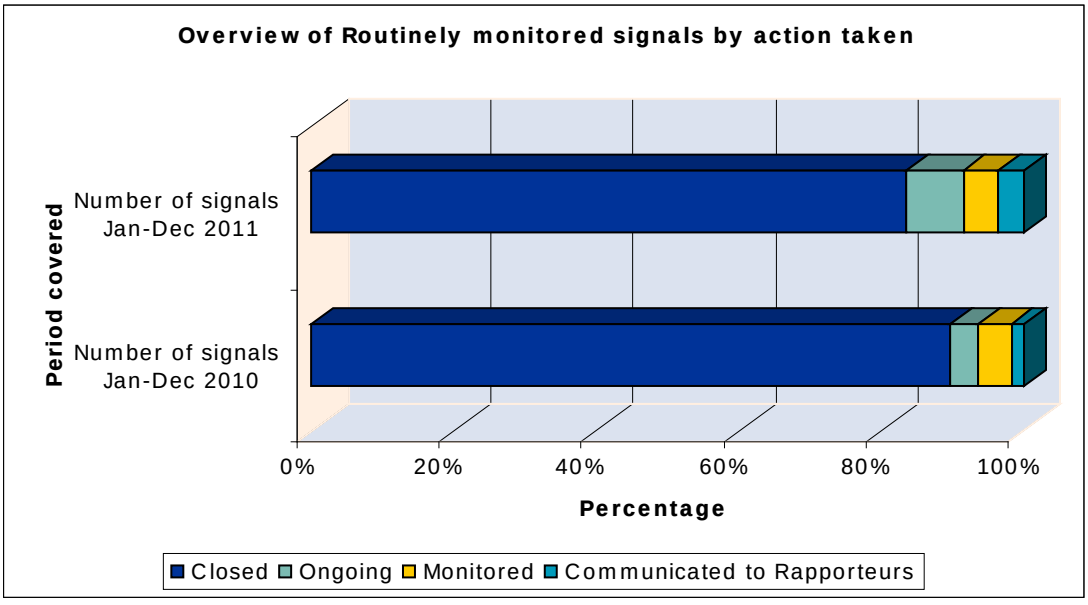
1.2. Routinely monitored products

Action taken	Number of signals Jan-Dec 2011	% of total	Number of signals Jan-Dec 2010	% of total
Closed	610	83.4%	1013	89.6%
Ongoing	59	8.1%	45	4.0%
Monitored	36	4.9%	52	4.6%
Communicated to rapporteurs	26	3.6%	20	1.8%
Total	**731**	*100.0%*	**1130**	*100.0%*

The evaluation, supported by the new tool for signal detection, focused on a lower number of potential signals compared to 2010 (a decrease of approx. 35%). In total, 731 potential signals were evaluated during the period of this report for routinely monitored products. It has to be noted that 88 intensively monitored products (counted at brandname level) were switched to routine monitoring in accordance with the SOPs mentioned in section 1. of this report.

26 signals (approx. 3.6%) were validated and communicated to rapporteurs. Three signals were not validated by the rapporteur; labelling changes were requested in 6 instances, a cumulative review was requested in 8 instances, 1 signal was escalated to the PhVWP and 8 signals were recommended for review/monitoring in the next regulatory procedure.

Additionally, 36 signals (approx. 5%) were kept under monitoring.



1.3. Overview of new signals communicated to rapporteurs

Signal detection processes at the EMA use complementary statistical and established pharmacovigilance methods. The Retrospective Validation study (Validation of Statistical Signal detection for CAPs in EudraVigilance, Drug Saf 2010; 33:(6):475-487; presented to HMA June 2009) concluded that:

- The use of statistical tools substantially enhances the signal detection process.
- The use of the Proportional Reporting Ratio (PRR) method in EudraVigilance can provide significantly earlier detection of drug safety issues in about 54% of the cases where a clinically important ADR was found (compared to routine pharmacovigilance).
- Established pharmacovigilance methods and PRR analysis are complementary.

In the following tables a summary of the signals communicated to the rapporteurs during the period covered by this report are presented. Please note:

- The feedback received from the rapporteur and the subsequent regulatory outcomes have been classified as indicated below:
  - Signal assessed by the rapporteur:
    - 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);
  - No response received from the rapporteur.

1.3.1. Intensively monitored products

Drug	Issue	Regulatory action/outcome
Abiraterone - Zytiga	Anaemia	Signal to be reviewed by the MAH in the next appropriate regulatory procedure (PSUR)
Bevacizumab - Avastin	Tumour lysis syndrome	Signal to be reviewed by the MAH in the next appropriate regulatory procedure (PSUR)
Dabigatran - Pradaxa	Serious and fatal haemorrhagic accidents (incl. neurological) in acutely injured patients	Signal to be reviewed by the MAH in the next appropriate regulatory procedure (ongoing FUM)
Dronedarone - Multaq	Acute hepatic failure and temporal persistence of the signal of liver failure in EudraVigilance	Signal to be reviewed by the MAH in the next appropriate regulatory procedure (ongoing Article 20 referral procedure)
Dronedarone - Multaq	Aplastic anaemia / bone marrow failure	Signal to be reviewed by the MAH in the next appropriate regulatory procedure (PSUR)
Dronedarone - Multaq	Serious and severe allergic reactions	Labelling change requested
Dronedarone - Multaq	Serious and severe allergic reactions	Signal to be reviewed by the MAH in the next appropriate regulatory procedure (PSUR)
Human normal immunoglobulin-Flebogammadif, Kiovig, Privigen, Hizentra	Necrotizing enterocolitis neonatal	Signal not validated by the rapporteur
Human papilloma virus vaccine - Gardasil	Vasculitis (SMQ Narrow)	Signal to be reviewed by the MAH (cumulative review) in the next appropriate regulatory procedure (PSUR)
Liraglutide - Victoza	Angioedema	Signal to be reviewed by the MAH in the next appropriate regulatory procedure (PSUR)
Mercaptopurine - Novapurine	Hepatosplenic T-Cell Lymphoma	Signal to be reviewed by the MAH in the next appropriate regulatory procedure (PSUR)
Natalizumab - Tysabri	Autoimmune hepatitis	Signal to be reviewed in the next appropriate regulatory procedure
Pandemic influenza vaccine (H1N1) - Pandemrix	Idiopathic thrombocytopenic purpura	Signal to be reviewed by the MAH in the next appropriate regulatory procedure (PSUR)
Pantoprazole - Pantoloc Control and associated names (and other proton pump inhibitors)	Potential increased risk of cardiovascular events in patients with first time MI treated with aspirin	Cumulative review requested to MAH

Drug	Issue	Regulatory action/outcome
Pantoprazole - Pantozol Control	Pneumonia	Signal to be assessed by the PhVWP
Pioglitazone - Actos (and other brandnames)	Interstitial pneumonia	Signal to be reviewed by the MAH in the next appropriate regulatory procedure (PSUR)
Pirfenidone - Esbriet	Agranulocytosis/febrile neutropenia	Cumulative review requested to MAH
Prasugrel - Efient	Serious angioedema with a possible cross-reactivity with clopidogrel	Labelling change requested
Ranibizumab - Lucentis	Hypertensive crisis	Cumulative review requested to MAH
Rituximab - Mabthera	Intestinal obstruction	Signal to be reviewed by the MAH in the next appropriate regulatory procedure (PSUR)
Rituximab - Mabthera	Skin melanoma	Signal to be reviewed by the MAH in the next appropriate regulatory procedure (PSUR)
Rituximab - Mabthera	Transverse myelitis	Cumulative review requested to MAH
Romiplostim - Nplate	Hypersensitivity	Signal to be reviewed by the MAH (cumulative review) in the next PSUR
Sitagliptin - Januvia, Xelevia, Tesavel, Ristaben	Interstitial pneumonia	Signal to be reviewed by the MAH in the next appropriate regulatory procedure (renewal)
Sorafenib - Nexavar	Leukocytoclastic vasculitis	Signal to be reviewed by the MAH in the next appropriate regulatory procedure (PSUR)
Sumatripan - Sumatripan Perrigo	Ventricular fibrillation/TdP/ QT prolongation	Signal to be addressed by the PhVWP
Sunitinib - Sutent	Erythema multiforme/ Stevens-Johnson syndrome/toxic epidermal necrolysis	Signal to be reviewed by the MAH in the next appropriate regulatory procedure (PSUR)
Tolvaptan - Samsca	Drug-drug interaction with sodium chloride leading to severe neurological complications secondary to hypernatraemia	Labelling change requested
Tolvaptan - Samsca	Serious, sometimes fatal cases of rapid correction of hyponatraemia	Cumulative review requested to MAH
Varenicline - Champix	Deafness/sudden hearing loss	Cumulative review requested to MAH
Vinflunine - Javlor	Reversible Posterior Leukoencephalopathy Syndrome (RPLS)	Labelling change requested

1.3.2. Routinely monitored products

Drug	Issue	Regulatory action/outcome
Adalimumab - Humira, Trudexa	Autoimmune hepatitis	Cumulative review requested to MAH
Arsenic trioxide - Trisenox	Torsade de pointes	Signal not validated by the rapporteur
Biphosphonates incl. zoledronate, pamidronate, ibandronate and alendronate - Zometa/Aclasta, Aredia, Bondronat, Fosamax	Heart valve disorders	Cumulative review requested to MAH
Busulfan - Busilvex	Premature menopause	Cumulative review requested to MAH
Capecitabine - Xeloda	Cutaneous lupus erythematosus	Signal to be reviewed by the MAH in the next appropriate regulatory procedure (PSUR)
Clopidogrel - Plavix, Iscover	Cross-reactivity between clopidogrel and ticlopidine among patients with allergic or haematologic reactions to one of these products	Signal to be assessed by the PhVWP
Erlotinib - Tarceva	Uveitis	Labelling change requested
Etanercept - Enbrel	Glomerulonephritis rapidly progressive	Cumulative review requested to MAH
Hydroxycarbamide - Siklos	Dermatomyositis	Signal to be reviewed by the MAH in the next appropriate regulatory procedure (PSUR)
Hydroxycarbamide - Siklos	Interstitial lung disease	Signal to be reviewed by the MAH in the next appropriate regulatory procedure (PSUR)
Hydroxycarbamide - Siklos	Palmar-plantar erythrodysaesthesia syndrome	Signal to be reviewed by the MAH in the next appropriate regulatory procedure (PSUR)
Ibandronic acid - Bonviva and associated names	Anaphylactic shock	Labelling change requested
Ibandronic acid - Bonviva and associated names	Syncope	Signal not validated by the rapporteur

Drug	Issue	Regulatory action/outcome
Interferon beta-1A - Avonex, Rebif	Autoimmune thyroiditis	Signal to be reviewed in the next appropriate regulatory procedure (PSUR)
Lenalidomide - Revlimid	P-Glycoprotein (P-gp) substrate & temsirolimus (TORISEL) interaction	Labelling change requested
Olanzapine - Zyprexa and associated names	Hyponatraemia/SIADH	Cumulative review requested to MAH
Orlistat - Xenical, alli	Acute kidney injury	Cumulative review requested to MAH
Orlistat - Xenical, alli	Hypokalaemia	Cumulative review requested to MAH
Orlistat - Xenical, alli	Syncope	Signal not validated by the rapporteur
Paclitaxel - Paxene, Abraxane	Macular oedema	Signal to be reviewed by the MAH in the next appropriate regulatory procedure (PSUR)
Ranolazine - Ranexa	Drug interaction with simvastatin leading to rhabdomyolysis	Labelling change requested
Ranolazine - Ranexa	Tacrolimus interaction	Signal to be reviewed by the MAH in the next appropriate regulatory procedure (FUM)
Rituximab - Mabthera	Late neutropenia in RA	Labelling change requested
Sevelamer - Renagel, Renvela	Dysphagia/choking/ aspiration	Signal to be reviewed by the MAH in the next appropriate regulatory procedure (PSUR)
Sildenafil - Viagra	Penile haemorrhage/ haematospermia	Labelling change requested
Voriconazole - Vfend	Periostitis	Cumulative review requested to MAH

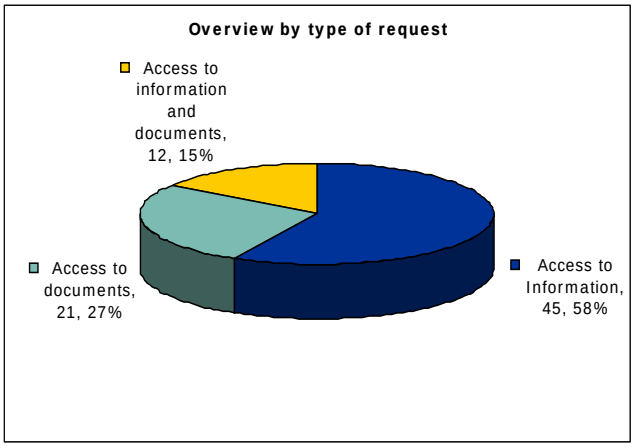
2. Data analysis

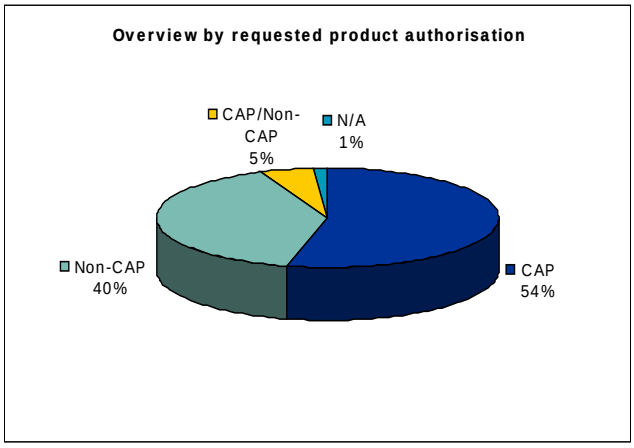
EMA responds to requests for EudraVigilance data in line with the EudraVigilance Access Policy and the EU legislation on access to documents and on personal data protection.

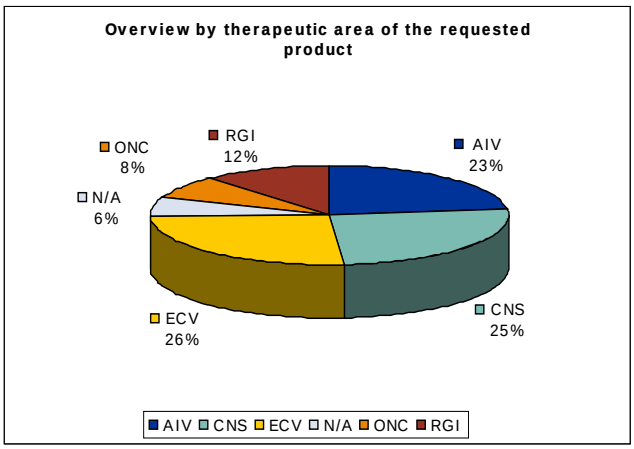
Seventy-eight requests were answered during 2011, representing approx. a 150% increase compared to 2010 (n=31). These requests were for EudraVigilance data and/or related data analysis. An overview is provided below, including a brief summary of the outcomes.

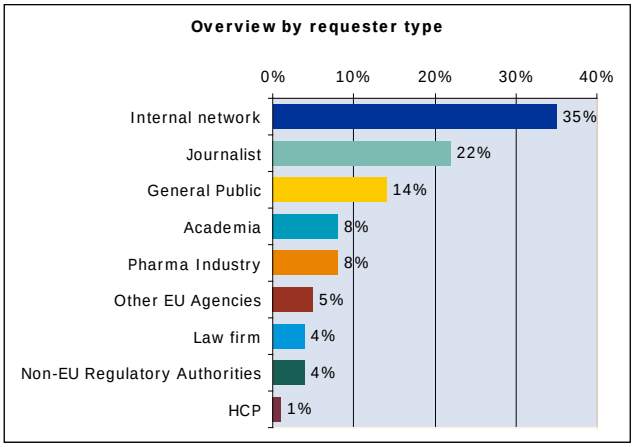
Responding to request for EudraVigilance data requires in many instances the building of specialised queries. Each query is internally validated and redacted, when needed, according to the EudraVigilance Access Policy.

Overviews by type of request, requested product authorisation method, therapeutic group and type of requester are provided below. Response times by the P-PV-SDA Section are also recorded below. 39% queries were replied to within 14 calendar days, 60% within 31 days and 94% within 2 months.









Requester	DRUG / substance	Issue / risk	Type of request
Health care professionals	Adalimumab - Humira and other TNF inhibitors	Eosinophilia	Access to information
Journalist	Agomelatine - Thymanax, Valdoxan	Liver related ADRs: increased transaminases, bilirubinaemia, icterus, liver injury and hepatitis.	Access to information
Non-EU Authorities	Antipsychotics - CAPs only	Extrapyramidal symptoms (EPS) or withdrawal symptoms in newborns whose mothers were treated with antipsychotic drugs	Access to information
EU Regulatory Network	Antisense oligonucleotides	Renal adverse reactions	Access to information
EU Regulatory Network	Apixaban, rivaroxaban	Guillain-Barre syndrome	Access to information and documents
Journalist	Benfluorex	All ADRs - date of report, sender details, summary of report.	Access to documents
EU Regulatory Network	Bortezomib - Velcade	Intrathecal administration	Access to information and documents
Pharmaceutical industry	Buflomedil	ADRs from France	Access to documents
EU Regulatory Network	Cladribine - Movectro	Case of fulminant hepatitis identified during MAA - outcome	Access to documents
Academia	Cytostatics	Cardiotoxic effect (during 2004-2011) - Long QT syndrome, ECG QT prolongation	Access to documents
Journalist	Dabigatran - Pradaxa	Fatal cases, serious haemorrhages with fatal outcome, myocardial infarction	Access to information
Healthcare professionals	Dialysis products	Number of reported cases of sterile peritonitis	Access to information
EU Regulatory Network	Domperidone	Arrhythmias	Access to Information
Academia	Domperidone	Cardiac adverse reactions	Access to information and documents
EU Regulatory Network	Domperidone	Death (Belgian data)	Access to information
Academia	Dronedarone - Multaq	Acute kidney failure	Access to documents
Journalist	Dronedarone - Multaq	Liver injuries	Access to information
EU Regulatory Network	EGFR inhibitors (Tarceva, Erbitux, Iressa, Vectibix)	Keratitis and related terms	Access to information and documents
Pharmaceutical industry	Eptacog alfa - Novoseven	Intracardiac thrombus	Access to documents
Public (incl. consumers and lawyers)	Escitalopram	Pregnancy-related risks	Access to information
Journalist	Exenatide - Byetta, Liraglutide - Victoza	Number of reports of renal insufficiency and acute kidney failure; number of reports also mentioning nausea, vomiting, diarrhoea or dehydration.	Access to Information
EU Regulatory Network	Fingolimod - Gilenya	Fatal case of a patient treated with fingolimod	Access to documents
Public (incl. consumers and lawyers)	Flutamide	Deaths reported since year 2000	Access to Information
Healthcare professionals	Glukopyrron - Robinul	Fatal case notified by requester	Access to documents

Requester	DRUG / substance	Issue / risk	Type of request
Public (incl. consumers and lawyers)	Human papillomavirus vaccine - Gardasil and Influenza vaccine (H1N1)v (split virion, inactivated, adjuvanted) - Pandemrix	Autoimmune hepatitis	Access to information
EU Regulatory Network	Infanrix IPV, Infanrix Hexa and other pertusis containing vaccines	Limb swelling, skin disorder, erythema, pain in extremity, erysipelas, cellulitis, oedema peripheral	Access to documents
Public (incl. consumers and lawyers)	Infliximab - Remicade	Cardiovascular effects, haematological effects, renal effects, hepatic effects	Access to documents followed by access to information
EU Regulatory Network	Influenza split virion inactivated trivalent vaccine - Preflucel	Batch recall due to a possible emerging safety signal - information on EudraVigilance data	Access to information
Non-EU Authorities	Influenza vaccine - Fluad	All post-marketing ADRs	Access to documents
Journalist	Influenza vaccine (H1N1) (surface antigen, inactivated, adjuvanted) - Focetria; Influenza vaccine (H1N1)v (whole virion, inactivated, prepared in cell culture) - Celvapan; Influenza vaccine (H1N1)v (split virion, inactivated, adjuvanted) - Pandemrix	Total number of reports of serious ADRs and number of patients with multiple sclerosis and Guillain-Barré syndrome	Access to information
Public (incl. consumers and lawyers)	Influenza vaccine (H1N1)v (split virion, inactivated, adjuvanted) - Pandemrix	All ADRs between Jan 2010 and Jan 2011	Access to Information
Public (incl. consumers and lawyers)	Influenza vaccine (H1N1)v (split virion, inactivated, adjuvanted) - Pandemrix	Narcolepsy	Access to Information
Journalist	Influenza vaccine (H1N1)v (split virion, inactivated, adjuvanted) - Pandemrix	Narcolepsy - by age groups and country	Access to information
EU Regulatory Network	Influenza vaccine (H1N1)v (split virion, inactivated, adjuvanted) - Pandemrix	Update of the number of cases of narcolepsy/cataplexy with Pandermix	Access to information
EU Regulatory Network	Influenza vaccine (H1N1)v (split virion, inactivated, adjuvanted) - Pandemrix	Updated number of cases of narcolepsy/cataplexy	Access to information
EU Regulatory Network	Influenza vaccine (H1N1)v (split virion, inactivated, adjuvanted) - Pandemrix	Updated number of cases of narcolepsy/cataplexy	Access to information
EU Regulatory Network	Influenza vaccine (H1N1)v (split virion, inactivated, adjuvanted) - Pandemrix	Updated number of cases of narcolepsy/cataplexy	Access to Information
Other EU Agencies	Influenza vaccine (H1N1)v (split virion, inactivated, adjuvanted) - Pandemrix	Updated number of cases of narcolepsy/cataplexy	Access to information
Other EU Agencies	Influenza vaccine (H1N1)v (split virion, inactivated, adjuvanted) - Pandemrix	Updated number of cases of narcolepsy/cataplexy	Access to information
Non-EU Authorities	Intralipid 20% and propofol 1%	All ADRs	Access to documents
Journalist	Isotretinoin	All ADRs	Access to Documents
Public (incl. consumers and lawyers)	Isotretinoin	Suicide and suicide attemps in Europe between 1982 and 2000	Access to Information
Journalist	Isotretinoin	Depression, mental disorders, suicide attempts and suicides since the 1980s	Access to information

Requester	DRUG / substance	Issue / risk	Type of request
Pharmaceutical industry	Lovastatin	All ADRs in EU	Access to information
Journalist	Memantine - Ebixa	Corneal adverse reactions, such as superficial punctuate keratitis, punctuate subepithelial opacification, epithelial oedema, stromal oedema or any cases of visual impairment or vision loss. Reports of prostate cancer.	Access to information and documents
Journalist	Meningococcal group A, C, W-135 and Y conjugate vaccine - Menveo	Guillain-Barré syndrome and suicidal ideation	Access to Information
EU Regulatory Network	Metoclopramide	Neurotoxicity - extrapyramidal syndrome, convulsions	Access to information
EU Regulatory Network	Mycophenolate mofetil - Myfenax	Possible quality defect associated with a particular batch	Access to information and documents
Academia	n/a	Number of postmarketing cases currently held in EudraVigilance	Access to information
EU Regulatory Network	N/A	Reports of PML in EudraVigilance, irrespective of medicinal product	Access to information
Public (incl. consumers and lawyers)	Natalizumab - Tysabri	Progressive multifocal leukoencephalopathy: fatal reports	Access to documents
Pharmaceutical industry	Octenidine	All adverse reactions	Access to documents
Other EU Agencies	Oxitriptan	Any indication about the misuse of this substance (as a precursor to psychoactive 5-hydroxytryptamine)	Access to documents
Pharmaceutical industry	Oxygen; Nitrous oxide; Combination oxygen + nitrous oxide; Combination Helium + Oxygen; Nitric oxide; Combination oxygen + carbon dioxide	Number of ADRs in Europe in 2010 and in 2009	Access to information
Journalist	Pelargonium (herbal extract)	Number of ADRs	Access to information
EU Regulatory Network	Pfizer products	Reports for Pfizer products in general	Access to information
Other EU Agencies	Phenazepam	Any data received by EMA	Access to information
EU Regulatory Network	Pioglitazone - Actos	Bladder cancer/any malignancy	Access to information and documents
EU Regulatory Network	Piribedil	RMR separated for oral and parenteral forms during period of interest 01.04.-2008 - 31.03.2011	Access to information
EU Regulatory Network	Products containing Polysorbate 80	Safety profile of intravenous administeration in neonates (ICH definition= from birth to 27 days)	Access to information and documents
Public (incl. consumers and lawyers)	Quetiapine, methadone	ADRs related to concomitant use of methadone and quetiapine	Access to information and documents
EU Regulatory Network	Rasagiline - Azilect	Number of reports of muscle/ligament/cartilage disorders	Access to information
EU Regulatory Network	Rituximab - Mabthera	Potential contamination issue	Access to information
Academia	Saxagliptin - Onglyza, sitagliptin - Januvia and vildagliptin - Galvus	Any adverse events or suspected adverse events	Access to information and documents
Non-EU Authorities	Sevelamer - Renagel, Renvela	Dysphagia and associated events such as aspiration, choking, and esophageal	Access to information

Requester	DRUG / substance	Issue / risk	Type of request
		retention	
EU Regulatory Network	Somatropins	Follow-up from 2010 - analysis of fatal cases reported with growth hormones	Access to information and documents
Public (incl. consumers and lawyers)	SSRI	All ADRs	Access to Information
EU Regulatory Network	Statins (simvastatin, atorvastatin, pravastatin, rosuvastatin, fluvastatin)	Diabetes	Access to information and documents
EU Regulatory Network	Strontium ranelate - Protelos	DRESS, deep vein thrombosis, pulmonary embolism (French data)	Access to information
Public (incl. consumers and lawyers)	Sulfamethoxazole, trimethoprim - Septrin	All ADRs	Access to documents
Journalist	Terbinafine	Hearing disturbances, including loss of hearing and tinnitus	Access to information
Public (incl. consumers and lawyers)	Tocilizumab - RoActemra	Cardiovascular effects, haematological effects, renal effects, hepatic effects	Access to documents followed by access to information
Journalist	Tranexamic acid	Thrombotic events	Access to documents
Public (incl. consumers and lawyers)	Tryptophan	All adverse reactions	Access to information and documents
Journalist	Vareniclin - Champix; bupropion and nicotine	Aggressiveness, violence and suicidal ideation	Access to information
Journalist	Varenicline - Champix	All ADRs reported during past year and since 2006	Access to Information
Journalist	Varenicline - Champix	Hyperglycaemia in diabetic and non-diabetic patients	Access to documents
EU Regulatory Network	Varenicline - Champix	Suicidal behaviour/suicide, self harm reactions, neurological reactions etc…	Access to information

3. Signal management in the EU

As part of its mandate to improve the Signal Management process in the EU, the PhVWP Signal Management Drafting Group agreed to look in detail into current processes taking into consideration the upcoming implementation of the new pharmacovigilance legislation.

The new legal obligations concerning data monitoring and signal management will require the assessors in the Member States to have appropriate (scientific) expertise, and the capacity to collaborate with the Agency and the other Member States. These new obligations will have some impact on the organisation of the work at EU level, as well as the cooperation between the Member States and the EMA as regard the development and adaptation of processes, logistics and working instructions.

For the purposes of identifying potential challenges and to contribute to the ongoing implementation of the new legislation, the PhVWP decided to start a Pilot on the Signal Management in the EU. The specific aim was to use the experiences gained with this exercise to identify the needs and possible adaptations required of the Network in the near future. Following the completion of this Pilot, a set of proposals was made to support the implementation of the new legislation and to contribute to the improvement of the protection of public health.

At the April 2011 meeting, the PhVWP agreed on a two step-approach for the Signal Management Pilot:

- Phase 1 to consist of working in line with the "*Roles, responsibilities and tools for exchange of information relating to signals between EU competent authorities*" document (EMA/731874/2010), to see if improvements might be needed and to identify possible challenges. This phase started in May 2011 for a period of 6 months.
- Phase 2 to allow an evaluation of the performance of the whole system.

A set of Key Performance Indicators (KPIs) was developed and was being used to analyse the progress made each month during the DG/PhVWP meetings.

Although the Pilot progressed well, the initial 6 months period for phase 1 was considered insufficient. An extension to 9 months (ending in January 2012) was agreed by the PhVWP plenary at its meeting in September 2011.

In parallel, a full day workshop titled: "Expert meeting on Signal Detection Strategies" was organized in November 2011 to progress on some of the key issues regarding Signal Management and Signal Detecetion in the coming years.

In December 2011, a progress report on the achievements of Pilot Phase 1 was drafted. The document was then subsequently adopted by the Signal Management Drafting Group of the PhVWP in January 2012 and by the PhVWP itself in February 2012. This report notably includes the methodology used during the pilot, a summary of the Signal Management Drafting Group meetings held since May 2011 and lessons learnt during Pilot Phase 1.

The key recommendations issued by the group and the next steps to be considered during Pilot Phase 2 are as follow:

- The experience gained so far 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.

- Clarifications should be provided and consensus reached among the NCAs/EMA regarding terminologies, roles and responsibilities for signal management in general and update of EPITT.

- The KPIs should be used to estimate the effectiveness of the Network in preparation for the new legislation implementation.

The guidance document "*Roles, responsibilities and tools for exchange of information relating to signals between EU competent authorities*" dated June 2011 as well as the comments and lessons learnt identified during Pilot Phase 1 have constituted a solid basis for the drafting of Module IX of the Good Vigilance Practices on Signal Management.

4. Status of human EudraVigilance

During 2011, an average of 71,211 ICSRs (all report types) were received per month and made available for analysis to the EMA and the Member States. During the same period, almost 3,500 data analyses were conducted per month by experts from NCAs using EudraVigilance Data Analysis System (EVDAS).

EudraVigilance supports signal detection and data analysis by Member States including regular notification of Reaction Monitoring Reports in the context of the EudraVigilance Support Programme.

In the context of the implementation of the EudraVigilance Access Policy, the EMA has been operating a contract to perform ICSR data quality checks on data transmitted to EudraVigilance by all stakeholders. The activities that have been initiated focus currently on the detection and management of duplicate cases from EudraVigilance, the recoding of medicinal product information reported in ICSRs and a routine review of the quality of ICSRs. The recoding of medicinal product information is 3 months ahead of target and is scheduled to have recoded every product reported in ICSRs by March 2012. In 2011 the duplicate detection algorithm created by the Agency was of such high specificity (61% of detected potential duplicates were true duplicates) that approximately 10% more duplicates were removed from the system than originally forecasted, reducing costs compared to those originally forecasted.

The EMA continues to be actively engaged in harmonisation activities at International Conference on Harmonization (ICH) and International Standards Organisation (ISO) level in the context of preparing for the implementation of the new pharmacovigilance legislation.

Significant efforts have been made during 2011 to prepare for the new pharmacovigilance legislation. In particular, the EMA, in cooperation with the Member States, has contributed to draft Commission implementing measures regarding the format and content of electronic transmission of suspected adverse reactions by Member States and marketing authorisation holders, the use of internationally agreed terminology, formats and standards for the performance of pharmacovigilance activities, including a guideline on the detection and management of duplicate cases in pharmacovigilance databases.

Also in the context of the new legislation, detailed business requirements for the future EudraVigilance system have been prepared and discussed with the Member States.

A detailed summary of EudraVigilance activities during the period covered by this report follows.

4.1. Current status of implementation of EudraVigilance-human covering the period 1 January 2011 – 31 December 2011

The following activities should be highlighted:

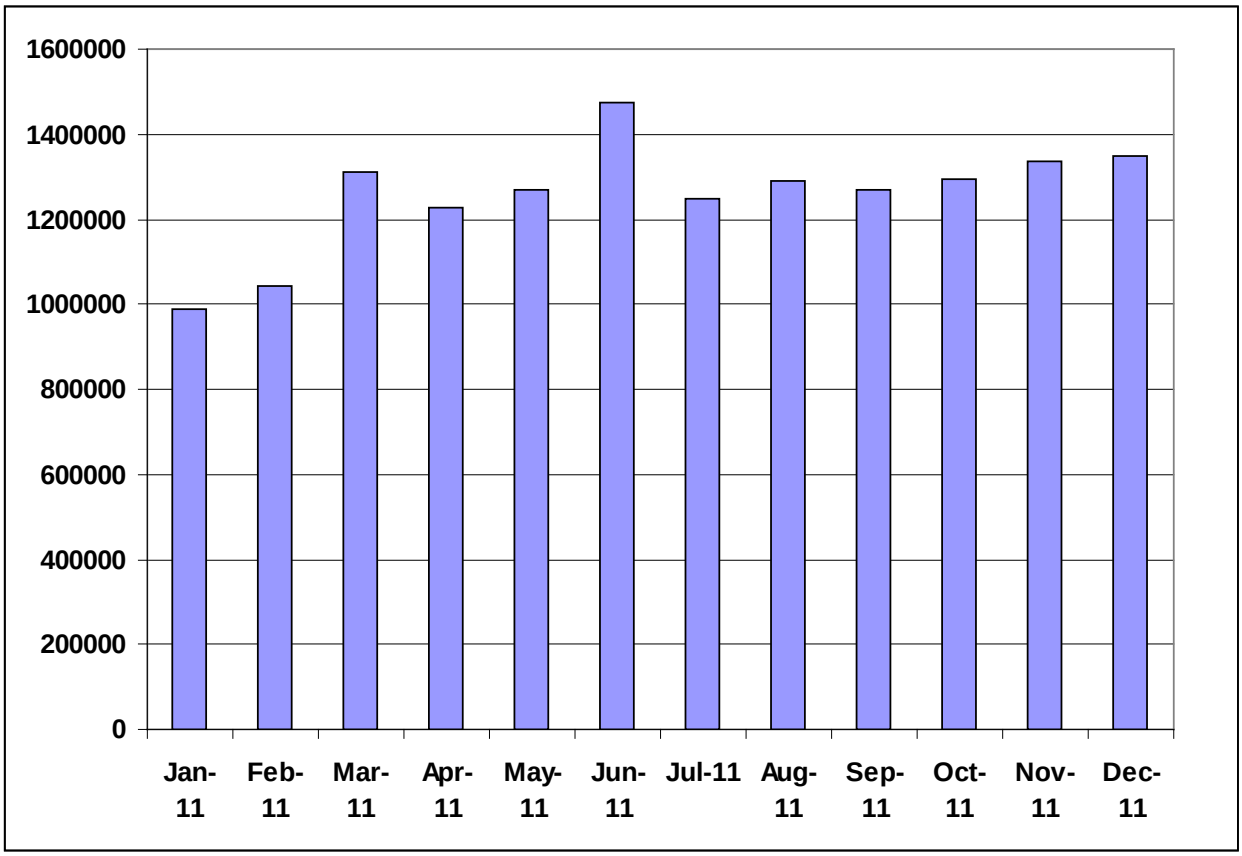
- Cleaning the data in EudraVigilance to improve signal detection and prepare for the proactive release of data as part of the EudraVigilance Access policy:
  - Over 566,000 cases (~24% of the database) had the medicinal products reported in them manually recoded against the EudraVigilance Medicinal Product Dictionary (EVMPD) during the reporting period.
  - Over 46,500 duplicate cases were removed from the database and a further 16,600 possible duplicate pairs were identified as requiring assessment by the sending organisation.
- The continuation of the EVDAS roll-out to the NCAs: The EudraVigilance Support Programme was continued, sending bi-weekly reaction monitoring reports to NCAs to aid routine pharmacovigilance. 14 NCAs are now routinely receiving these monitoring reports for 167 different active substances & 145 medicinal products.
- Ensuring that MAHs for CAPs and NCAs are complying with the mandatory electronic reporting of ICSRs:
  - All Member States were in production with EudraVigilance for the electronic reporting of ICSRs in the post-authorisation phase.
  - 100% of ICSRs for CAPs are being transmitted electronically to EudraVigilance.
  - Retrospective population of EudraVigilance continued to increase; 6,314 backlog cases, both Post-Marketing and Clinical Trials, were submitted during 2011.
- 6 EudraVigilance Expert Working Group meetings and 2 EudraVigilance Steering Committee meetings were held during 2011.
- The three-day user training courses for the EVWEB application, the one-day training course for the EVMPD, the three-day EVDAS training course for NCAs continued during the reporting period.

4.1.1. EudraVigilance Gateway

With regard to 2011 a total of 15,096,000 transactions (including message disposition notifications) were performed by the EudraVigilance Gateway (production). These transactions included messages exchanged between the EMA, pharmaceutical companies, sponsors of clinical trials and NCAs and rerouted messages to and from NCAs, sponsors of clinical trials and pharmaceutical companies.

Overall, between the establishment of the EudraVigilance Gateway in November 2001 and 31 December 2011, a total of 51,317,355 transactions have been performed.

Figure 1. Total number of transactions performed per month at the level of the EudraVigilance Gateway during 2011.



4.1.2. EudraVigilance database

4.1.2.1. E-reporting status for MAHs and sponsors of clinical trials

- A total of 521 MAHs (at headquarter level) have sent reports to the EudraVigilance Post-authorisation Module (EVPM) in the period between 1 January 2002 and 31 December 2011.
- A total of 310 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 2011.

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 & Sponsors to EVPM & EVCTM during 2011

EV Module	Transmission type	Number of transmissions
EVPM	ICSRs	559,091
	Individual Cases	383,675
	Backlog Cases	382
EVCTM	ICSRs	75,297
	Individual Cases	36,958
	Backlog Cases	110

Table 2. Combined 15-day reporting compliance to EVPM for all MAHs and Sponsors.

Percentage of ICSRs transmitted to EVPM within 15 days:	91%

Please note that compliance is not provided at the level of individual MAHs & Sponsors because of the very large number of MAHs and Sponsors that transmit data to EudraVigilance.

4.1.2.2. 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 AFSSAPS;
  - The MPA (Sweden) changed their reporting requirements and now all ICSRs transmissible to the MPA by MAHs are transmitted direct to EudraVigilance.

Tables 3 below shows the total (both expedited and non-expedited) number of unique cases and ICSRs transmitted by NCAs to EVPM and EVCTM.

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 retransmission 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 total NCA 15-day reporting compliance increased from 79% in 2010 to 84% in 2011.

Table 3. Number of ICSRs and unique cases transmitted by NCAs to EVPM & EVCTM during 2011

EV Module	Transmission type	Number of transmissions
EVPM	ICSRs	194,130
	Individual Cases	126,618
	Backlog Cases	4,460
EVCTM	ICSRs	10,985
	Individual Cases	5,653
	Backlog Cases	1,362

During 2011, the following 12 NCAs transmitted SUSARs to EVCTM:

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	National Agency for Medicines

Member State	National Competent Authority
Germany	Federal Institute for Drugs and Medical Devices
Germany	Paul-Ehrlich-Institut
Greece	National Organisation for Medicines
Hungary	National Institute of Pharmacy
Malta	Medicines Authority
Netherlands	College ter beoordeling van geneesmiddelen
Portugal	INFARMED
United Kingdom	Medicines and Healthcare Products Regulatory Agency

During 2011, the following 6 NCAs transmitted a total of 5,327 backlog cases to EVPM & EVCTM:

Member State	National Competent Authority
Austria	Agentur fuer Gesundheit und Ernaehrungssicherheit
Belgium	Federal Agency for Medicines and Health Products
Czech Republic	State Institute for Drug Control
Greece	National Organisation for Medicines
Slovenia	Agency for Medicinal Products and Medical Devices
United Kingdom	Medicines and Healthcare Products Regulatory Agency

4.1.2.3. Summary of e-reporting status by all stakeholders (NCAs, MAHs and sponsors of clinical trials), excluding backlog

In the period from 1 January 2002 to 31 December 2011 a total, including both expedited and non-expedited cases and ICSRs, of:

- 3,498,935 ICSRs were reported to EVPM referring to 2,179,526 individual cases.
- 518,183 ICSRs were reported to EVCTM referring to 203,846 individual cases.

4.1.2.4. Summary of e-reporting status by all stakeholders (NCAs, MAHs and sponsors of clinical trials) to EVPM split by EEA and Non-EEA, excluding backlog

In the period from 1 January 2002 to 31 December 2011 a total, including both expedited and non-expedited cases and ICSRs, of:

- 1,350,791 EEA ICSRs were reported to EVPM referring to 826,120 EEA individual cases.
- 2,148,144 non-EEA ICSRs were reported to EVPM referring to 1,353,406 non-EEA individual cases.

4.1.2.5. Summary of e-reporting status by all stakeholders (NCAs and sponsors of clinical trials) to EVCTM split by EEA and Non-EEA, excluding backlog

In the period from 1 May 2004 to 31 December 2011 a total, including both expedited and non-expedited cases and ICSRs, of:

- 264,042 EEA ICSRs were reported to EVCTM referring to 102,362 EEA individual cases.
- 254,141 non-EEA ICSRs were reported to EVCTM referring to 101,484 non-EEA individual cases.

Figure 2. Number of reports and cases reported to EVPM during the reporting period, excluding backlog

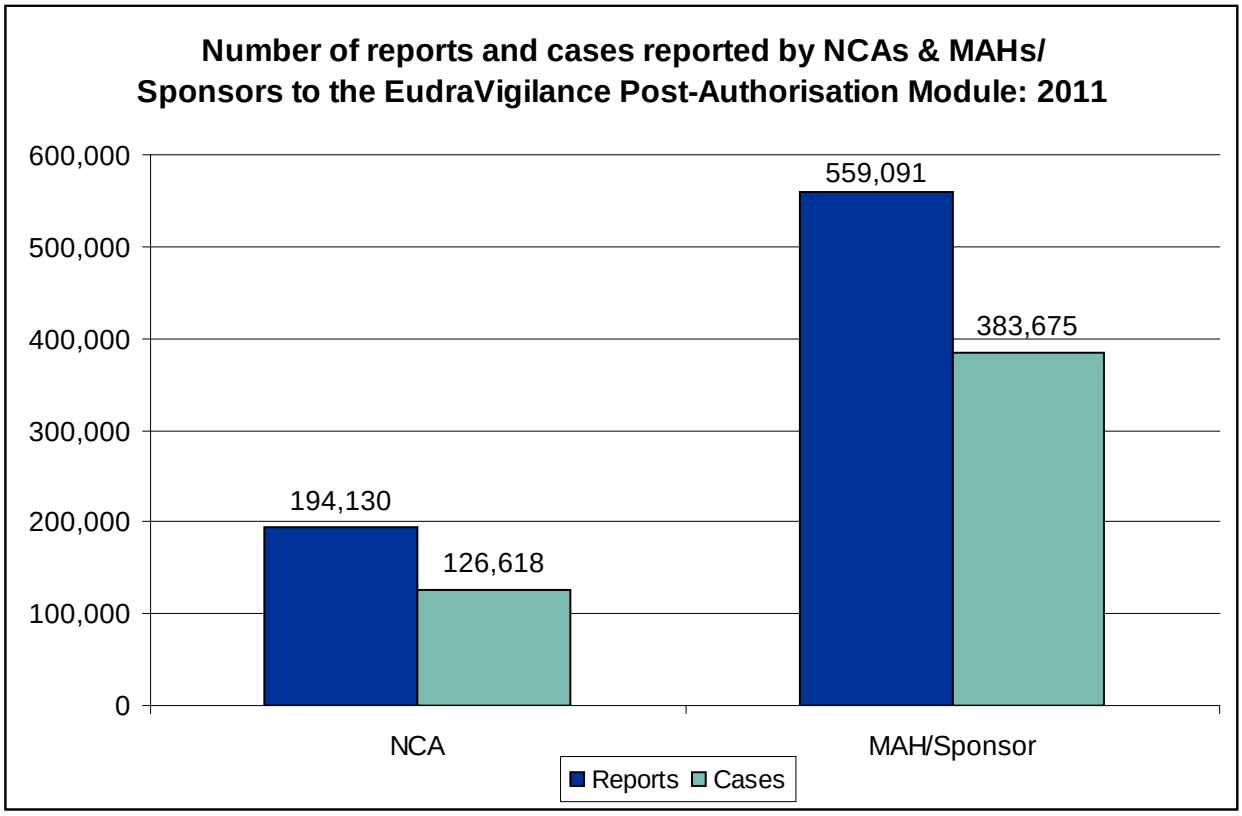


Figure 3. Number of reports and cases reported to EVCTM during the reporting period, excluding backlog

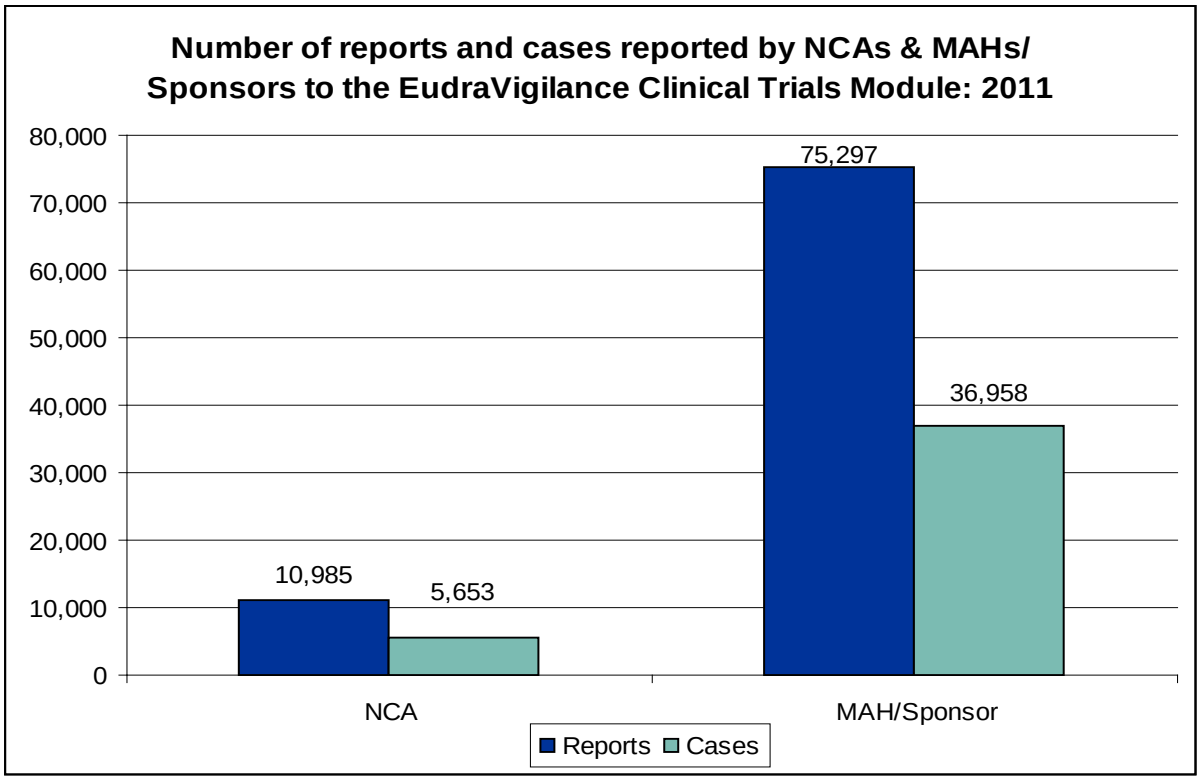
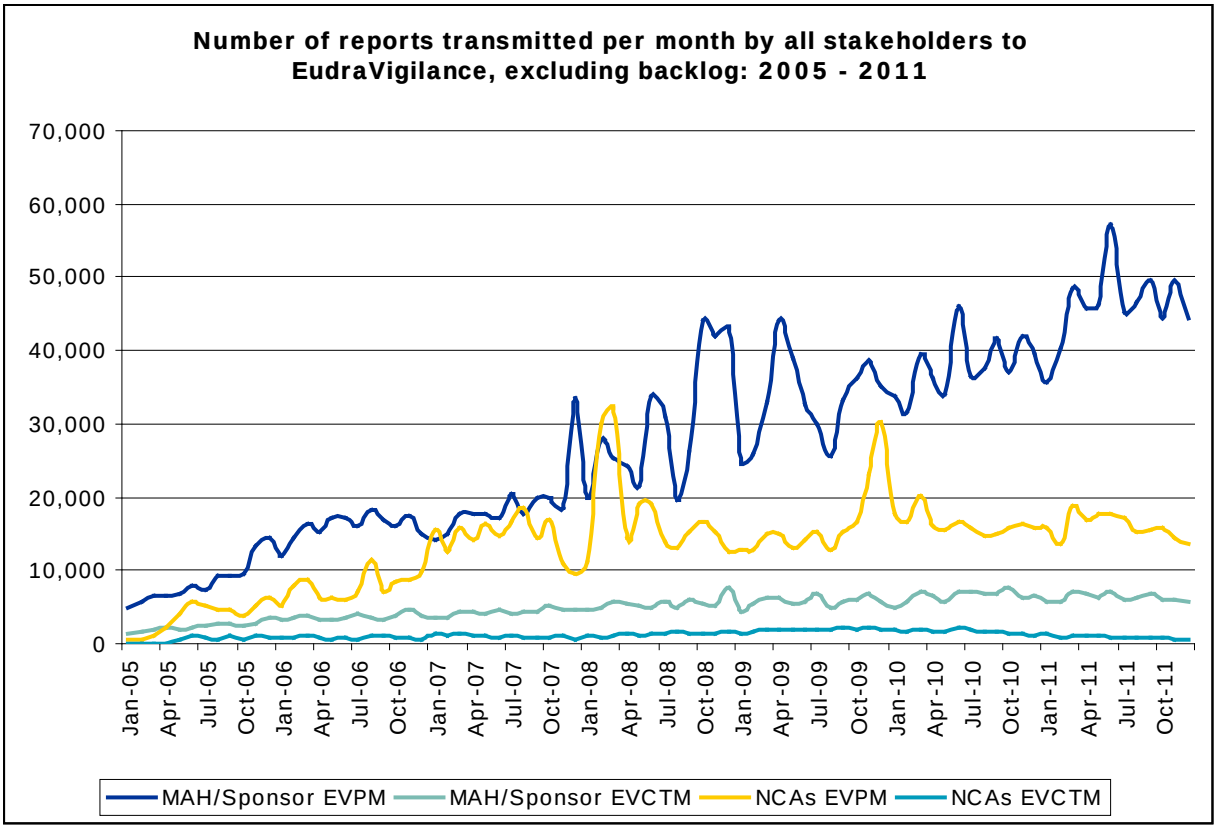


Figure 4. Number of ICSRs submitted per month, excluding backlog



4.1.3. EudraVigilance data management

In December 2010 the contractors appointed by the EMA to perform EudraVigilance data management activities started work performing “data cleaning” (manual recoding) of medicinal product data reported in ICSRs and managing duplicate cases. In June 2011 the contractors started work on the checking of the quality of ICSRs.

Manual recoding of medicinal product data is performed by taking a term reported in a drug section of an ICSR, but which is not an exact match of a term in the EVMPD (the reference dictionary for medicinal product information), and matching it to the appropriate term.

Duplicate detection and management is performed by assessing potential duplicate pairs identified by the duplicate detection algorithm and taking the appropriate action based on a review. Duplicates transmitted to EudraVigilance by different senders are marked as duplicates and merged under a master case. The cases are still in the database for the purposes of receiving follow-up information, but are not counted for signal detection. Where duplicates are transmitted to EudraVigilance by the same sender organisation (e.g. MAH, NCA, Sponsor), that sender organisation is contacted and asked to assess the cases and take appropriate action.

During the period 2011 the following data cleaning work was performed:

Manual recoding:

- 139,157 terms were manually recoded, which led to the recoding of
  - 1,334,055 drug sections
  - 965,122 reports
  - 566,670 cases

The quantity of work performed in the 12 months of 2011 was the same as was forecasted for 15 months. The backlog of unrecoded medicinal product terms to be recoded should be completed by end-March 2012, as opposed to the originally forecast end-June 2012.

Duplicate detection:

- 46,514 duplicate cases were removed from signal detection counts
- 16,594 possible duplicate pairs were identified for sending to the sender for their assessment
- 40,184 of the identified potential duplicate pairs were not duplicates

In total 61% of the detected potential duplicates were identified as being true duplicate pairs.

Initially, during the process of drawing up the Invitation To Tender for the current contract, the EMA had estimated that 40% of detected potential duplicates would be true duplicates. The increased specificity of detecting duplicates achieved by the EMA has meant that the contractors have spent more time working productively removing true duplicates from the system and less time working unproductively, marking false positives as ‘not duplicates’. This means that in 2011 over 6,000 more true duplicates (or 10% of the number of true duplicates) were removed from EudraVigilance than originally forecasted. Because removing duplicates from the system takes more time than simply marking a couple as ‘not duplicates’, this has meant that in 2011 the contractors assessed fewer couples than originally forecasted. This has meant that the Agency reduced costs on this work stream, and achieved 10% more productivity at the same time.

ICSR Data Quality:

- The ICSR data quality workstream started in June 2011. The data quality of the cases of 67 MAHs was assessed from June – Dec 2011.
- The data from the ICSR data quality workstream assessments has been shared with pharmacovigilance inspectors from the National Competent Authorities upon their request and used to feed into inspections.

4.1.4. EudraVigilance Medicinal Product Dictionary (EVMPD)

During 2011:

- 1,282 presentations for Investigational Medicinal Products and 62,683 presentations for Authorised Medicinal Products were entered into EVMPD.

In total there are 160,846 valid presentations in the EVMPD.

4.2. EMA initiatives to progress with the implementation of EudraVigilance in the field of human medicines

4.2.1. EudraVigilance datawarehouse & analysis system training for NCAs

During 2011, EVDAS training was held at the Agency on 7 occasions, training 64 experts from 20 different NCAs.

174 users from 30[3] National Competent Authorities (counting post-marketing and clinical trial competent authorities separately) have analysed data in EVDAS. These users ran a combined total of 40,549 queries.

4.2.2. Activities related to the international standardisation work in the context of the International Conference on Harmonization and the International Standards Organisation

In the context of the ISO Technical Committee (TC) 215 'Health Informatics' Working Group 6 'Pharmacy and Medicines Business' activities, the following milestones have been achieved:

- May 2011: ISO IDMP
  - Resolution approved the release of IDMP Final Draft International Standard (FDIS) for ballot. Should the FDIS pass the ballot it would become an international standard.
- April 2011: ISO ICSR standard
  - The ICSR Final Drafts International Standard (FDIS) documents were submitted to ISO for preparation for release.
- August 2011: ISO ICSR Standard
  - The ballot was published in August and resulted in a positive vote.
- December 2011: ISO ICSR Standard
  - The final ISO ICSR standard was published in December 2011.

[3] This figure rises to 45 if regional pharmacovigilance centres are counted separately.

4.2.3. EudraVigilance Information Day

Eight EudraVigilance Information Days were held during 2011. There were two information days on each of the following four subjects: (i) general EudraVigilance Information Day, (ii) the new ISO ICSR standard, (iii) Development Safety Update Reports and (iv) the new Identification of Medicinal Products (IDMP) International Standard and ICH M5/M2.