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2010 EudraVigilance-Human Annual Report

1 January 2010 – 31 December 2010

Key messages

- This report presents a summary of routine and ad-hoc activities covering the period 1st January to 31st December 2010, and focuses on activities related to Centrally Authorised Products (CAPs).
- A total of 2,054 potential safety issues were detected in 2010. This represents an increase of 350 issues (20.5%) compared to 2009.
- During the period of this report, a total of 39 of the previously identified potential safety issues were validated as signals and communicated to the respective Rapporteurs. Of these, 19 were raised on products belonging to the intensively monitored group, and 20 to the routinely monitored group.
- A three-fold increase in requests for data from EudraVigilance was observed in 2010 compared to 2009. Of the numerous queries received during the period covered by this report, 31 complex queries relating to EudraVigilance data were received from European Pharmacovigilance Network stakeholders. The requests were for either data or scientific analysis of EudraVigilance data. 64.5% queries were replied to within 14 calendar days and 80.6% within 31 days. The range for time to response was 0 – 103 days, median 8 days and average 23 days.
- The monitoring of pandemic A/H1N1 influenza vaccines and antivirals continued throughout the period of this report. A total of 75 weekly or fortnightly Reaction Monitoring Reports (RMRs) for pandemic influenza vaccines and antivirals were produced, distributed to the EU Regulatory Network and the Rapporteurs, and assessed at the EMA. The Pandemic Pharmacovigilance Rapid Response Expert Group (PREG) convened 14 times and 18 safety update reports were published on the EMA website.
- Following the assessment by the PREG of a weak signal of Guillain-Barré Syndrome (GBS) a dedicated expert group meeting was convened at the Agency on 29th March 2010. The experts concluded that the available data are reassuring and there is no sign of a risk of a similar magnitude as that found in the pandemic situation of 1976, and that although a possible association between the pandemic A/H1N1 vaccines and GBS cannot be totally ruled out, if this association exists, it would probably translate into a very small increase in the risk.
- Additionally, following media attention in Sweden and Finland in Aug 2010 associating Pandemrix with new-onset narcolepsy, the PREG concluded that the available evidence was insufficient to determine whether there is any link between Pandemrix and reports of narcolepsy, and that further

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studies were necessary to fully understand this issue. This issue is the subject of an ongoing regulatory procedure.

- Progress was made during 2010 as regards the use of EudraVigilance, illustrated by a significant increase of Member States working with the EudraVigilance Data Analysis System: the total number of queries run by NCAs users during 2010 was 35,507. These queries were made by 190 distinct users.
- The EMA has been closely working with Sponsors, Marketing Authorisation Holders and Member States to improve the quality of the data submitted to EudraVigilance. Major steps of this initiative include the publication of the new Business Rules, and the creation of a Guideline on Duplicate ICSR Detection & Management. In addition, a contract was awarded by the EMA to a service provider to perform data cleaning activities on the EudraVigilance data.
- A 3 year IT development plan was adopted by the EudraVigilance Steering Committee. It took into consideration the new pharmacovigilance legislation and will have to be amended based on the March 2011 Management Board decisions.
- Significant milestones were reached during 2010 in the context of international harmonisation and standardisation activities. The ISO Identification of Medicinal Products (IDMP) Draft International Standard (DIS) was released for a 5-month ballot period in September 2010. This is the penultimate stage of the process. The ISO ICSR standard was approved to enter the Final DIS (FDIS) stage.

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Introduction

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

This report presents a summary of routine and ad-hoc activities within the period of 1st January – 31st December 2010, and focuses on activities related to Centrally Authorized Products (CAPs).

The signal detection and signal management activities are performed 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 implementation of Human EudraVigilance 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 total of 2,054 potential safety issues were detected in 2010. This represents an increase of 350 issues, i.e. an increase of approx. 20.5% compared to 2009. These issues are presented below according to the frequency of monitoring for the respective medicinal products. Of these, 39 signals[1] were communicated to the Rapporteurs.

Of note, approx. 94% of potential safety issues presented above originated from EudraVigilance, with other sources accounting for: 33 potential safety issues from the Retrospective validation study, 19 from bibliography and 70 from communications received from other regulatory agencies worldwide.

Overview	2010	2009
Weekly monitoring	21	125
Intensive monitoring	903	733
Routine monitoring	1130	846
Total	2054	1704

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

- **Weekly monitored products**: Products for which, in the opinion of the EMA, a continuous monitoring of the safety profile is critical to protect patient health in Europe. This procedure includes the following steps:
  - the weekly production of a monitoring report that includes a compilation of all serious adverse reactions received in EudraVigilance for that product;
  - an immediate screening of this report by a member of the EMA Signal Validation team in order to identify and validate any new safety information;
  - a review within 2 days of any new signal in a meeting of the EMA Signal Validation team;

[1] A signal is information on an adverse event that is new or incompletely documented, that may have causal relationship to treatment and is recognised as being worthy of further exploration (SOP/H/3065).

- an immediate communication to Rapporteurs of new validated signals in order to allow a quick evaluation and a prompt decision-making if necessary.

- **Intensively monitored products**: Products for which, in the opinion of the EMA, a frequent monitoring of the safety profile is important to detect any new safety issue that may need to be reflected in the Product Information or to be further assessed. For these products, the monitoring report is produced and screened every other week. Following validation in the Signal Validation team meeting, signals are communicated to Rapporteurs for evaluation and further action if needed.

  Intensively monitored products include recent products for which the safety profile has not yet been fully characterised given their limited duration of marketing or the small number of treated patients. The safety profile needs also to be ascertained when a new indication has been granted for a new patient group. For these products, any new information needs to be identified and evaluated without delay. They include products for which an application for a marketing authorisation has been submitted to the Agency, products that have been authorised for less than 2 years, products with recent extension of indication or line extensions that could modify the target population, and products that have been authorised for longer but have had a substantial recent change in labelling (<2 years).

- **Routinely monitored products**: Well-known products for which, in the opinion of the EMA, a periodic monitoring of the safety profile is adequate to detect any new information that may need to be transmitted to the Rapporteur for further evaluation. For these products, the monitoring report is produced and screened once a month. Following validation in the Signal Validation team meeting, signals are communicated to Rapporteurs for evaluation and further action if needed. For these products, typical steps in the validation process consist in consulting assessment reports of Periodic Safety Update Reports (PSURs) for previous evaluations of a specific issue by the Rapporteur, the list of safety issues already discussed by the Pharmacovigilance Working Party or the literature.

  Routinely monitored products are those products for which the safety profile is well known, based on data collected over several years of marketing or extensive post-authorisation studies. New serious adverse reactions are not expected to occur frequently, but the Rapporteur is quickly informed if a new signal is detected.

  Routinely-monitored products include products that are not weekly or intensively monitored. Intensively-monitored products are transferred to the list of routinely-monitored products after two years of authorisation, unless this is decided otherwise in the Signal Validation team meeting. In such case, the product is kept in the list of intensively-monitored products for one year and re-evaluated after this period. Reasons for keeping a product as an intensively-monitored product may include a limited marketing during the two first years of authorisation, a new important identified or potential risk leading to an amendment of the Risk Management Plan (RMP), or the introduction of a new risk minimisation measure.

Also as described in the SOP above, following review of monitoring reports, signals are discussed and validated by the EMA Signal Validation Team. A validated signal is one that the Signal Validation Team decides should be communicated to the Rapporteur.

The action taken with potential signals is presented as:

- Closed (further investigation is not required).

- Ongoing (investigations are currently taking place).
- Monitored (not enough evidence to pursue, but will be kept under monitoring).
- Communicated to Rapporteurs (via EPITT (European Pharmacovigilance Issues Tracking Tool) and direct email).

2. Data analysis

Thirty-one requests were received and answered during the period of this report, representing approx. a three-fold increase compared to 2009. These requests were for either EudraVigilance data or for data analysis.

64.5% queries were replied to within 14 calendar days and 80.6% within 31 calendar days. The full range for time to response was 0 – 103 days, median 8 days and average 23 days.

3. Signal management in the EU

Following the establishment of a Drafting Group of the PhVWP on Signal Management monthly meetings were held in the margin of the PhVWP plenary.

The work of the Drafting Group is based on the fact that the agreed Signal Management principles in the EU are important to improve pharmacovigilance work practices.

The revised mandate of the Drafting Group was endorsed by the PhVWP at its meeting in May 2010. It proposed a stepwise approach:

- Step 1
  - Develop a concept paper based on the final report of Signal Management in the EU.
  - Develop a draft guideline on signal management in the EU based on the findings and subsequent recommendations of the Pilot, especially with regards to the full utilization of EPITT as a key tool to support signal sharing and management in the EU.
- Step 2
  - Start the consultation phase of the preparation of the guideline with the other relevant CHMP scientific groups and Experts Working Groups (incl. EudraVigilance Expert Working Group).
  - Supported by the EMA, collect and report to the PhVWP on the experience gained during the implementation phase, and make recommendations for the strengthening of signal management in the EU.

The objectives of step 1 were well in the way to completion by June 2010, with the first draft of the concept paper circulated within the Group for comments.

However, in view of the adoption of the new pharmacovigilance legislation by the European Parliament on 22 September 2010, the Drafting Group was obliged to revise this approach to consider integration of the new legislation and the impact of its implementation on Signal Management activities at EU level.

The concept paper on signal management in the EU was progressed as a working document titled 'Principles of Signal Management in the EU', which was presented and discussed at the PhVWP plenary in December 2010.

After careful consideration of the situation and the feed-back received from the plenary meeting, the drafting group decided to continue its work towards optimization of the process of Signal Management in the EU, and at the same time to contribute to the relevant project team for the implementation of the New Legislation in related areas.

4. Pandemic influenza A/H1N1 (2009) activities

The monitoring of pandemic A/H1N1 influenza vaccines and antivirals continued throughout the period of this report.

37 weekly Reaction Monitoring Reports (RMRs) for pandemic influenza vaccines were produced by P-PV-DCM, distributed to network stakeholders and reviewed internally by P-PV-SDA.

Similarly, 38 weekly RMRs for oseltamivir and zanamivir-containing products were produced and reviewed.

4.1. Pandemic pharmacovigilance updates

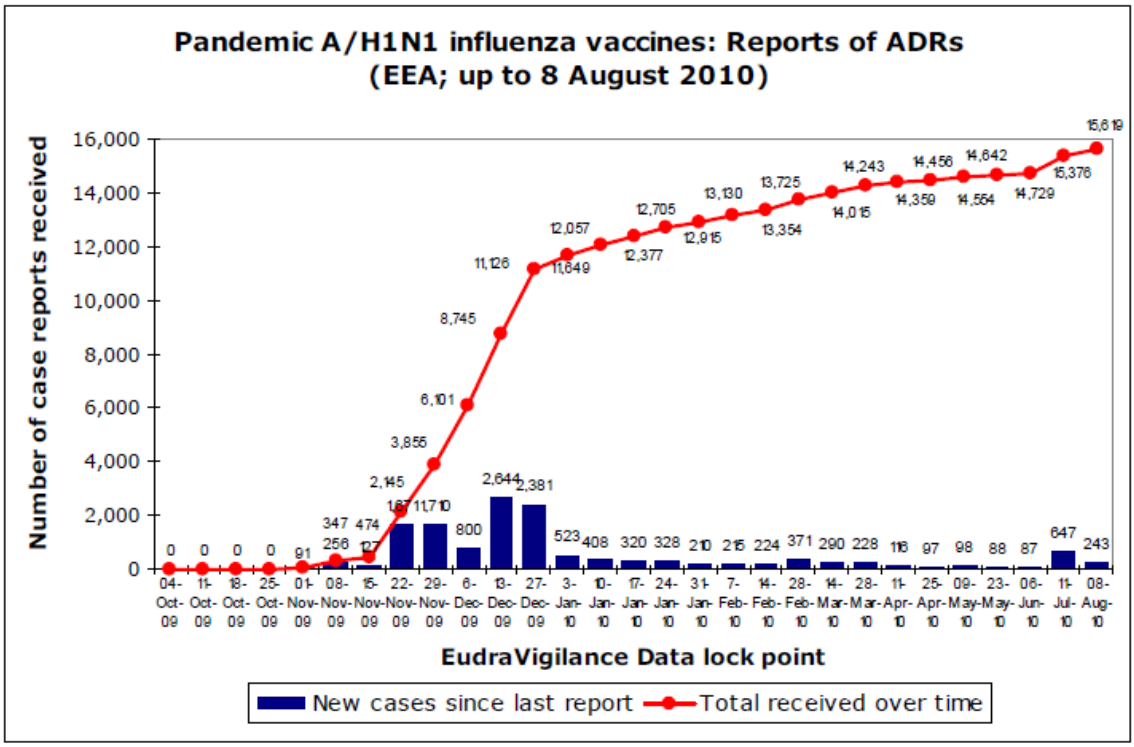
A weekly update to make safety information available to the public was implemented in late 2009, with the first Pandemic Pharmacovigilance Update published on Dec 3 2009 on the EMA website.

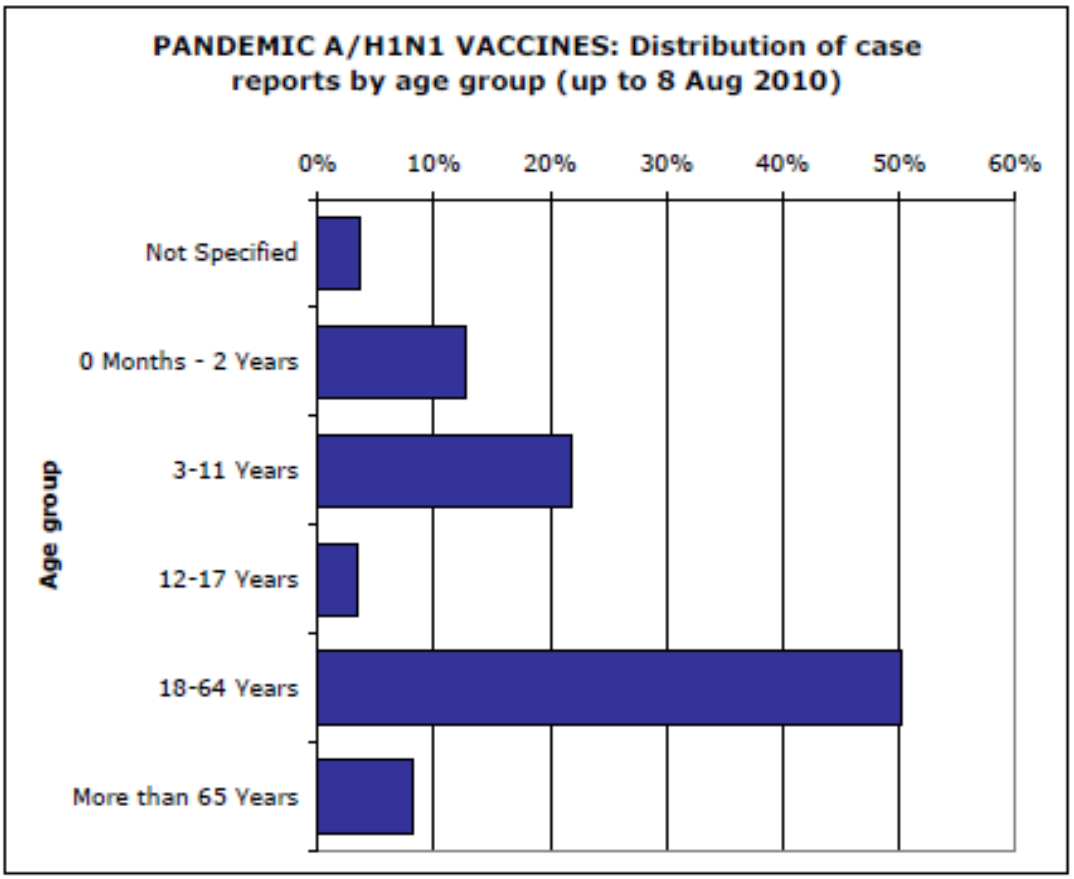
These reports contain key safety messages related to pandemic medicines, an overview of the pandemic situation in the EEA including summaries of new information from the European Centre for Disease Prevention and Control (ECDC) and WHO, an overview of safety information of centrally authorised vaccines including exposure data, and detailed reporting activity of the centrally authorised vaccines and Tamiflu, with numbers of reports per System Organ Class (high level grouping per organ systems), list of most frequently received adverse events per product and updated safety information including deaths for each product.

The weekly frequency of Pandemic Pharmacovigilance Updates was maintained up to the 12th pandemic update (published 24 Feb 2010), following which the frequency was switched to fortnightly. In June 2010, the frequency was switched to monthly after the 20th update (published 18 Jun 2010).

In total, 18 pandemic updates were produced and published on the Agency's website during the period of this report – list of all reports is available here. Following the announcement by the Director-General of the WHO on 10 August 2010 that the world has moved from phase 6 of influenza pandemic alert to the post-pandemic period (see WHO statement here), the pandemic updates were stopped with the last being the 22nd dated 19 Aug 2010.

As demonstrated on the chart below, the reporting of Adverse Drug Reactions (ADRs) to EudraVigilance decreased considerably in 2010 compared to 2009.


Pandemic A/H1N1 influenza vaccines: Reports of ADRs
(EEA; up to 8 August 2010)
Number of case reports received
16,000
14,000
12,000
10,000
8,000
6,000
4,000
2,000
0
0 0 0 0 91 347 474 2,145 11,710 800 2,644 2,381 523 408 320 328 210 215 224 371 290 228 116 97 98 88 87 647 243
256 127 1,67
8,745
6,101
3,855
11,126
12,057
11,649
12,705
12,377
12,915
13,130
13,354
13,725
14,015
14,243
14,359
14,456
14,564
14,642
14,729
15,376
15,619
04-Oct-09
11-Oct-09
18-Oct-09
25-Oct-09
01-Nov-09
08-Nov-09
15-Nov-09
22-Nov-09
29-Nov-09
6-Dec-09
13-Dec-09
27-Dec-09
3-Jan-10
10-Jan-10
17-Jan-10
24-Jan-10
31-Jan-10
7-Feb-10
14-Feb-10
28-Feb-10
14-Mar-10
28-Mar-10
11-Apr-10
25-Apr-10
09-May-10
23-May-10
06-Jun-10
11-Jul-10
08-Aug-10
EudraVigilance Data lock point
New cases since last report
Total received over time


PANDEMIC A/H1N1 VACCINES: Distribution of case reports by age group (up to 8 Aug 2010)
0%
10%
20%
30%
40%
50%
60%
Age group
Not Specified
0 Months - 2 Years
3-11 Years
12-17 Years
18-64 Years
More than 65 Years

An overview of issues reviewed during the period of this report is presented below:

SOC	Topic	Update number		
		Celvapan	Focetria	Pandemrix
Blood and lymphatic system disorders	Haematopoietic cytopenia			8
	Idiopathic thrombocytopenic purpura (ITP)			4, 6
	Leucocytosis, lymphocytosis			8
	Thrombocytopenia		6	6
Cardiac disorders	Cardiovascular accidents		5	
Ear and labyrinth disorders	Sudden hearing loss			4
Eye disorders	Eye disorders	4, 7	7	7
	Photophobia			7
Gastrointestinal disorders	Necrotising oesophagitis and necrotising stomatitis			6
	Pancreatitis	7		10
General disorders and administration-site conditions	Death, sudden death	10, 20	10, 20	10, 20
	Fever, local reaction and drowsiness following second dose in children 6-35 months old			1
	Injection site necrosis			3
Immune system disorders	Anaphylactic reactions in children			1
	Anaphylactic shock		2, 3	2
	Anaphylaxis, angioedema, hypersensitivity	2		
	Delayed hypersensitivity reaction type IV			4
	Serum sickness			6
	Transplant rejection			1, 2, 3
Infections and infestations	Herpes zoster	9	9	9
Injury, poisoning and procedural complications	Medication error	7, 10		7, 10

SOC	Topic	Update number		
		Celvapan	Focetria	Pandemrix
Nervous-system disorders	Acute disseminated encephalomyelitis (ADEM)		2, 3	
	Cerebral haemorrhage or infarction		1	3
	Demyelinating disorders	11	11	11
	Encephalitis		3, 5	
	Facial palsy or paresis	8	4, 8	7
	Guillain-Barré syndrome	4, 5, 11, 16, 20	2, 4, 5, 11, 16, 20	1, 3, 4, 5, 6, 11, 16, 20
	Multiple sclerosis	11	5, 11	5, 11
	Neuralgic amyotrophy			9
	Neuritis, polyneuritis, polyradiculoneuritis, peripheral neuropathy, polyneuropathy			6
	Paraesthesia	2		
	Paralysis and paresis	7	8	3
	Seizures		8, 13	13
	Seizures with fatal outcome			4
Pregnancy, puerperium and perinatal conditions	Intra-uterine death		4	
	Pregnancy-related events	11	2, 11	1, 2, 11
Skin and subcutaneous-tissue disorders	Bullous dermatitis		9	8
	Erythema multiforme, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)			3, 6
	Leukocytoclastic vasculitis		5	
	Photosensitivity reaction			2
	Systemic lupus erythematosus rash			8
Vascular disorders	Circulatory collapse	3		
	Vasculitis			6

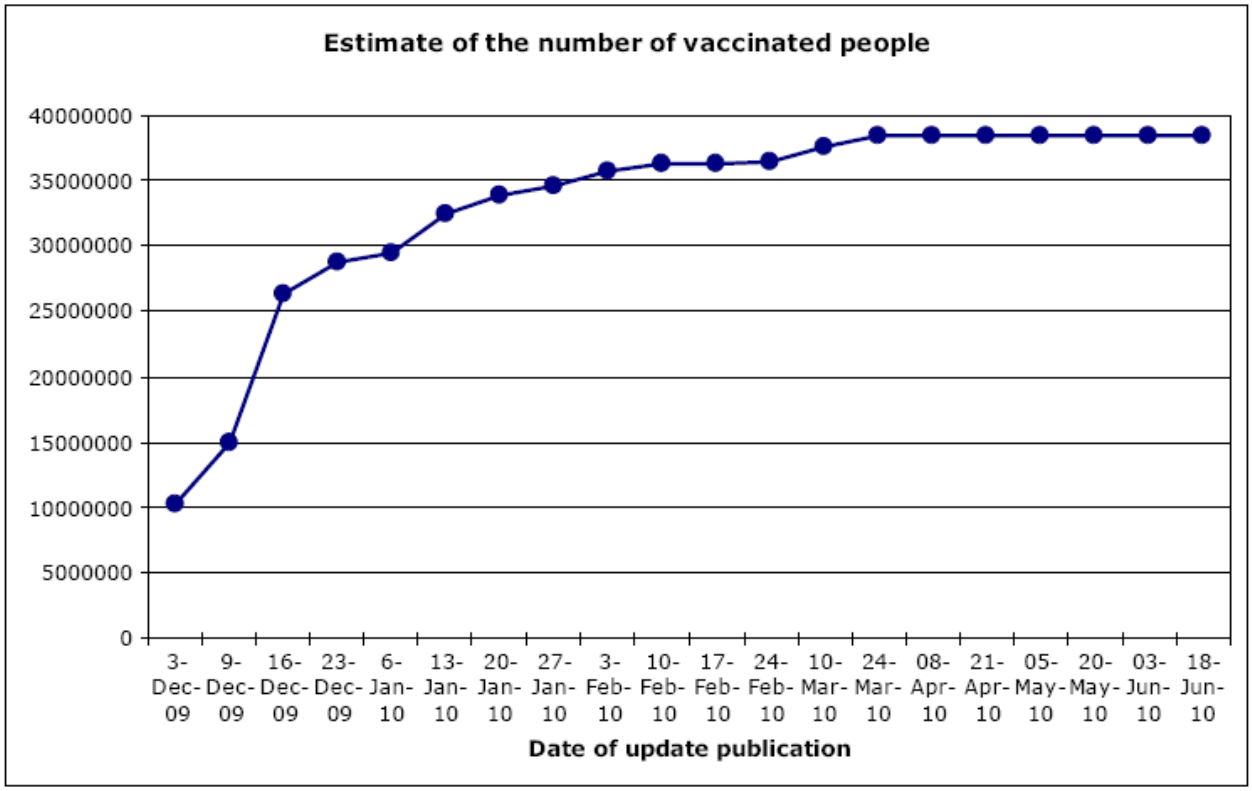
4.2. Collection of exposure data

The Agency continued to collate the information from the Member States and from the monthly PSURs from companies.

Following some initial adjustments and formatting modifications, the exposure table was distributed to all relevant stakeholders weekly from 2 December 2009 onwards (last updated on 19 Jul 2010). The information was stratified per vaccine brand name, separating number of distributed doses from vaccinated individuals. It also allowed for collection of exposure data regarding specific patient population (i.e. pregnant women), sex and age distribution.

Although the information collected was by no means complete, it proved very useful for data analysis purposes and became the exposure reference point for pharmacovigilance activities in the EU.

A graph summarising exposure data received during the period of this report is presented below. The dates presented are as per publication date of pandemic pharmacovigilance update.



4.3. PREG

Following consultation of the Pharmacovigilance Working Party and CHMP, a Pandemic Pharmacovigilance Rapid Response Expert Group (PREG) was created on 29 Oct 2009. The PREG remit included:

- To look into serious safety issues and information arising with potential to impact on the balance of risk and benefits;

- To review both new information and emerging information on known risks, since the possibility that data on adverse events already listed will impact on benefits risk could not be excluded (e.g. frequency of reporting);
- To address issues referred to the PREG by a member or a Member State;
- To provide advice on the collection of additional information and not specifically only on design of clinical trials.

In the period covered by this report, 14 PREG teleconferences took place compared to 8 during late 2009.

4.4. Guillain-Barré syndrome

Following an observed increase in reports for potential Guillain-Barré Syndrome (GBS), the PREG concluded that there was a potential weak signal of Guillain-Barré Syndrome, and that it needed to be further assessed. With that purpose, an expert group meeting was convened at the Agency on 29th March 2010.

This day-long meeting put together neurologists, epidemiologists and clinical statisticians to review and discuss the available data regarding the occurrence of GBS in patients vaccinated with an A/H1N1 influenza pandemic vaccine. The objectives of the meeting were to identify whether there was a possible association between the vaccine and the disease, to estimate the magnitude of the risk if any, to provide recommendations regarding further investigation of this issue and to advise on the need for collecting additional data.

From an analysis of spontaneous reports originating from European countries, the United-States and Canada, the experts concluded that the available data are reassuring and there is no sign of a risk of a similar magnitude as that found in the pandemic situation of 1976. A possible association between the pandemic A/H1N1 vaccines and GBS cannot be totally ruled out given the uncertainties in the current information. However, if this association exists, it would probably translate into a very small increase in the risk.

A summary including the conclusions of this meeting was published. It can be found in Appendix 1 of the Sixteenth Pandemic Pharmacovigilance Update, available here.

4.5. Narcolepsy

In Aug 2010, following media attention in Sweden and Finland associating the pandemic vaccine Pandemrix with new-onset narcolepsy, a review was initiated at the request of the European Commission under Article 20 of Regulation (EC) No 726/2004, on 27 August 2010.

The CHMP has reviewed all available data on the suspected link between narcolepsy and Pandemrix. The Committee concluded that the available evidence was insufficient to determine whether there is any link between Pandemrix and reports of narcolepsy, and that further studies were necessary to fully understand this issue. Such study is to be conducted by a network of research and public health institutions (VAESCO) in several EU Member States.

More information is available in the associated press release and updated press release.

5. Status of Human EudraVigilance

During 2010, an average of 62,490 reports (all report types) were received per month and made available for analysis to the EMA and the Member States. During the same period, 190 users from 25 National Competent Authorities (NCAs) have analysed data in the EudraVigilance Data Analysis System (EVDAS). An average of almost 3,000 data analyses using the EudraVigilance Data Analysis System were conducted per month, an increase of 50% compared to 2009. The total number of queries performed by NCAs during 2010 was 35,507. At least 190 different users performed these queries. Availability of the database for analysis by the Member States and the EMA was 96%.

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, which includes all pandemic influenza vaccines for circulation to all Member States and ECDC.

In the context of making the data in EudraVigilance accessible to the Member States and, in the future, all stakeholders, the EMA has been undertaken work in relation to the quality of the Individual Case Safety Reports (ICSRs) reported by NCAs, MAHs and clinical trial sponsors. In addition to performing "data cleaning" of medicinal product data and checking the quality of the reported ICSR data the EMA awarded a contract to perform ICSR data quality checks on data transmitted to EudraVigilance by all stakeholders, to detect and remove duplicate cases from EudraVigilance, to populate the EudraVigilance Medicinal Product Dictionary (EVMPD), to recode the medicinal product data transmitted in ICSRs against the EVMPD and, when required, to translate case narratives into English. This will ensure that all the data in EudraVigilance is of the highest possible quality and consistency, to provide the most accurate possible results for the pharmacovigilance analysis.

In addition to the "data cleaning" efforts undertaken by the EMA on the data currently in EudraVigilance, the EMA has introduced, after consultation with all stakeholders, a series of measures designed to ensure that data received in the future is of the highest standard. These measures, including notifications on expedited reporting compliance, support to pharmacovigilance inspectors, the creation of a Guideline on the Detection and Management of duplicate ICSRs and, in June 2010, enhanced business rules, will further benefit the protection of public health as the analysis of the adverse reaction data in EudraVigilance will be further strengthened. Notifications of compliance with the business rules, which became mandatory in February 2011, were initiated in July 2010.

Looking to the future, 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 the ongoing international standardisation work, and has produced a 3-year development plan (intended to ensure compliance with the new pharmacovigilance legislation and technical developments) which was adopted by the EudraVigilance Steering Committee. The development plan incorporates the following amendments to the system: making the appropriate data available to all EU citizens in line with the revised EudraVigilance Access Policy, upgrading the EVMPD to incorporate the Medicinal Product ID (MPID) fields (see section 5.2.2 for more information relating to the MPID) and upgrading the system infrastructure to ensure, amongst other benefits, compliance with the EMA's Business Continuity Plan.

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

5.1. Current Status of Implementation of EudraVigilance-Human Covering the Period 1 January 2010 – 31 December 2010

The following activities should be highlighted:

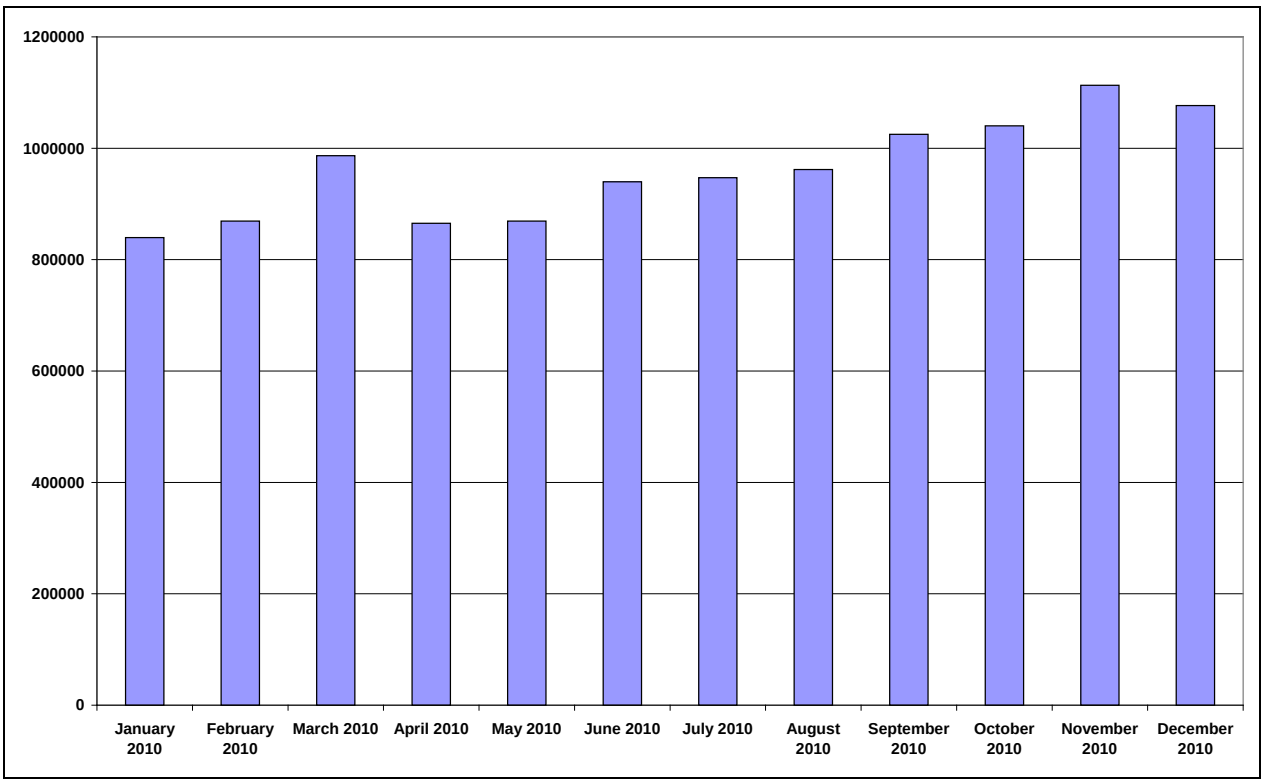
- The continuation of the EVDAS roll-out to the NCAs. The EudraVigilance Support Programme was continued, sending bi-weekly reaction monitoring reports to NCAs to aid routine pharmacovigilance. 14 NCAs are now routinely receiving these monitoring reports for 140 different active substances & 84 medicinal 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; 35,780 backlog cases, both Post-Marketing and Clinical Trials, were submitted during 2010.
- 9 EudraVigilance Expert Working Group meetings and 3 EudraVigilance Steering Committee meeting were held during 2010.
- 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 and a combined and truncated course for pharmacovigilance inspectors was piloted in 2010.

5.1.1. EudraVigilance Gateway

With regard to the reporting period from 1 January 2010 – 31 December 2010 a total of 13,563,388 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 2010, a total of 36,221,355 transactions have been performed.

Figure 1. Figure 1. Total number of transactions performed per month at the level of the eudravigilance Gateway from 1 January 2010 – 31 December 2010.



5.1.2. EudraVigilance Database

5.1.2.1. E-reporting status for MAHs and Sponsors of Clinical Trials

- A total of 448 MAHs (at headquarter level) have sent reports to the EudraVigilance Post-authorisation Module (EVPM) in the period between 1 January 2002 and 31 December 2010.
- A total of 497 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 2010.

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 2010

EV Module	Transmission type	Number of transmissions
EVPM	ICSRs	455,511
	Individual Cases	301,702
	Backlog Cases	8,718
EVCTM	ICSRs	77,532
	Individual Cases	32,567
	Backlog Cases	560

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

Percentage of ICSRs transmitted to EVPM within 15 days:	92.1%

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.

5.1.2.2. E-reporting status for NCAs

- All 31 NCAs have been authorised to enter into production with EV.
- 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 are transmitted direct to EudraVigilance.

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

Table 3. Number of ICSRs and unique cases transmitted by NCAs to EVPM & EVCTM during 2010

EV Module	Transmission type	Number of transmissions
EVPM	ICSRs	196,466
	Individual Cases	121,615
	Backlog Cases	26,477
EVCTM	ICSRs	20,456
	Individual Cases	9,257
	Backlog Cases	25

During 2010, the following 11 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
Germany	Federal Institute for Drugs and Medical Devices
Germany	Paul-Ehrlich-Institut
Greece	National Organisation for Medicines
Hungary	National Institute of Pharmacy
Netherlands	College ter beoordeling van geneesmiddelen
Portugal	Infarmed
United Kingdom	Medicines and Healthcare Products Regulatory Agency

During 2010, the following 6 NCAs transmitted a total of 26,477 backlog cases to EVPM & EVCTM:

Member State	National Competent Authority
Belgium	Federal Agency for Medicines and Health Products
Czech Republic	State Institute for Drug Control
Germany	Federal Institute for Drugs and Medical Devices

Member State	National Competent Authority
Greece	National Organisation for Medicines
Netherlands	College ter beoordeling van geneesmiddelen
Slovenia	Agency for Medicinal Products and Medical Devices

5.1.2.3. 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 2010 a total, including both expedited and non-expedited cases and ICSRs, of:

- 2,752,877 ICSRs were reported to EVPM referring to 1,687,102 individual cases.
- 431,934 ICSRs were reported to EVCTM referring to 166,373 individual cases.

5.1.2.4. 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 2010 a total, including both expedited and non-expedited cases and ICSRs, of:

- 1,081,481 EEA ICSRs were reported to EVPM referring to 651,539 EEA individual cases.
- 1,671,396 non-EEA ICSRs were reported to EVPM referring to 1,035,563 non-EEA individual cases.

5.1.2.5. 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 2010 a total, including both expedited and non-expedited cases and ICSRs, of:

- 223,790 EEA ICSRs were reported to EVCTM referring to 85,027 EEA individual cases.
- 208,144 non-EEA ICSRs were reported to EVCTM referring to 81,346 non-EEA individual cases.

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

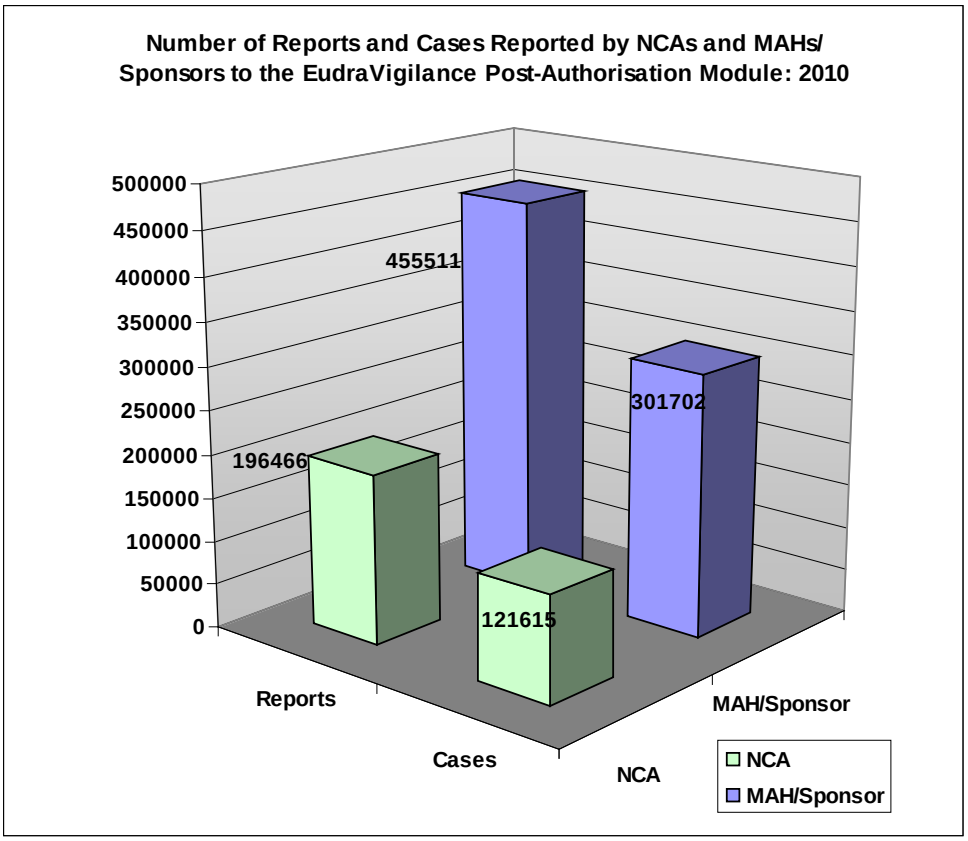


Figure 3. Number of reports and cases reported to EVCTM during the reporting period, excluding backlog

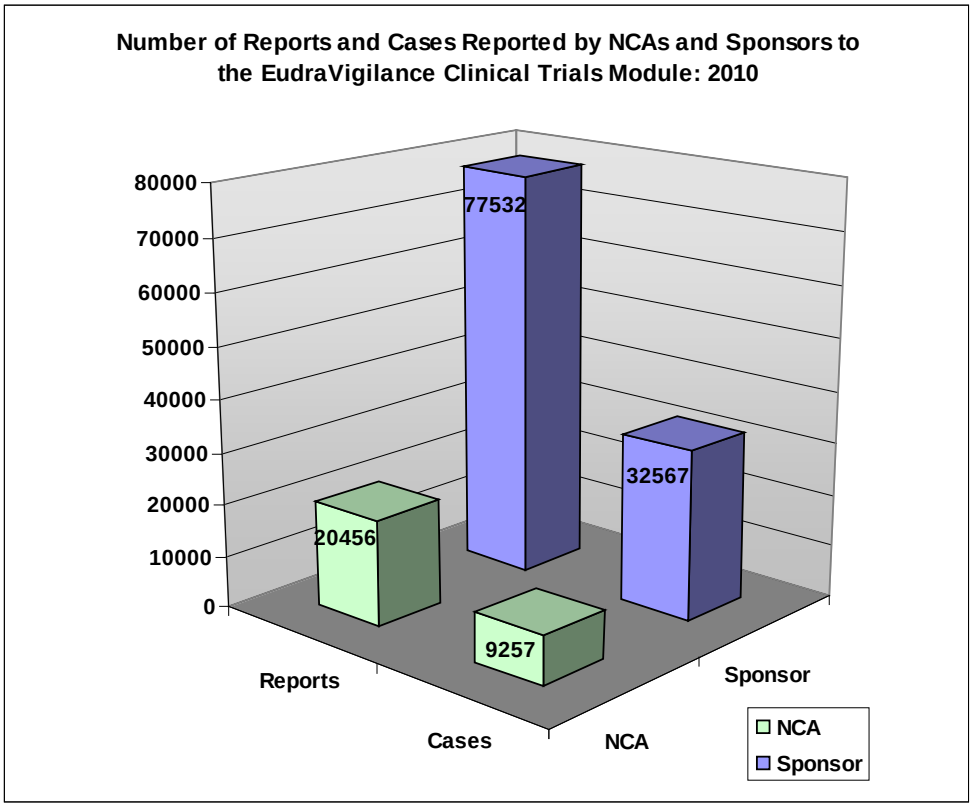
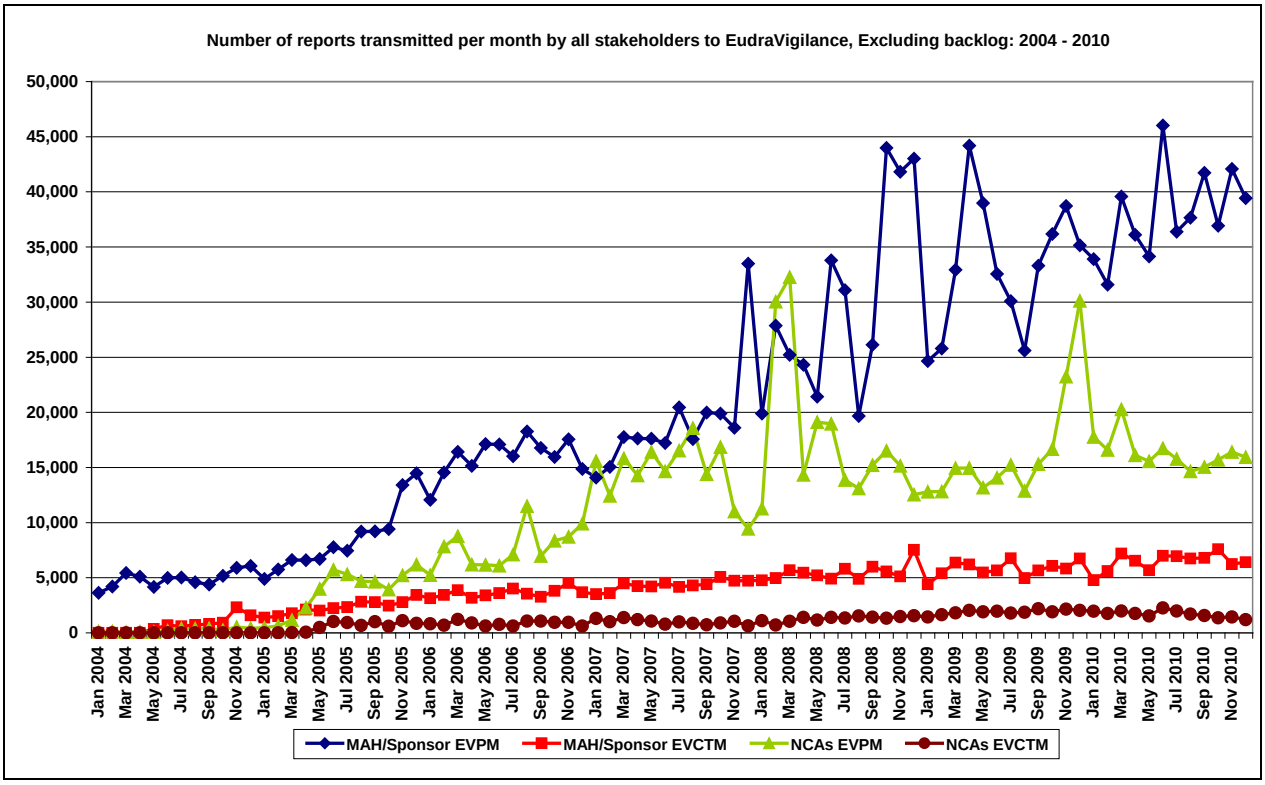


Figure 4. Number of ICSRs submitted per month, excluding backlog



5.1.3. EudraVigilance Medicinal Product Dictionary

During the period 1 January 2010 – 31 December 2010:

- 893 presentations for Investigational Medicinal Products and 21,952 presentations for Authorised Medicinal Products were entered into EVMPD.

In total there are 104,119 valid presentations in the EVMPD.

5.2. EMA Initiatives to Progress with the implementation of EudraVigilance in the Field of Human Medicines

5.2.1. EudraVigilance Datawarehouse & Analysis System Training for NCAs

During 2010, EVDAS training was held at the Agency on 7 occasions, training 51 experts from 19 different NCAs.

During 2010, the numbers of queries run in EVDAS increased by 50% compared with 2009, indicating a significant uptake in the usage of the system.

During 2010, 2 EVDAS training sessions for pharmacovigilance inspectors were held at the Agency.

5.2.2. 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 important developments have occurred:

- May 2010: ISO TC215/WG 6 Plenary Meeting in Rio de Janeiro
  - Resolution approved the release of IDMP Drafts International Standard (DIS) for ballot. The ballot will run between September 2010 and February 2011. Should the DIS pass the ballot that would initiate the final step of the development process.
- October 2010: ISO TC215/WG 6 Plenary Meeting in Rotterdam
  - Resolution approved the release of ICSR Final Drafts International Standard (FDIS) for ballot. The ballot documents to be submitted to ISO no later than February 2011. Assuming that the two month FDIS Ballot results in a positive vote the ISO ICSR standard will be published towards the end of 2011.

5.2.3. EudraVigilance Information Day

Four EudraVigilance Information Days were held during 2010. Two were general EudraVigilance Information days, one specifically covered the forthcoming ISO ICSR standard and one specifically covered the forthcoming ISO IDMP standard.