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Commission Report

Pharmacovigilance related activities of Member States and the European Medicines Agency concerning medicinal products for human use (2012 – 2014)

{COM(2016) 498 final}

EXECUTIVE SUMMARY

- The European Union (EU) Member States, the European Medicines Agency (EMA), and the European Commission work together in a network to support safe and effective use of medicines by patients and healthcare professionals. Safety of medicines is monitored and assessed continuously after marketing.
- New European legislation which came into operation in mid-2012 has been designed to build on and enhance pharmacovigilance in the EU. The **new legislation** has built on existing activities and structures and brought new tools which allow regulators better ways to proactively optimise safe and efficacious use of medicines for the benefit of EU citizens.
- A new EU-level expert committee, the **Pharmacovigilance Risk Assessment Committee** (PRAC), brings together Member State and other experts and patient and healthcare professional representatives, to share effort and best available expertise in many key pharmacovigilance tasks.
- This report describes the development of the system over the period from July 2012 (when the new legislation came into operation) to June 2015, with data collected to the end of December 2014. Some of its key findings are:

  – **Side-effect reporting** has improved, with reporting of suspected adverse reactions from the European Economic Area (EEA) increasing from around 240,000 in 2012 to nearly 290,000 in 2014.

  ❖ all Member States have implemented measures to allow and encourage patients to report side effects as well as healthcare professionals; this strengthened patient involvement is shown by an increase of around 50% in individual patient reports.

  – Member States and the EMA are contributing collaboratively to the detection and validation of **signals** (information about new or changing safety issues potentially caused by a medicine); nearly 200 such signals were assessed by the PRAC during the period of the report. About half of confirmed signals led to updates of the product information, and a further quarter to other regulatory measures.

  – The safety of medicines is increasingly being managed proactively through **risk management plans**. These identify known and potential risks of marketed medicines and the measures planned to manage them, as well as detailing binding commitments on how they will be monitored for safety and actions to be taken to provide evidence where it is lacking.

  ❖ The PRAC is now assessing around 600 risk management plans each year for centrally authorised medicines, while over the period of the report some 20,000 risk management plans have been submitted to the Member States for nationally authorised medicines; and publication of public summaries of risk management plans has been trialled.

  – During the reporting period discussion of the protocols (study designs) for **post-authorisation safety studies** were included in the PRAC agenda on over 230 occasions, and results of such studies were discussed on around 60 occasions. In addition, since the introduction of the relevant legislation some 14 **post-authorisation efficacy** studies have been imposed by the regulator. Member States assessed a further 17 safety studies and one efficacy study.

- Regular re-assessment of the benefit-risk balance of marketed medicines is being carried out via submission of **periodic safety update reports** (PSURs) for assessment by regulators. Member States evaluated over 12,000 PSURs for purely nationally authorised medicines. In addition, the PRAC reviewed and finalised over 900 assessments for centrally authorised medicines, or for active substances used in both centrally and nationally authorised medicines. From the last quarter of 2014 all nationally authorised medicines containing substances listed in the EU Reference Date (EURD) list will have a periodic safety update report single assessment (PSUSA) reviewed by the PRAC and the number of procedures through the PRAC for substances only included in nationally authorised medicines increased significantly in 2015.
- There were 31 **safety-related referrals** to the PRAC during the period. The revised legislation has improved the efficiency of the referral procedure, with greater involvement of patients and other key stakeholders in the process, and improvement in the identification of key evidence for assessment, with outcomes communicated clearly and appropriately.
- Around 200 **pharmacovigilance inspections** have been carried out yearly (167 in 2014) and the proportion of these related to centrally authorised medicines increased over the period from 26 in 2012 to 48 in 2014. It is routine practice for a copy of the pharmacovigilance master file and logbook to be requested in all inspections by the regulatory authorities.
- A clearer focus on **medication errors** is expected to help reduce associated harms. Side-effect reports related to medication errors increased from around 4,500 in 2012 to over 7,000 in 2014, in part because of increased awareness and a clearer legal basis. Member States and the EMA have used various channels to communicate about the risks of medication errors, and in 2013 were involved with key stakeholders in a major workshop to develop an EU action plan to complement the various national activities already being carried out.

- The activity and performance measures relating to the EU pharmacovigilance system, particularly for signals, PSURs and referrals suggest that the new system delivers faster detection of safety issues and faster advice and warnings to users of medicines. Through **faster warnings**, patients and healthcare professionals are empowered to use medicines more safely.
- The EU pharmacovigilance system now provides an unprecedented level of **transparency**, with prompt **communication** to the public on safety concerns regarding medicines as they are investigated and managed. There is public access to the agendas and minutes of the PRAC, outcomes of signals and PSURs, and aggregated data on suspected side effects. An early-notification system (ENS) and circulation of agreed lines-to-take help ensure that messages are co-ordinated and consistent across the EU regulatory network.
- The focus on **engaging patients and healthcare professionals** is a key pillar of the new legislation. Patients and healthcare professionals report suspected side effects, contribute to the decision-making process and add the invaluable perspective of those most affected by diseases and their treatment.
- The EU pharmacovigilance system has **improved co-ordination and collaboration** between regulators and other stakeholders, including academia and industry, and has developed an enhanced infrastructure to support its new tasks.

- The extensive work over the reporting period and the experience gained gives a solid foundation to further **develop and streamline** the system in coming years.

This document builds on the one-year report on the European Medicines Agency human medicines pharmacovigilance tasks published in May 2014[1], which covered the reporting period July 2012 to July 2013 and described the initial implementation of the revised pharmacovigilance legislation with a particular focus on the tasks of the EMA.

This report provides data on key pharmacovigilance tasks over a three-year period (including quantitative data from July 2012 to December 2014) and importantly, given their major contribution, includes Member State tasks. In addition the report provides evidence of the continuing development and improvement of the system as regulators and other stakeholders have gained experience in the use of the tools the legislation provides. It also includes some information on ongoing developments and anticipated future elaborations of the system.

While certain impacts of the tasks of pharmacovigilance are highlighted in this report, it does not attempt to provide a comprehensive impact assessment.

[1] European Medicines Agency. One-year report on human pharmacovigilance tasks by the European Medicines Agency: http://ec.europa.eu/health/files/pharmacovigilance/2014_ema_oneyear_pharmacov_en.pdf.

INTRODUCTION

This report describes the activities of the networked and collaborative system for monitoring and controlling the safety of human medicines in the EU over a period covering three years following the start of operation of new European legislation designed to improve that system.

While the legislation foresees different timelines for reports on tasks of the Member State and of the EMA, reporting on the EMA tasks has been brought forward for this report in order to allow a joined-up overview of the tasks of the EU network.

This report specifically includes quantitative data gathered over the period from July 2012 to December 2014 (the data lock point), but includes information on some relevant tasks and processes over the whole 3-year period up to July 2015. The body of the report gives a summary of the activities with technical data provided in full in annexes. It contains a high-level description of the EU pharmacovigilance system (the system for monitoring and maintaining the safety of medicines in Europe), the roles of various parties within that system, key activities undertaken by the system during the reporting period, discussion of the co-operation between various stakeholders and interested parties, and consideration of the ways in which the system is being developed and adapted for future improvement.

PHARMACOVIGILANCE IN THE EUROPEAN UNION (EU)

What is pharmacovigilance?

> **Pharmacovigilance** is **planned monitoring of the safety of medicines** so that anything that affects their safety profile can be swiftly detected, assessed, and understood and appropriate measures can be taken to manage the issue and assure public health.

Before a medicine is authorised for use, evidence of its safety and efficacy is usually limited to the results from clinical trials. This means that at the time of a medicine's authorisation, it will only have been tested in a relatively small number of patients for a limited length of time.

Some side effects or 'adverse reactions' may only be seen in patients with particular characteristics or may be so rare that they are not seen until a very large number of people have received the medicine and used it over longer time periods. This can only happen once healthcare professionals begin prescribing. It is therefore vital that the safety of all medicines is monitored throughout their use in healthcare practice. This monitoring applies both to the hundreds of **centrally authorised medicines** (CAPs, those with a single marketing authorisation adopted by the Commission which is valid across the EU on the basis of an evaluation by the EMA) and to the many thousands of **nationally authorised medicines** (NAPs, authorised in particular Member States following national evaluation procedures including the mutual recognition and decentralised procedures).

The EU network

Over the years the EU Member States have developed systems for monitoring the safety of medicines on their markets. EU legislation has gradually built on their best practice to create a networked system that joins the knowledge and resources of the Member States together, co-ordinated and supported by the EMA, with the European Commission providing the legal authority and legislative tools that the system requires.

Regulatory context

The legislation

The legal framework of pharmacovigilance for medicines for human use marketed within the EU is provided for in Regulation (EC) No 726/2004[2] and in Directive 2001/83/EC[3], as amended. These were updated by the new pharmacovigilance legislation contained in Regulation (EU) No 1235/2010[4] and Directive 2010/84/EU[5], which entered into force from July 2012 and were further refined by Regulation (EU) No 1027/2012 [6] and Directive 2012/26/EU [7] which provided strengthened measures for monitoring medicines safety and carrying out reviews at a European level.

In addition in 2012 the Commission Implementing Regulation (EU) No 520/2012[8] laid down the rules concerning the roles and responsibilities regarding certain aspects of pharmacovigilance for marketing authorisation holders, national competent authorities and the EMA.

Member States and the EMA have also produced, in consultation with relevant stakeholders, good pharmacovigilance practice guidelines (GVP) [9] which explain in detail how pharmacovigilance activities should be carried out.

The role of the Member States

The individual Member States of the EU power the entire system. The national medicines regulators (**national competent authorities**) supervise the collection of information on suspected side-effects of medicines, particularly spontaneous reports from patients and healthcare professionals. Equally, they provide much of the resource base and knowledge needed to assess signals of possible emerging side effects. Member State experts also take the lead (as the so-called rapporteur and co-rapporteur teams) in evaluating and analysing data when a safety issue is assessed at the European level (a referral). They play a critical role in tailoring and communicating safety messages to healthcare professionals, patients and the public at a national level.

Member States also maintain the inspectorates that carry out the work of ensuring that medicines marketed in the EU are manufactured appropriately and are of suitable quality, that the pharmacovigilance systems of industry are working as they should, and which check that the

[2] Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, OJ L 136, 30.4.2004, p. 1.
[3] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, OJ L 311, 28.11.2001, p. 67.
[4] Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) No 1394/2007 on advanced therapy medicinal products, OJ L 348, 31.12.2010, p.1.
[5] Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use, OJ L 348, 31.12.2010, p. 74.
[6] Regulation (EU) No 1027/2012 of the European Parliament and of the Council of 25 October 2012 amending Directive 2001/83/EC as regards pharmacovigilance, OJ L 316, 14.11.2012, p. 38.
[7] Directive 2012/26/EU of the European Parliament and of the Council of 25 October 2012 amending, as regards pharmacovigilance, Directive 2001/83/EC, OJ L 299, 27.10.2012, p.1.
[8] Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council, OJ L 159, 20.6.2012, 0.5.
[9] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp

clinical studies that provide the evidence of the safety and effectiveness of medicines are performed in line with appropriate standards.

The role of the European Medicines Agency (EMA)

The EMA has a central role the EU system, co-ordinating its activities and providing technical, regulatory and scientific support to the Member States and industry. It also provides essential infrastructure required by the system and has specific tasks laid down in the legislation in the conduct of pharmacovigilance including signal detection for centrally authorised products.

The new EU pharmacovigilance legislation established an additional scientific committee, the **Pharmacovigilance Risk Assessment Committee** (**PRAC**), whose members include experts in pharmacovigilance and regulation working within the national competent authorities of the Member States (plus Iceland and Norway), representatives of patients and healthcare professionals, and scientific experts in areas such as epidemiology, signal detection, biological medicines and risk communication nominated by the European Commission. The PRAC meets monthly and is responsible for the assessment of safety issues at EU level. It also monitors many of the pharmacovigilance activities foreseen in the legislation. It works closely with other scientific committees, especially the Committee for Medicinal Products for Human Use (CHMP) which leads on centrally authorised medicines, and also with the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), a body representing the national regulators of the EEA, which leads on many issues relating to nationally authorised medicines.

The staff of EMA develop and maintain various essential databases and information technology (IT) functions that support the system, in particular a database called **EudraVigilance** that is used to collate worldwide reports of suspected side effects (adverse reactions) and underpins the detection of potential signals regarding side effects and their analysis. The EMA also supplies specialist scientific, legal and regulatory knowledge to support activities such as safety reviews, and helps ensure that communications about safety issues are provided in a timely, transparent and co-ordinated fashion across the EU.

The role of the Commission

The European Commission is the competent authority for centrally authorised products and supplies the legal authority that underpins the EU pharmacovigilance system. It provides the legislative framework needed to carry out its functions in the most efficient way.

Tasks and procedures

Key tasks carried out by the network for the purpose of pharmacovigilance include:

- assessing the known and potential risks of each medicine before marketing and developing plans to collect data and minimise those risks (risk management planning);
- collecting and managing case reports of possible side effects (adverse drug reactions);
- analysing reports of side effects to identify signals (signal management);
- routine benefit-risk monitoring of medicines via periodic safety update reports (PSURs) and maintaining the EU Reference Date (EURD) list of when they should be submitted;
- managing information on products which are subject to additional monitoring, and products that have been withdrawn;
- Europe-wide reviews of important safety and benefit-risk issues (referrals);
- assessing and co-ordinating studies after marketing (post-authorisation safety studies, post-authorisation efficacy studies);

- carrying out inspections to ensure company pharmacovigilance systems comply with good pharmacovigilance practice;
- communicating in a clear, effective and timely manner about safety-related issues to relevant stakeholders;
- continuous development and improvement of systems (including IT infrastructure), guidelines and standards for the system, and promotion of research to address gaps in knowledge;
- interacting with and engaging key stakeholders, including patients, healthcare professionals, the pharmaceutical industry, other parts of the regulatory system (including international regulators), academia, the media, global standards bodies, and wider civil society;
- monitoring the performance of the system and its components, including compliance with legal obligations and standards;
- training and capacity building.

SOURCES OF DATA

Information regarding Member State activities has been supplied by the national competent authorities of the different countries (*see Annex 10*), and includes data from the SCOPE project[10], funded as a Joint Action by the European Commission and co-ordinated by the UK Medicines and Healthcare products Regulatory Agency (MHRA). Data on centralised activities, particularly those carried out by the PRAC and some other areas such as side-effect reporting, has been collected by the EMA in its co-ordinating role within the EU network.

Qualitative information, including some descriptive case studies, is included in the report in order to illustrate the way the legislation works at the level of individual issues and to demonstrate the experiences of stakeholders.

How was it measured/analysed?

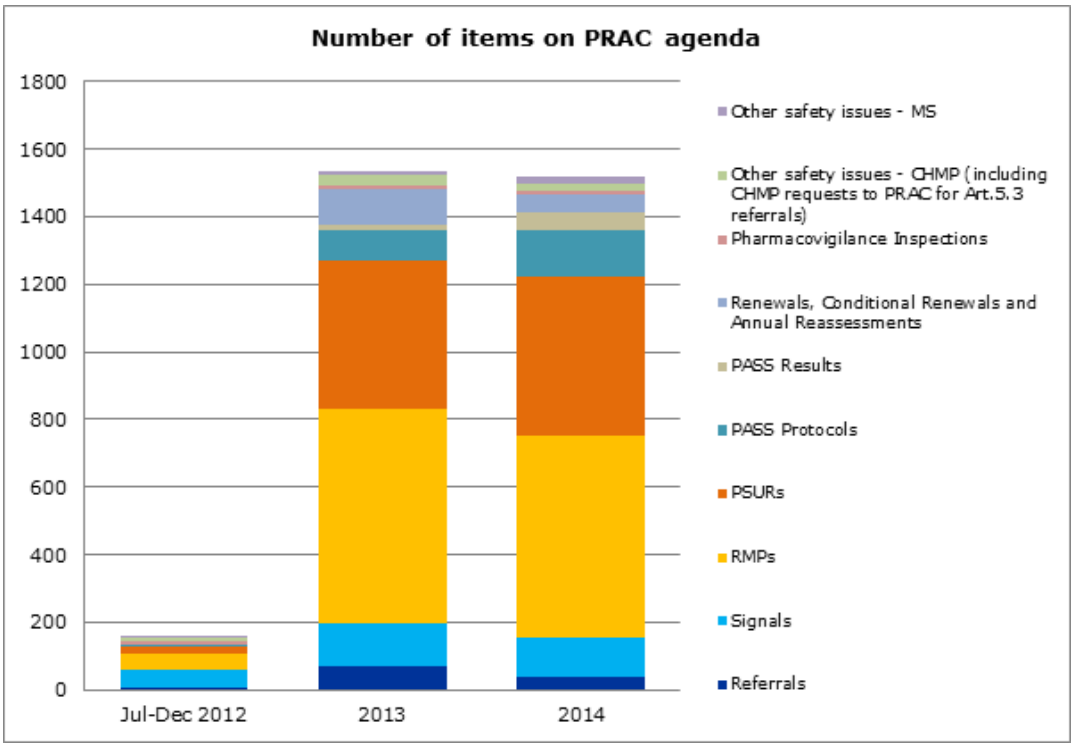
The quantitative data for the report covers the period from July 2012 to December 2014 (the data lock point). Measures of relevant tasks are provided using a variety of indicators. Some represent basic activity measurements, e.g. simple counts of numbers of procedures or submissions. Others have been used as part of the pharmacovigilance system governance by the EMA, including key performance indicators, which have been specifically developed to measure how well it is carrying out its tasks and to reflect specific outputs required by the new legislation.

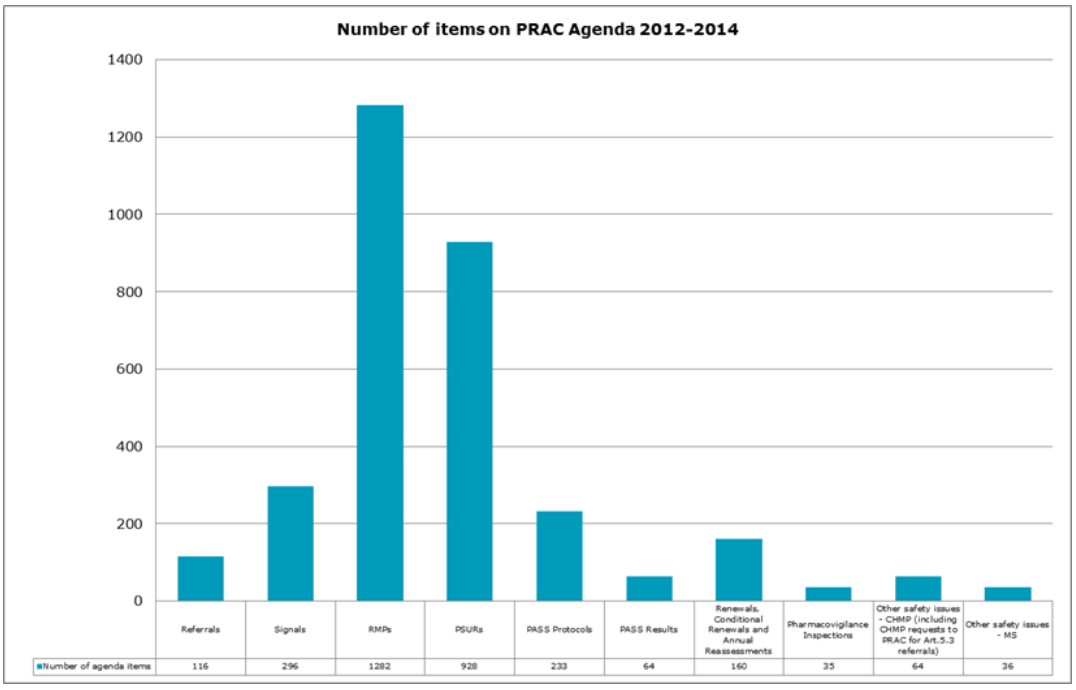
[10] Strengthening Collaboration for Operating Pharmacovigilance in Europe, an EU-funded Joint Action project involving regulators from 23 EU Member States plus Norway and Iceland.

OVERVIEW OF KEY ACTIVITIES

A number of key pharmacovigilance activities over the period from July 2012 to December 2014 (the data lock point), or in some cases over the whole 3-year period up to July 2015, are described in more detail in the following sections.

Since establishment of the PRAC by the new legislation, the EU pharmacovigilance network carries out many of these activities in this forum, allowing broad access to expertise and a consistent and resource-efficient approach to medicines safety across the EU. The relative frequency with which various pharmacovigilance activities appear on the PRAC agenda is indicated by the figures below (*see also Annex 9*).



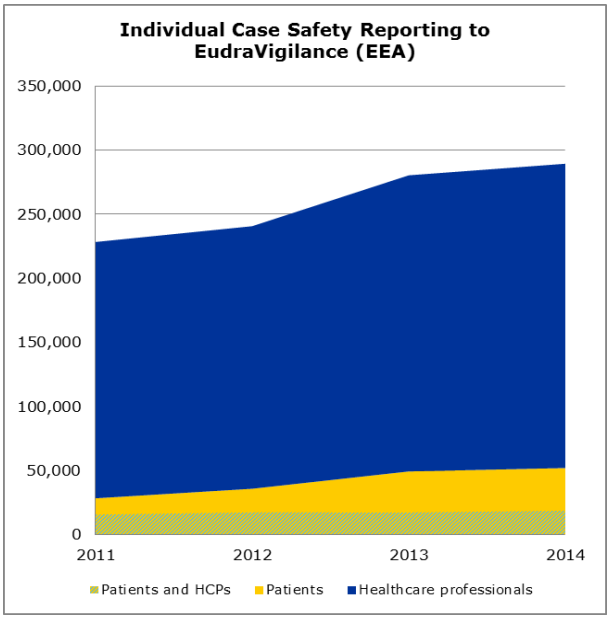


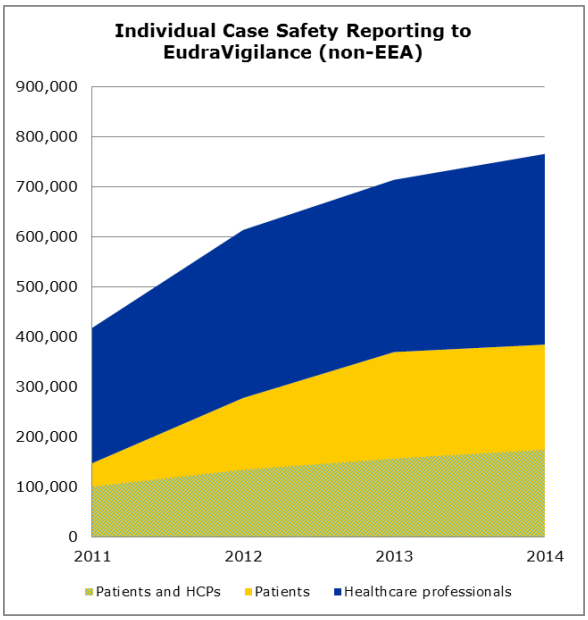
Side effect reporting

see also Annex 1

Reports of suspected side effects (**adverse reactions**) submitted by patients and healthcare professionals are collected by the national competent authorities of the Member States or by industry. EU law requires all **serious adverse reactions** occurring in the EEA to be included in the EudraVigilance database by the Member States and marketing authorisation holders. The latter are also required to include serious reports gathered outside the EEA in EudraVigilance. An **ICSR** (**individual case safety report**) is the standardised format used by regulators for reports of suspected adverse reactions (side effects) or problems with the safety and quality of medicines.

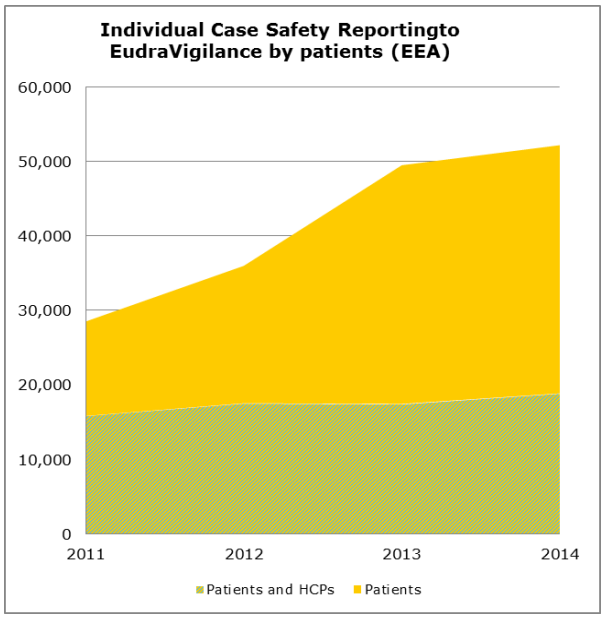
The number of serious adverse reactions (SARs) received by EudraVigilance (EV) has been used as the measure of adverse drug reaction (ADR) reporting. Reports of ADRs following the authorisation of medicines (i.e. postmarketing) from the EEA have increased steadily following the implementation of the new legislation, from around 240 000 in 2012 to nearly 290 000 in 2014. There has also been an increase in similar reports from outside the EEA.

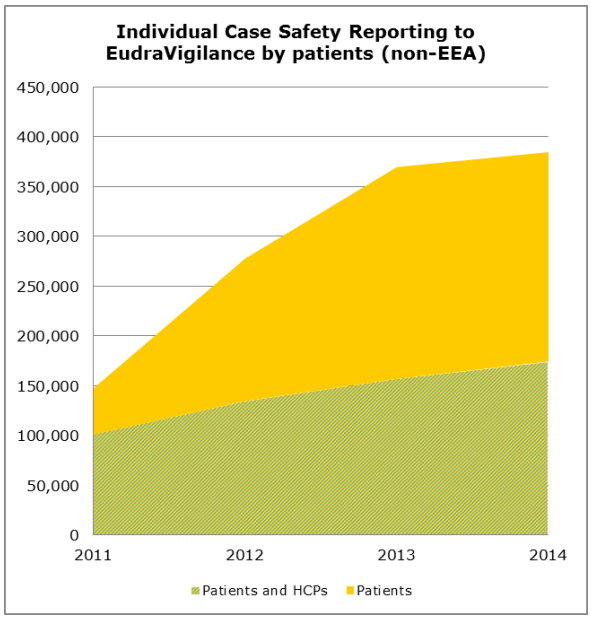




One of the aims of the legislation was to **strengthen patient involvement** in the safety monitoring of medicines. All 28 Member States have patient reporting systems in place, with the majority introducing them in 2012/13 (although the first of them to introduce this process did so in 1968 and the second in 1996). Overall, the number of individual patient reports from the EEA has increased over the two and a half years of the reporting period by around 50%. This includes ADR reports not notified by other reporters such as healthcare professionals, which represent information that would not otherwise be captured

Data on national activities in this area has been obtained from a survey of the Member States carried out via the SCOPE Joint Action. In 24 Member States patients can report via mail, in 21 via e-mail, 20 through fax and web-based forms, and in 19 via telephone. One also specified mobile reporting, and 2 others that patients can report in person. Most (22) Member States have more than one type of reporting form, with the majority having 2 different types of forms for different users (such as patients and healthcare professionals).





The Member States make patient reporting forms available through a variety of sources; the most common source, aside from national competent authorities, are regional centres (8 Member States), patient organisations (7), marketing authorisation holders (7) and healthcare websites (6). In addition paper forms are made available via pharmacies in 7 Member States.

The single most important tool for encouraging side-effect reporting is institutional webpages. However, 23 Member States also use educational material and letters for healthcare professionals, and 20 Member States make information publicly available in annual reports.

In addition, nearly a third (28%) of Member States engage with the media (through advertising hoardings, radio, television, internet, newspapers) in side-effect reporting campaigns. Engagement via regional centres, e-learning platforms, and social media like Facebook and Twitter (in 4 Member States) is less frequent.

The majority (64%) of Member States have a strategy in place to raise awareness about reporting, although only a third of the countries have a specific budget dedicated to raising awareness.

About 40% of Member States have organised a public campaign about reporting side effects, with 62 campaigns in total across all the countries. During campaigns, Member States primarily collaborate with healthcare professional organisations, and to a lesser extent with patient organisations. Campaigns have focussed on a number of areas, the top three being: the importance of reporting; content of reports; and, highlighting the schemes in place for reporting.

Some Member States work with patient organisations to facilitate side effect reporting. The number of patient organisations involved per Member State varies from 1 to 20. For example, in Denmark the regulator holds meetings with all major patient organisations.

The Member States, the EMA and marketing authorisation holders work collaboratively to **improve the quality** of suspected ADR reports. This includes the use of technology to support reporting (e.g. web forms), training, quality review and feedback, follow-up with reporters and detection and amalgamation of duplicate reports. During 2013 and 2014, over 250 000 potential duplicate couples of case reports were assessed and approximately 110 000 merged 'master' ICSRs were created.

Suspected side effects due to biological medicinal products

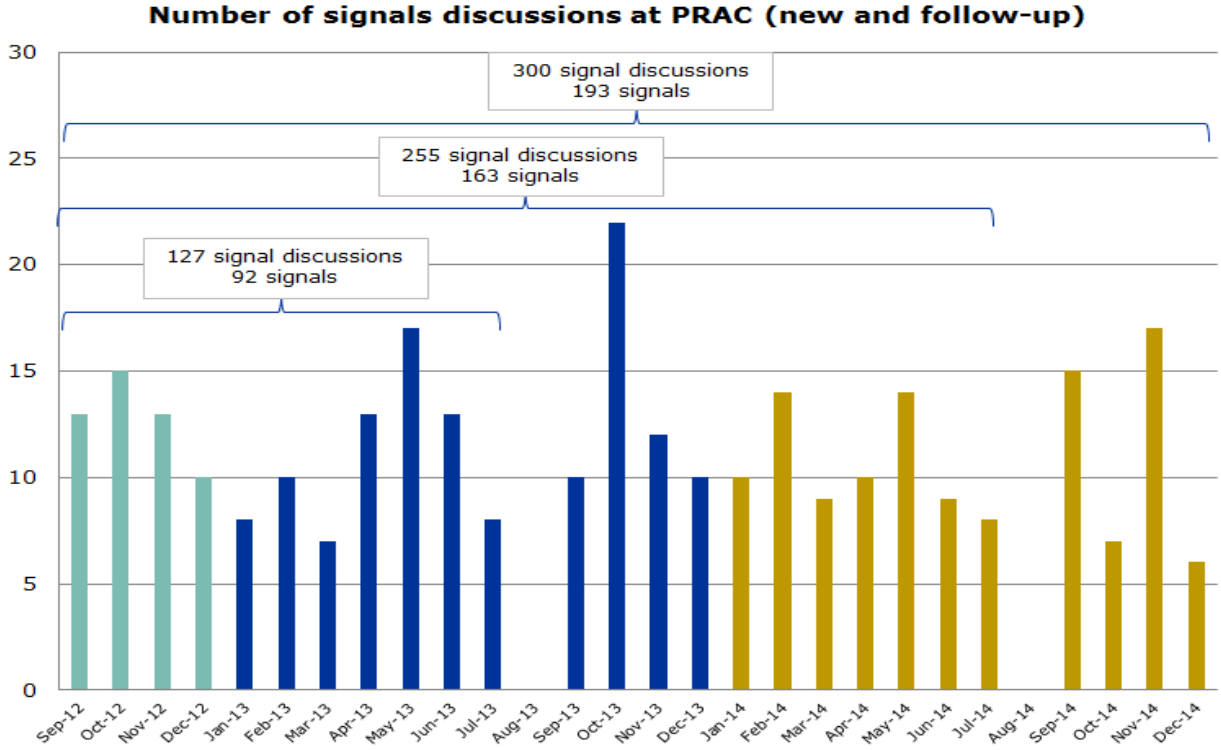
EU legislation requires Member States to clearly identify so-called biological medicinal products (medicines that contain one or more active substances made by or derived from a biological source) that are associated with suspected adverse reactions. These active substances are larger and more complex than those of nonbiological medicines, and their complexity and the way they are produced may result in small variations in the molecule, especially between different brands and also between batches of the same brand.

The numbers of ICSRs received for biological centrally authorised products over the period increased slightly from around 34 500 in July-December 2012, 73 000 in 2013 and 77 500 in 2014. Most Member States require the batch/brand in reporting forms, and if not present, will generally follow up with the reporter.

Signals

see also Annex 2

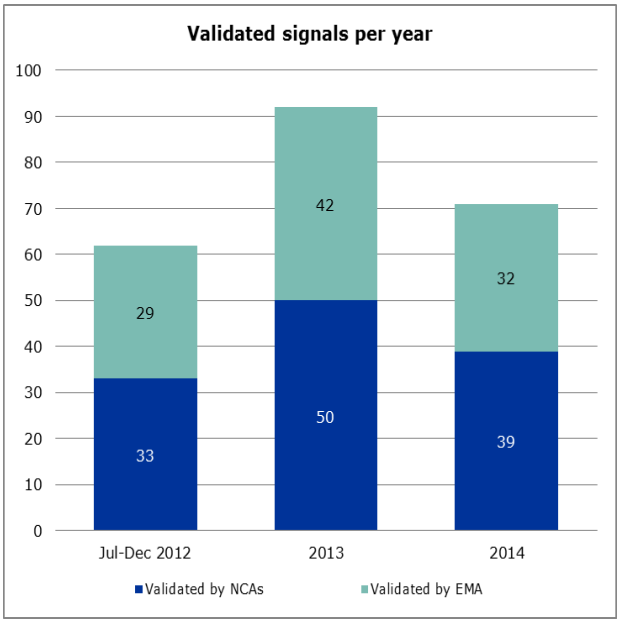
A safety **signal** is information on a new or known adverse event that is potentially caused by a medicine and that warrants further investigation. Signals may be generated from any information source but most come from ICSRs, clinical studies or the scientific literature. This information undergoes an initial examination to determine that it can be considered a possible signal (validation), before being confirmed as a possible signal for evaluation by the PRAC and regulatory action if necessary.

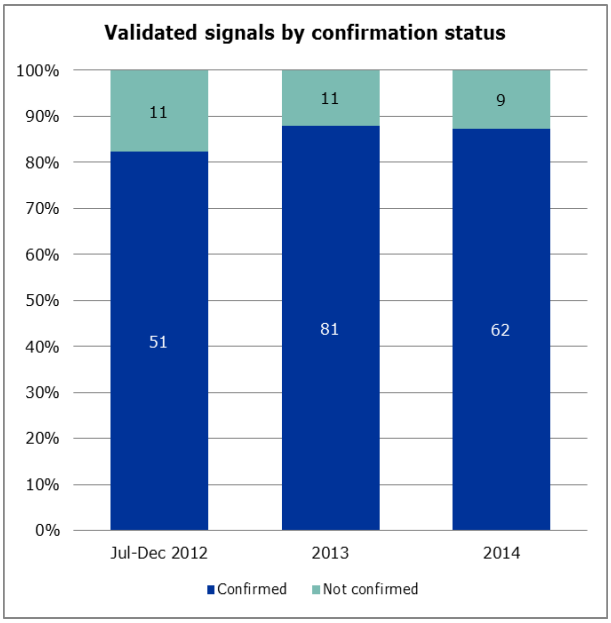


The work of detecting signals is shared between the Member States and the EMA. Since July 2012, revised signal detection processes have been put in place for all centrally authorised medicines. For active substances in nationally authorised medicines, Member States have shared between them the task of monitoring new data and validating and confirming signals on behalf of

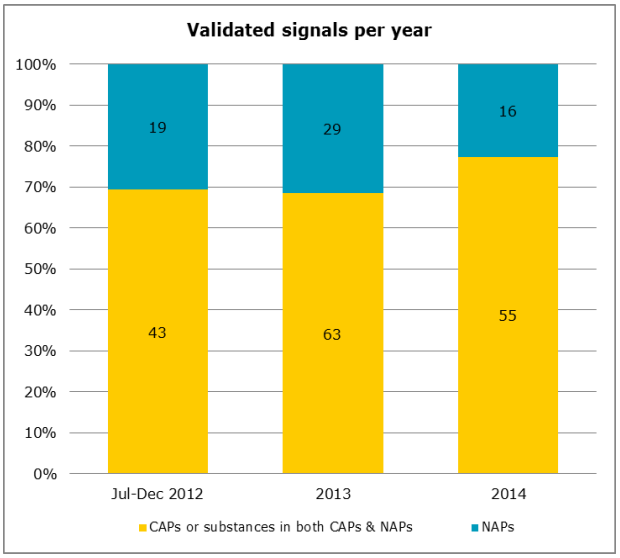
the rest of the EU system, with EMA supporting them in applying the new signal detection processes. Each country may be Lead Member State (LMS) for a number of active substances. This allows the different Member States to contribute according to their resources and permits more efficient use of those resources by avoiding duplication and clearly defining responsibilities.

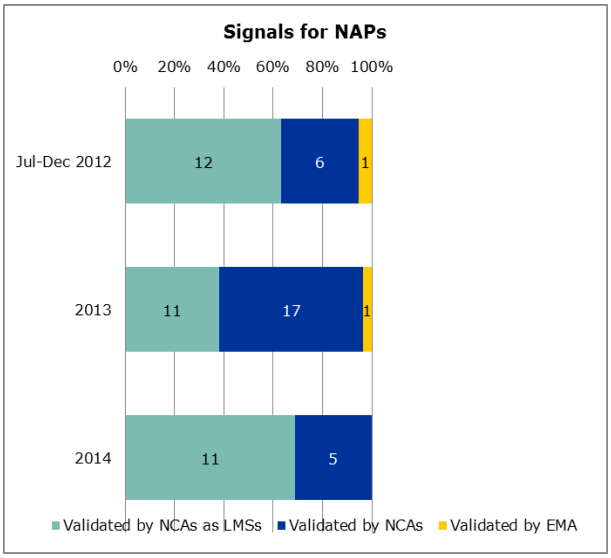
Some 193 unique signals were evaluated by the PRAC over the period of this report. The work of validation was shared more or less evenly between the Member States and the EMA.





Over two-thirds of signals are for substances found in centrally authorised products, or in both centrally and nationally authorised products, which would include the great majority of new active substances entering the EU market.

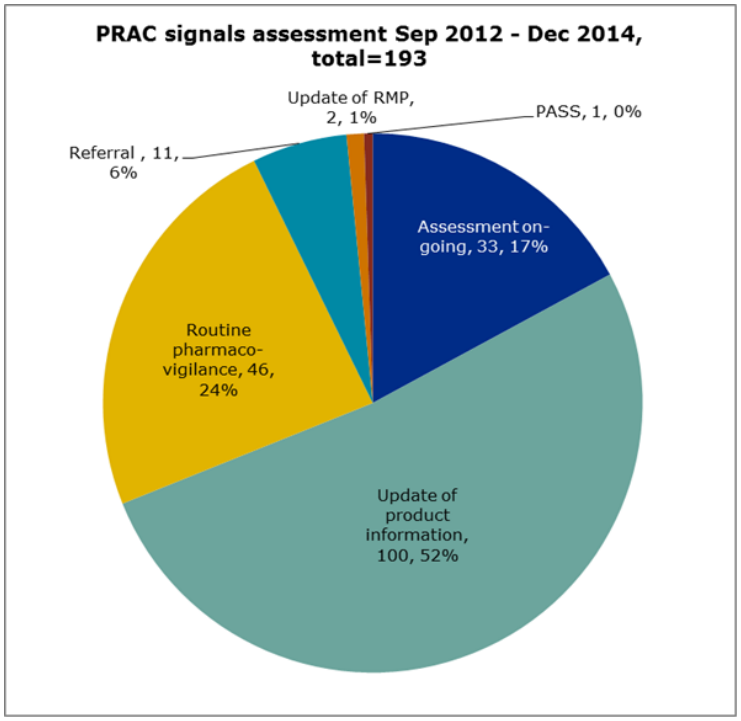




Validated by NCAs as LMS = reviewed by the lead Member State (the Member State taking the lead on a given active substance); validated by NCAs = reviewed by another Member State; validated by EMA = reviewed by the European Medicines Agency

After a signal is evaluated by the PRAC, it may result in an update of the product information for the medicine(s) concerned – for example, to add a warning or mention a new side effect, or to update information on the frequency of a known one – or the regulatory authorities may require the manufacturer to carry out further study, or put in place additional measures to minimise any risk. A list of signal recommendations is published after each meeting of the PRAC[11].

Over the reporting period and up to the start of 2015, about half of all confirmed signals evaluated by the PRAC resulted in recommendations to update the product information (PI) used by doctors and patients, and a further quarter to other routine pharmacovigilance measures such as changes to frequency or content of periodic safety update reports, while about 1 in 20 led to more intensive action in the form of a European-level safety review or 'referral'.



The functioning of the signal assessment process under the legislation can be illustrated by two case studies, one representing a signal picked up by routine signal monitoring activities at the EMA and one a signal first identified by a Member State.

Case study: Filgrastim and pegfilgrastim (Neulasta and other products) – signal of systemic capillary leak syndrome and cytokine release syndrome

What was the signal and what evidence supported it?

Filgrastim, or its modified, longer-acting version pegfilgrastim, are substances similar to a natural protein called granulocyte colony-stimulating factor (G-CSF) which encourages the bone marrow to produce more white blood cells. They are used under various names, representing both centrally and nationally authorised products, to help reverse a shortage of white blood cells (neutropenia) that can be caused by cancer chemotherapy and which leaves patients vulnerable to infection.

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

In 2012, routine signal monitoring activities by the EMA identified 15 cases of two potentially life-threatening conditions, systemic capillary leak syndrome and cytokine release syndrome, in patients treated with these medicines. After discussion with the rapporteur for the centrally authorised pegfilgrastim product Neulasta, the PRAC was requested in December 2012 to assess the signal.

How was it evaluated?

The PRAC agreed the signal needed further investigation and noted that the two conditions might be hard to distinguish. It asked the company holding the marketing authorisation to systematically review the scientific literature and provide within 60 days an analysis of all reports of either condition in patients receiving filgrastim or pegfilgrastim for assessment by the rapporteur (UK).

On the basis of this assessment and the PRAC discussion the Committee considered that there was fairly strong evidence that systemic capillary leak syndrome was associated with treatment with filgrastim or pegfilgrastim, and that given the potential seriousness of the condition there was a need to inform prescribers of the risk. The evidence for a link with cytokine release syndrome was more limited, but needed to be kept under review.

What action was taken?

As a result of its evaluation, in March 2013 the PRAC recommended[12]:

- the update of the product information (for both centrally and nationally authorised products) within 30 days to include a warning of the potential risks;
- the preparation of a letter for healthcare professionals explaining the changes to the product information and the possible risks of the condition;
- the update of the risk management plan to include systemic capillary leak syndrome as an important identified risk and cytokine release syndrome as a potential risk, with appropriate ongoing monitoring.

Conclusions

The system enables effective detection of new side effects and rapid action to manage them.

Case study: Basiliximab (Simulect) – signal of cardiovascular instability resulting in fatal outcome associated with off-label use in cardiac transplantation

What was the signal and what evidence supported it?

Basiliximab (Simulect) is a centrally authorised medicine approved for use as part of combination treatment to prevent rejection of a transplanted kidney. It contains the active substance basiliximab, an antibody that reduces proliferation of activated T-lymphocytes, a type of white blood cells that play a major role in rejection of a transplanted organ.

In 2013 the Swedish Medicines Agency identified 3 cases of patients who had died when basiliximab was used outside its approved uses (off-label) to help prevent rejection of a transplanted heart rather than a kidney. A search in EudraVigilance also identified cases of heart failure and cardiac arrest in patients who had been given basiliximab for its approved indication. Sweden requested that the PRAC assess the signal.

[12] Pharmacovigilance Risk Assessment Committee. Minutes of 4-7 March 2013 meeting. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2013/04/WC500142504.pdf.

How was it evaluated?

The PRAC agreed that the signal needed further investigation. It asked the company holding the marketing authorisation for an initial analysis of all cases describing events due to clots obstructing blood vessels (thromboembolic events), disorders of heart rhythm (arrhythmia, bradycardia), or heart failure. Subsequently it requested further analysis of effects on the heart and data from studies in heart transplantation.

The PRAC found that data from studies in renal transplantation and from the literature were reassuring when the medicine was used for its authorised indication. However, although the evidence did not show a strong signal of increased heart risk in patients undergoing heart transplantation, data from 6 clinical trials which were examined did not indicate benefit in these patients.

What action was taken?

As a result of its evaluation, the PRAC recommended that[13]:

- the product information be updated within 60 days, to include a warning about use in heart transplantation, advising healthcare professionals that benefit had not been demonstrated and that serious effects on the heart had been reported more often than with other anti-rejection medicines;
- a letter be sent to remind heart surgeons and doctors in heart transplant centres in the EU that basiliximab is only approved for use in kidney transplantation;
- the risks of effects on the heart be included in the risk management plan for the product and to be included in regular ongoing safety monitoring (PSURs).

Conclusions

Signal evaluation by the PRAC offers a new instrument for early interventions on safety issues, increasing the flexibility present in the system and improving its response time.

Risk management plans

see also Annex 3

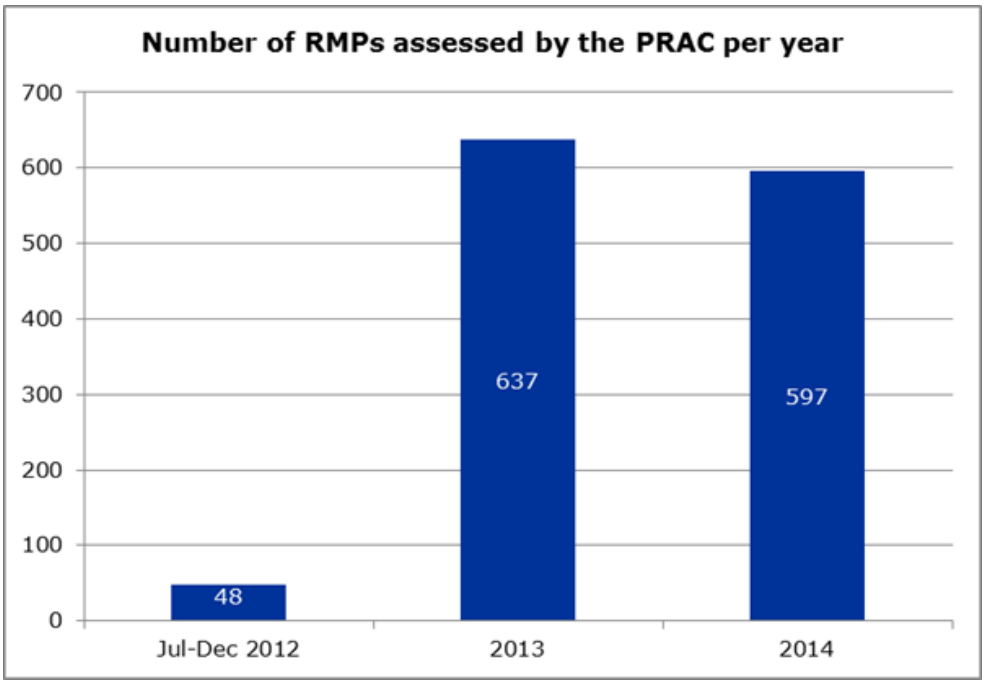
Every medicine approved for marketing in the EU is now required to include a **Risk Management Plan** (**RMP**) as part of the dossier submitted by the company. The plan identifies known and potential safety issues with the medicine, and includes binding commitments on how the medicine will be monitored for safety during its lifetime. It also identifies the actions that will be taken to minimise the risks and provide evidence where it is lacking, so as to ensure the most favourable balance of risks against the medicine's benefits.

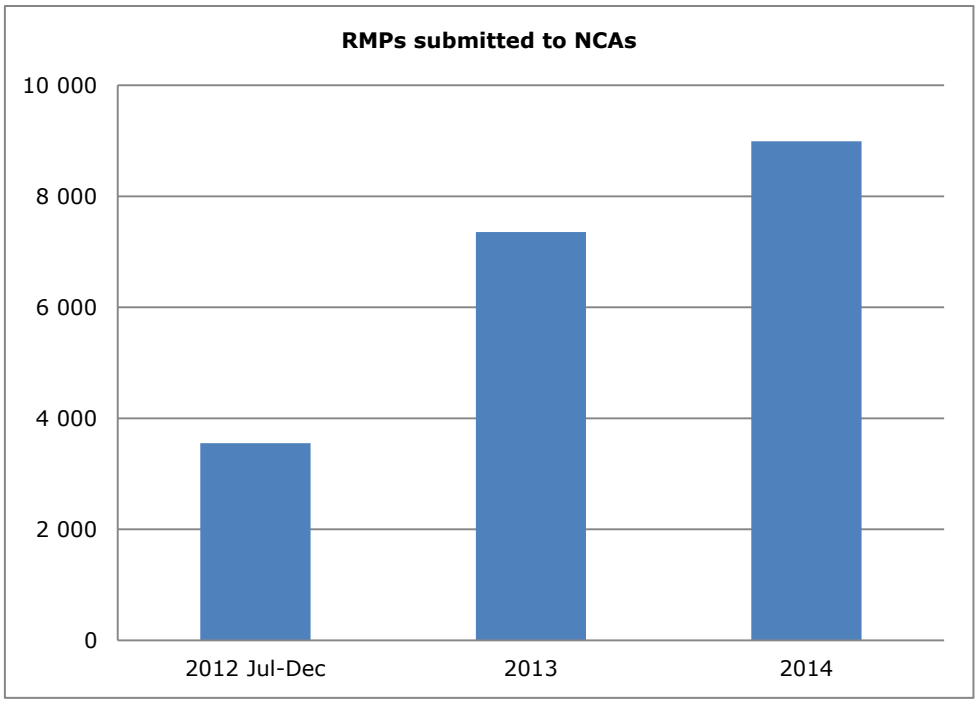
Risk management plans for centrally authorised medicines are reviewed by the PRAC, with initial detailed evaluation by assessors in the Member States who take the lead in evaluating the medicine, and approved by the CHMP. RMPs for nationally authorised medicines are evaluated at Member State level with consultation of the PRAC only at the request of a Member State.

[13] Pharmacovigilance Risk Assessment Committee. Minutes of 3-6 February 2014 meeting. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2014/03/WC500163384.pdf.

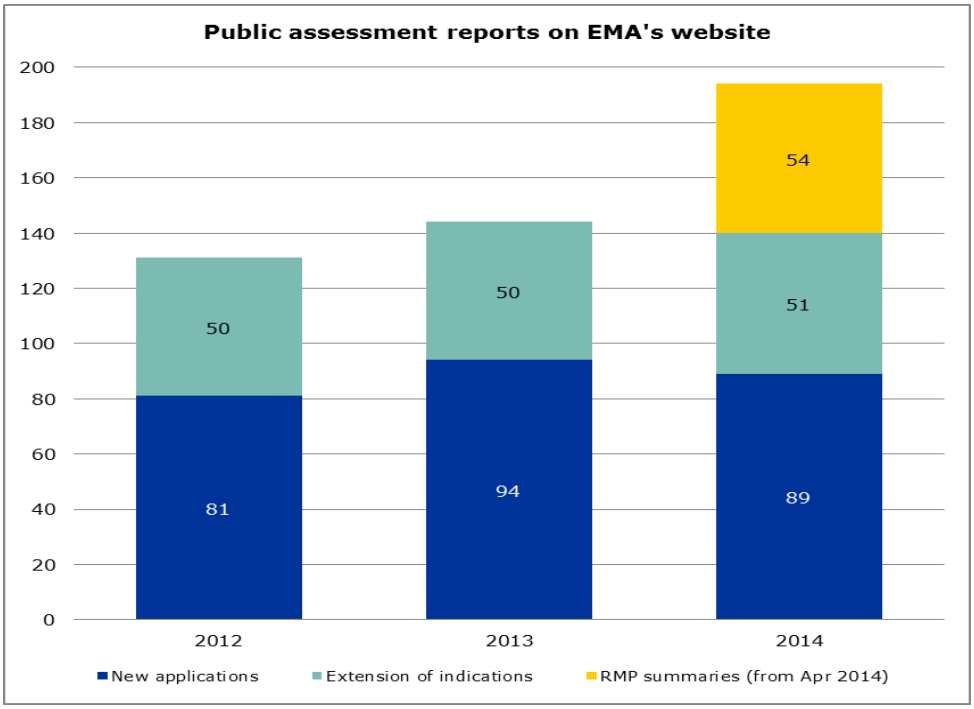
Risk management plans represent an important part of the move to proactive pharmacovigilance. Every new medicine and significant extension of indication approved during the reporting period has a risk management plan, meaning that a binding plan for risk minimisation and further study, as envisaged by the legislation, is in place for these products.

There were 48 RMP assessments handled by the PRAC during June-December 2012, 637 in 2013 and 597 in 2014, representing about 20% of the discussion time in the meetings of the PRAC. During the same period, around 3 500, 7 500, and 9 000 RMPs respectively were submitted to the Member States for nationally authorised medicines.





The complete risk management plan is a very lengthy technical document, and is not published in full. However, public assessment reports are required to be published for all marketing authorisations for new medicines and significant extensions of indication for existing medicines, and these include discussion of the safety and relevant risk management aspects. To further increase transparency and, as required by the updated legislation, to provide information on RMPs to the public, a pilot of the publication of summaries of the RMP plan was carried out in 2014. For further details, see the section on Communications and Transparency, below.



Periodic safety update reports

see also Annex 4

European legislation requires marketing authorisation holders to submit regular reports providing an evaluation of the benefit-risk balance of a medicine. These periodic benefit-risk evaluation reports (PBRERs), known as **periodic safety update reports** (**PSURs**), must be submitted for both centrally and nationally authorised medicines at defined time points following a medicine's authorisation. They include the results of studies carried out with the medicine, as well as any other new information on safety or benefits, and cover both authorised and unauthorised uses.

The information is reviewed by the PRAC to determine if there are new risks identified for a medicine or whether the balance of benefits and risks of a medicine has changed. If it has not, then the marketing authorisation can be maintained, but the PRAC can also decide if further investigations need to be carried out or can take action to protect the public from any new risks identified, such as updating the information provided for healthcare professionals and patients through a variation, or potentially even suspending

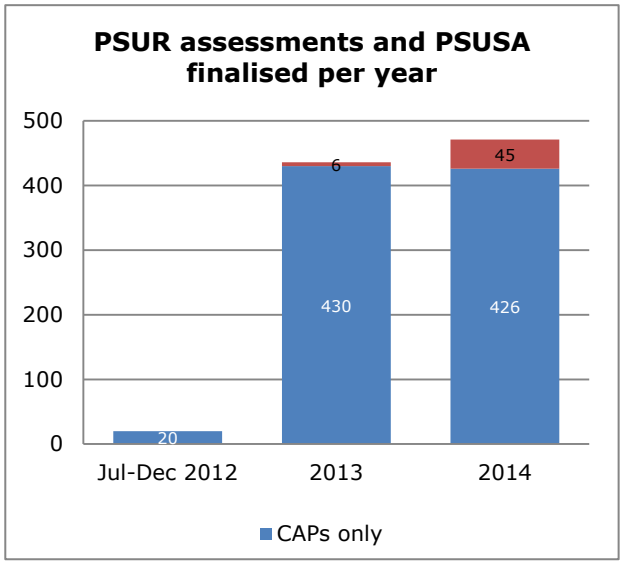
or revoking the authorisation. A list of dates for submission of PSURs (the EURD list) is made available on the EMA website[14].

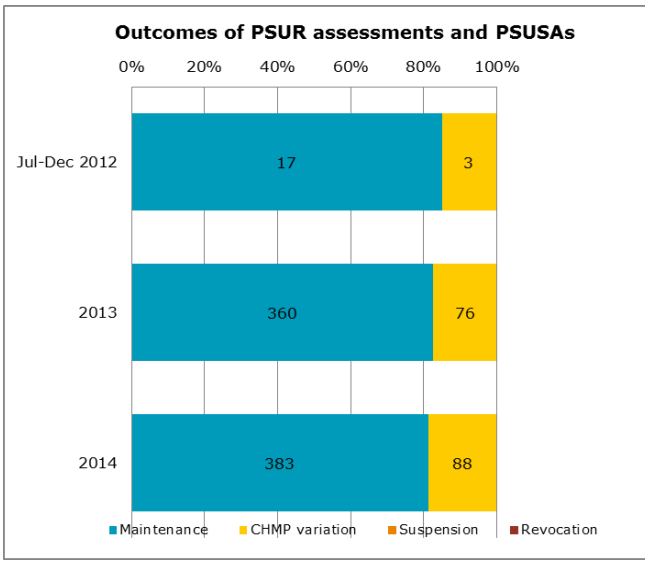
A single assessment of related PSURs (known as a **PSUSA**) is carried out for medicines that contain the same active substance or combination of active substances and whose assessment period has been synchronised. This allows for more efficient use of resources and also ensures that these related medicines are evaluated in a consistent way.

The regular re-assessment of benefit-risk represented by the PSURs is a fundamental part of ensuring the safe use of medicines for EU citizens; it ensures that the benefit-risk balance is regularly monitored, with appropriate action where needed, but also allows the regulatory burden to be proportionate to the risks, with more frequent assessments where the PRAC deems necessary, for example for newer medicines.

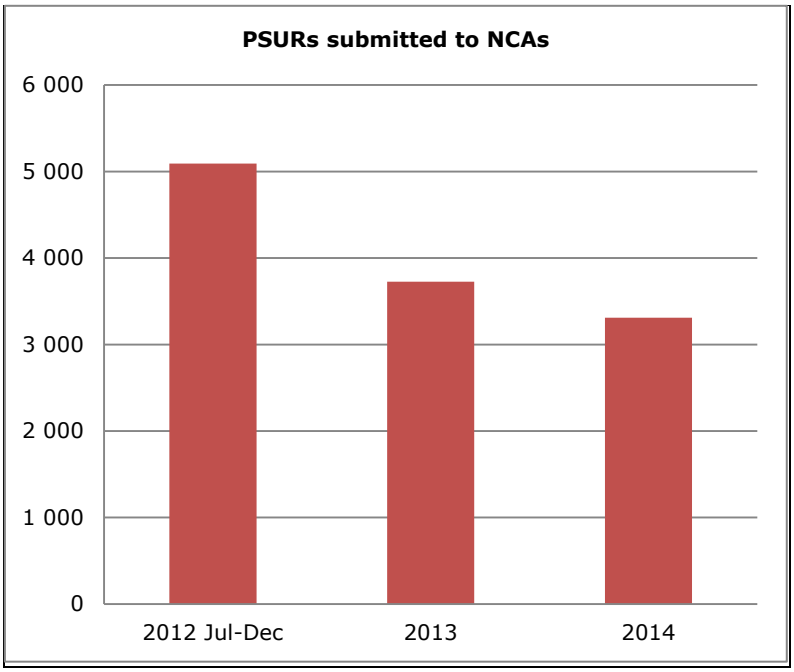
The number of PSURs reviewed by the PRAC was 20 during the starting period of July-December 2012 relating to active substances that were contained in only centrally authorised medicines, but increased to 436 in 2013 and 471 in 2014 as the scope of the PRAC's assessments was broadened to PSUR single assessments (PSUSA) for active substances contained in both centrally and nationally authorised medicines. In most cases the marketing authorisations were maintained unchanged, but around 1 in 5 of the PSUR assessments during the reporting period resulted in variations to the terms of the authorisation resulting in changes such as updates of the product information to improve information on side effects or precautions when using the medicine.

The number of PSURs additionally submitted to national competent authorities in the Member States for purely national assessments were around 5 000, 3 700 and 3 300 for the same periods.





[14] http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/10/WC500133159.xls



There were 62, 151 and 116 PSUR worksharing procedures for purely nationally authorised medicines during the same periods (where one country acted as 'reference Member State', carrying out the review on behalf of other countries). Since the last quarter of 2014 all nationally authorised medicines containing substances listed in the EURD list will have a PSUSA reviewed by the PRAC, which should increase the consistency of the review and allow Member States access to a shared pool of expertise.

An example of the way in which the PSUR can lead to further action to ensure safety, as well as of the checks and balances built into the system, is the strontium ranelate containing medicines Protelos and Osseor:

Case study: Protelos/Osseor and risk of cardiovascular (heart and circulatory) events

What is Protelos/Osseor

Protelos (strontium ranelate) is a medicine approved for the treatment of osteoporosis (a bone disorder associated with weakness of the bones and an increased risk of fractures). This medicine (also marketed as Osseor) was approved in the EU in 2004 for use in preventing fractures in women who have been through the menopause, and extended for use in men in 2012. In March 2012, the product information of the medicine was amended to warn against use in patients who were immobile or at risk of blood clots, following an EU level review of the risks of blood clots in the veins (venous thromboembolism (VTE)) and severe allergic skin reactions[15].

What were the PSUR findings?

PSURs for strontium ranelate are submitted on a three-year cycle. In April 2013, the PRAC completed a routine PSUR of the medicine, which included key data from studies in around 7 500 post-menopausal women, which showed an increased risk of heart attack (myocardial infarction) and VTE in women taking the medicine who had uncontrolled high blood pressure or a past

[15] See Community register: http://ec.europa.eu/health/documents/community-register/html/h288.htm and the EMA assessment report: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000560/WC500131789.pdf.

history of circulatory or heart problems. As a result, the PRAC recommended further restriction of the product's use as an interim risk-minimisation measure, and considered further in-depth analysis of the data was needed.

What happened next?

In May 2013, the European Commission requested a further in-depth review by the PRAC (a so-called Article 20 referral). This was carried out in a matter of months, and initially led (in January 2014) to a recommendation that the medicine's marketing authorisation should be suspended.

The PRAC recommendations were forwarded to the CHMP. While in overall agreement with the PRAC analysis of the risks, the CHMP considered that the medicine might still have a place for patients with no alternative treatment, provided they were carefully monitored for the development of cardiovascular problems. After further discussion, it therefore agreed to restrict the use of the medicine to patients who could not be treated with other medicines approved for osteoporosis and that treatment should be stopped if patients developed heart or circulatory problems. As previously recommended, use should be avoided in patients with a history of such problems.

Conclusions

The case16 illustrates the value of routine reassessment of benefits and risks in delivering timely and risk-proportionate regulation. The two committees working together, with complementary knowledge and expertise, allowed the best balance to be achieved between the acknowledged risks of the medicine on the one hand and the unmet medical need of those with few treatment alternatives on the other.

Additional monitoring

In 2013, the EU introduced a new system to label medicines that are being monitored particularly closely by regulatory authorities[17]. These medicines are described as being under 'additional monitoring' and are monitored more intensively than other medicines. This is generally because there is less information available, for example because a medicine contains a new active substance, is a biological product, or it has been approved in circumstances where there are limited data on its long-term use. Additional monitoring does not mean that the medicines are unsafe.

Medicines under additional monitoring have a black inverted triangle displayed in their package leaflet and in the information for healthcare professionals called the summary of product characteristics, together with a short explanation that the symbol means the product is subject to additional monitoring and particularly encouraging users to report suspected side effects. There was a consultation of the Member States and other stakeholders, especially patients and healthcare professionals, on the choice of symbol and its implementation.

The black triangle is now being used in all EU Member States to identify medicines under additional monitoring. It started appearing in the package leaflets of the medicines concerned from the autumn of 2013, and was accompanied by a communications campaign to the public,

[16] European Medicines Agency. Protelos/Osseor to remain available but with further restrictions (published 18/09/2014). Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Protelos_and_Osseor/human_referral_prac_000025.jsp&mid=WC0b01ac05805c516f.

[17] Defined by Article 23 of Regulation (EC) No 726/200 and Article 11 of Directive 2001/83/EC; the implementing regulation for the black symbol is Commission Implementing Regulation (EU) No 198/2013 of 7 March 2013 on the selection of a symbol for the purpose of identifying medicinal products for human use that are subject to additional monitoring, OJ L 65, 8.3.2013, p. 17.

developed by Member States, the EMA and the European Commission with the aid of relevant stakeholders[18]. In addition, a European list of medicines under additional monitoring is published and is updated monthly to include new medicines and any changes in monitoring status of those on the list[19]. At the end of 2014 the list included 193 centrally authorised and 8 nationally authorised medicines. The annexes related to medicines that had certain conditions imposed, for example as an outcome of referrals, included a further 1 269 nationally authorised medicines.

Referrals

see also Annex 5

A pharmacovigilance **referral** is a procedure used to resolve issues such as concerns over the safety or the benefit-risk balance of a medicine or a class of medicines. The matter is 'referred' to the European Medicines Agency, so that it can make a scientific assessment leading to a recommendation for a harmonised position across the European Union.

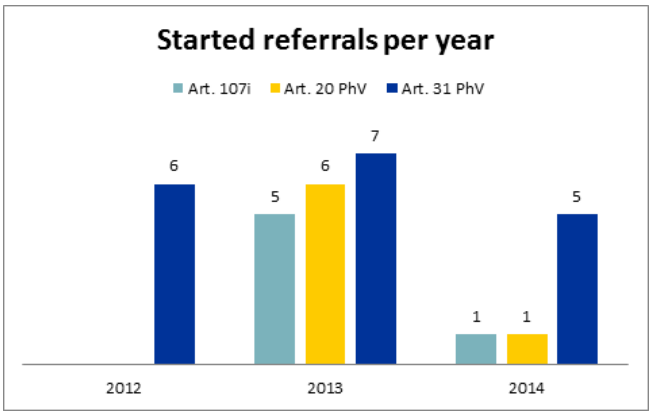
Pharmacovigilance referrals follow a defined procedure. The PRAC appoints members as rapporteurs and co-rapporteurs, and their expert teams in the Member States perform an initial assessment of the data on the PRAC's behalf to help it reach its recommendations. An opinion is then provided either by the CHMP (for referrals including centrally authorised medicines) or CMDh (for nationally authorised medicines). This is passed to the European Commission for a final, legally binding decision (except for consensus decisions of CMDh, which can be implemented directly at national level).

Pharmacovigilance referrals can be governed by several articles of the legislation. Procedures triggered when it is considered that urgent action for nationally authorised medicine(s) is necessary because of a safety issue are covered by **Article 107(i)** of Directive 2001/83/EC. Concerns relating to the safety or benefit-risk of a medicine or a class of medicines that include nationally authorised products are assessed by procedures triggered under **Article 31** of Directive 2001/83/EC. Safety or benefit-risk issues with medicines that have been authorised via the centralised procedure only are covered by **Article 20** of Regulation (EC) No 726/2004.

A total of 31 safety referrals were dealt with by the PRAC over the reporting period. Nine of these referrals involved centrally authorised medicines, the remainder dealt solely with nationally authorised products.

[18] European Medicines Agency. Medicines under additional monitoring. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/document_listing_000365.jsp&mid=WC0b01ac058067bfff.

[19] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000366.jsp



The outcomes of these referrals included variations of marketing authorisation in 24 cases, suspensions of marketing authorisation in 6 cases (reversible if the marketing authorisation holder can provide new evidence to justify the lifting of the suspension), and permanent revocations of marketing authorisation in 4 cases. (When a referral concerns a group of medicines, combined outcomes, such as variations of certain indications within the marketing authorisations and revocation of others, are possible.)

The revised legislation has improved the efficiency of the referral procedure, providing a more flexible and more transparent mechanism for reviewing safety and resulting in more effective and co-ordinated action to protect public health across the EU when needed.

The increased flexibility available with the new legislative tools, the greater transparency and the involvement of patient and healthcare professional representatives have had important impacts on safety referrals during this period, as illustrated by the below case study.

Case study: Combined hormonal contraceptives (CHCs), Article 31 referral on risk of thromboembolism

What was the reason for the referral?

Current combined hormonal contraceptives (CHCs) contain two types of hormone, a low dose of an oestrogen together with one of a number of different progestogens. They have long been known to be associated with a rare but serious increased risk of clots forming within blood vessels (thromboembolism) and the type of progestogen chosen can influence this risk, as can risk factors affecting the woman taking the medicine.

Although reviews of this risk have previously taken place at both national and European level, with consequent changes to their product information, in February 2013 the French medicines regulator, ANSM, asked for a referral under Article 31 to further review the benefit-risk of CHCs, focusing particularly on information about the risk of thromboembolism and advice on reducing it. This was because of further data about the risk of thromboembolism and consequent complications such as pulmonary embolism, in CHCs containing newer progestogens rather than the older progestogens levonorgestrel or norethisterone.

What evidence was reviewed?

The PRAC reviewed the available data from clinical trials, pharmacoepidemiological studies, published literature and spontaneous reports of suspected adverse drug reactions as well as the

views of an ad-hoc expert meeting. This represented a large amount of high quality evidence and provided information from many millions of woman-years of use.

What were the recommendations of the scientific review?

In October 2013 the PRAC confirmed that CHCs provide highly effective contraception and their benefits continue to outweigh their risks as the risk of thromboembolism in the veins (VTE) is small. It confirmed that there were differences in this small risk depending on the progestogen chosen, with the lowest risk attached to the progestogens levonorgestrel, norethisterone or norgestimate. A table of relative risks was adopted by the PRAC following input from patient and healthcare professional representatives.

Risk of developing a blood clot (VTE) in a year	
Women not using a combined hormonal pill/patch/ring and are not pregnant	About 2 out of 10 000 women
Women using a CHC containing levonorgestrel, norethisterone or norgestimate	About 5 to 7 out of 10 000 women
Women using a CHC containing etonogestrel or norelgestromin	About 6 to 12 out of 10 000 women
Women using a CHC containing drospirenone, gestodene or desogestrel	About 9 to 12 out of 10 000 women
Women using a CHC containing chlormadinone, dienogest or nomegestrol	Not known at time of review so studies were expected or recommended to allow estimation of the risk

The PRAC recommended modifying the product information of CHCs to give up-to-date information to women and prescribers on the risks and how to minimise them, and communicating the outcome of the review through educational materials including a letter to healthcare professionals.

What was the outcome?

The PRAC's recommendations were supported by the CHMP, which gave a positive opinion on the recommendations in November 2013, and the European Commission adopted a legally binding decision in January 2014 modifying the product information of all CHCs throughout the EU[20].

Conclusions

Previous experience has shown that concerns about side effects of CHCs can, if mishandled, lead to undesirable consequences including increases in the rate of unintended pregnancy (which itself can increase the risk of VTE) and abortion. The 2013 referral was a good example of the way that the tools and expertise now available to the EU network allowed for a rapid, collaborative review of the available evidence, with unprecedented levels of transparency and communication co-ordinated across the network, without triggering excessive public concern. The involvement of

[20] European Medicines Agency. Benefits of combined hormonal contraceptives (CHCs) continue to outweigh risks (published 31/01/2014). Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Combined_hormonal_contraceptives/human_referral_prac_000016.jsp&mid=WC0b01ac05805c516f.

patient and healthcare professional representatives was key to ensuring that the risks and benefits of the medicines were communicated clearly and appropriately. The ultimate outcome is that women and prescribers have the best available evidence to support making an informed decision about the choice of contraceptive.

Another case-study of a referral, illustrating the important input of those affected by adverse effects, is included under *Cooperation and Coordination with Stakeholders*, below.

Issues that do not lead to referral

Some additional concerns at a national level which could potentially have led to a referral under Article 107(i) were also discussed by the CMDh to decide on whether an EU level assessment was required but did not ultimately trigger a referral. Such discussions were held on two occasions in 2013 and six in 2014.

Post-authorisation studies

see also Annex 6

A **post-authorisation safety study** (**PASS**) is a study that is carried out after a medicine has been authorised to obtain further information on its safety, or to measure the effectiveness of risk-management measures. Under EU legislation, regulators may proactively impose a requirement for a PASS on a marketing authorisation holder or may require one as part of the risk management plan because of an identified safety concern before or after marketing.

The protocol for imposed non-interventional PASSs (i.e. their proposed study design) and their final outcomes are assessed by the PRAC. (A *non-interventional study* is one in which the medicine is prescribed in accordance with the approved indication, and patients who receive it do so in accordance with normal medical practice, with no special tests or monitoring.) All studies required by regulators are included in the risk management plan.

In addition, companies may *voluntarily* carry out a PASS to identify or characterise a safety concern, confirm the safety profile of a medicine, or measure the effectiveness of risk minimisation measures.

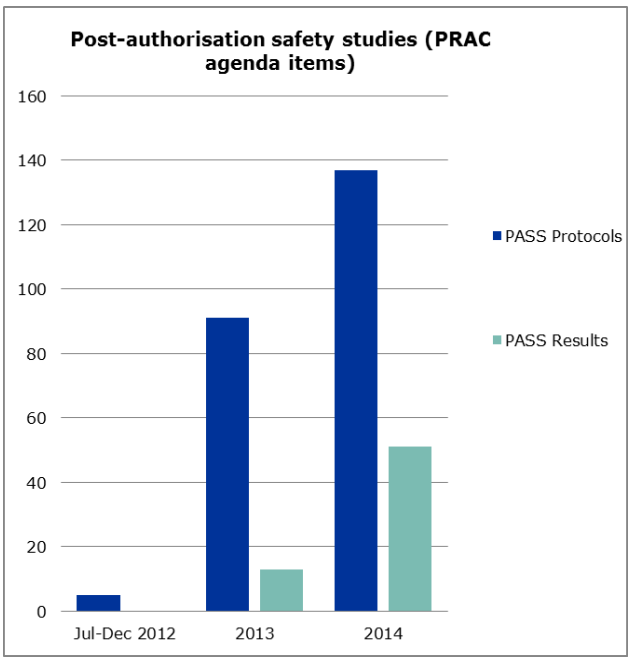
The protocols and abstracts of the final study reports of PASSs are published in the EU post-authorisation study (PAS) register on the European Network of Centres in Pharmacoepidemiology and Pharmacovigilance (ENCePP) website.

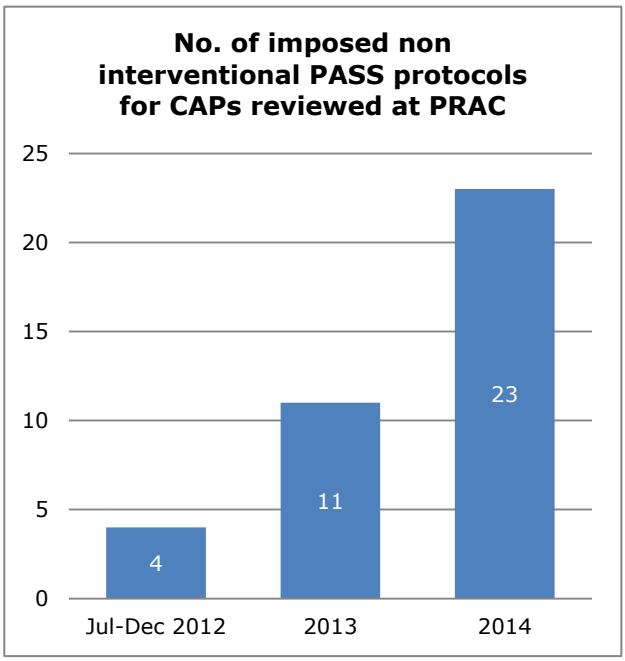
Understanding the benefits as well as the risks of a medicine is important in authorising its use. Sometimes, aspects of its efficacy may only be able to be resolved after it has been marketed. In addition, changes in the understanding of diseases or their study and treatment may mean that previous efficacy evaluations need to be revised. In such instances **post-authorisation efficacy studies** (**PAES**) may be required by regulators to complement available efficacy data.

The use of PASSs and PAESs represents a commitment from both regulators and marketing authorisation holders to address gaps in the evidence base in a more proactive and planned way.

Post-authorisation safety studies

During the reporting period, the PRAC reviewed protocols for 38 imposed non-interventional PASSs in order to approve them. In two cases the PRAC requested proposals for alternative study designs. The review of PASS protocols and their results by the PRAC is increasing, so that by 2014 around 140 (nearly 10%) of the items on the Committee agenda related to PASS protocols (some of these represented repeated consideration of the same protocol) and protocol results had been discussed on some 50 occasions. Member States have also evaluated an additional 17 PASS protocols for nationally authorised medicines.





Post-authorisation efficacy studies

Post-authorisation efficacy studies may be required by regulators in order to address some efficacy aspects and complement the available data. Because both benefits and risks have to be regularly assessed in order to be sure that the balance between them remains positive, post-authorisation studies of efficacy can also have relevance in the context of pharmacovigilance activities. A Commission Delegated Regulation (EU) No 357/2014[21] dealing with PAES was adopted in February 2014, towards the end of the three-year period covered by this report, and since this came into operation and up to July 2015, 14 PAES had been imposed by CHMP (although many of these post-date the data-lock point). One additional PAES was required by a Member State for a nationally authorised medicine.

Inspections

see also Annex 7

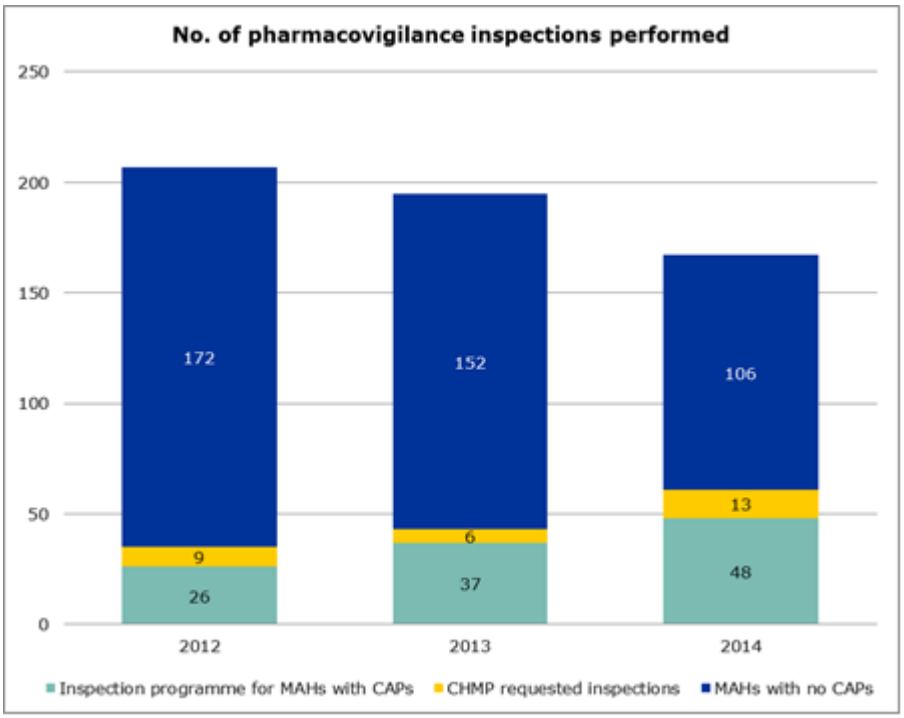
Rigorous programmes of inspection underpin the pharmacovigilance system, as they do also for the quality and manufacture of medicines. The ongoing work undertaken by inspectors helps to ensure that EU citizens receive the safe, high-quality medicines they deserve.

The total number of inspections undertaken was 207 in 2012 (for the whole year), 195 in 2013 and 167 in 2014. The proportion of these related to centrally authorised medicines increased in

[21] Commission Delegated Regulation (EU) No 357/2014 of 3 February 2014 supplementing Directive 2001/83/EC of the European Parliament and the Council as regards situations in which post-authorisation efficacy studies may be required, OJ L 107, 10.4.2014, p.1.

the same periods, being 26, 37 and 48 respectively. There were 9 inspections at the request of the CHMP during 2012 (7 taking place in July-December), 6 in 2013 and 13 (of which 3 were inspections of investigator sites related to conduct of a PASS) in 2014.

In 5 cases, penalties were imposed on marketing authorisation holders (MAHs) for failure to comply with obligations.



Master files/logbook

The pharmacovigilance system in place for each medicine that receives a marketing authorisation must be described by a pharmacovigilance system **master file**, held by the company, which includes a description of the persons, places, and procedures put in place by them to monitor the safety of the medicine. Companies must keep this file up to date and available for inspection, and a logbook detailing the history of any changes to the file must also be maintained.

It is routine practice for a copy of the master file and logbook to be requested during all safety inspections by the regulatory authorities.

Medication errors

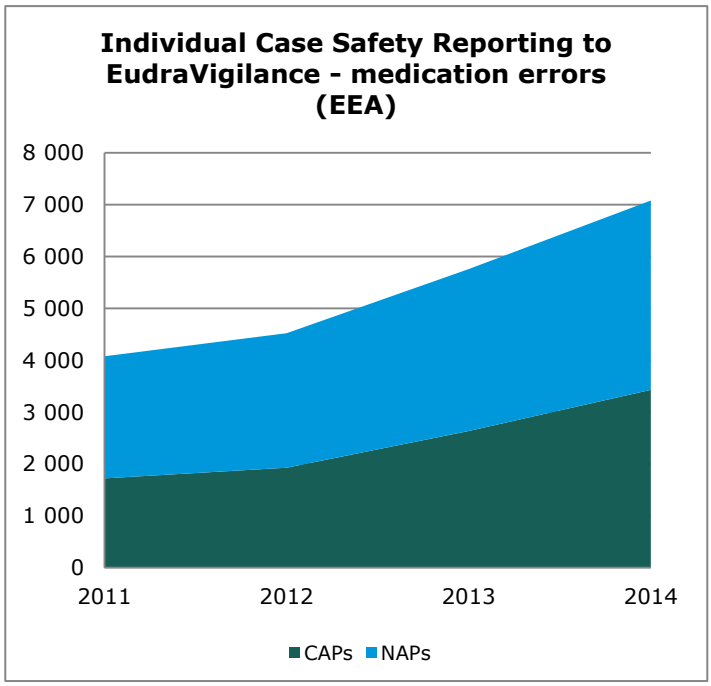
see also Annex 8

A **medication error** can be defined as an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient. This can include a patient taking or being given the wrong medicine, using the wrong dose or route of administration, or a medicine being given to the wrong patient. Medication errors do not necessarily lead to harm, however the cost to patients and healthcare systems can be high, and many medication errors are preventable.

In 2012 there were around 4 500 side effect reports received by EudraVigilance associated with medication errors, increasing to some 5 700 in 2013 and over 7 000 in 2014. It is likely that at least some of the apparent increase may be due to increased awareness and better reporting, in itself a positive outcome from the new legislation.

In the EU, national competent authorities and the EMA play a key role in identifying and reducing the risk of medication errors before and after the authorisation of a medicine. Direct patient reporting of side effects, including those caused by medication errors, as brought in by the revised pharmacovigilance legislation assists regulatory authorities in implementing risk minimisation measures at an early stage and avoiding further harm due to these errors.

Communication about medication errors is an important tool in reducing the risk. The Member States play a major role in such communication, along with other channels such as direct healthcare professional communications (DHPCs), educational material and communications from national patient safety organisations. Going forward, the EMA has prepared proposals to streamline its current 'safety communications' to consistently capture key information related to medication errors which are assessed by its scientific committees as a complement to information issued at a national level and a dedicated area on the its website will provide links to such communications[22].



A workshop took place in 2013 involving Member States and the EMA with stakeholders from all areas of healthcare to develop and share best practices for the prevention of medication errors. It helped develop a subsequent action plan for implementation during 2014 to 2015 on how the EU system could complement and facilitate (within existing frameworks) the extensive local and national programmes carried out in the Member States[23].

The clearer focus on medication errors as part of the pharmacovigilance process and the availability of new tools in the legislation that can be used to address them is expected to help reduce the harm that results from them.

COMMUNICATIONS AND TRANSPARENCY

In order for the EU regulatory network to function, good communication between its constituent members, and between the network and the wider public it ultimately serves, is vital. The system operates with a high level of transparency, as foreseen and guaranteed by legislation, and

[22] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000398.jsp&mid=WC0b01ac058098f1c0

[23] See European Medicines Agency. Medication errors: http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000570.jsp&mid=WC0b01ac0580659655.

communicates synchronously to the public about safety concerns of medicines at different stages of the regulatory process.

As mentioned above under *Side-effect reporting*, Member States engage extensively with the media and relevant stakeholders to communicate relevant safety messages and promote public understanding of issues of medicines safety. A survey conducted though the SCOPE project[24] showed that all 25 Member States who responded also provide safety-related information on a website, which may include information for healthcare professionals, industry and patients on different ways to report side effects. The survey found that 11 Member States have national/local guidelines stating what information should be presented on the website. At the time of the survey, some Member States were in the process of introducing changes to their web-pages including tailoring the information to audience type.

The increased work being done to assure the safety of medicines under the revised EU pharmacovigilance system has been complemented with greater public availability of information on the interim steps and outcomes of that work. The **agendas** and **minutes** of the monthly formal PRAC meetings are made available on the EMA website, and **highlights** of the outcomes are published the next working day after the conclusion of the meeting.

The system produces public safety communications on relevant issues, including announcements of the **start of referrals**, communication of the **recommendations issued by the PRA**C, and detailed **public health communication** of the final outcome (including elements tailored specifically to patients and healthcare professionals, which are produced with input from representatives of the relevant stakeholder groups). There were 14 such communications issued in the second half of 2012, 78 in 2013 and 57 in 2014.

In addition, a pilot project to produce **public summaries of the RMP** has been carried out. A summary was prepared for each new medicine approved centrally in 2014, resulting in a total of 54 such summaries being published. A survey of stakeholder responses to this pilot will inform the content and nature of future RMP summary publication.

The EMA helps co-ordinate communications within the EU network, providing an **Early Notification System** (**ENS**) to the national competent authorities, the European Commission and other network partners, which provides early warning of safety issues on the PRAC, the CMDh or the CHMP agendas. **Lines-to-take** for press and communication officers in the Member States to reply to enquiries from the media or other stakeholders are co-ordinated by the EMA with input from internal and scientific experts from national medicines regulators. Such lines-to-take were distributed within the network on 46 occasions from June-December 2012, 75 in 2013, and 47 in 2014.

In addition to the detailed communication on referrals already mentioned, public access to aggregated data from reports of suspected side effects contained in EudraVigilance has been ensured through the **European database of suspected adverse drug reaction reports**[25] which was launched in 2012 at the start of the period covered by this report. Initially providing access to suspected side effects for centrally authorised medicines, and subsequently extended in October 2014 to provide information on common active substances included in nationally authorised medicines. It now covers over 500 active substances for centrally authorised products and more than 1 500 for nationally authorised medicines. More detailed information can be made available to selected stakeholders on application, in accordance with the EudraVigilance access policy and data protection laws.

[24] http://www.scopejointaction.eu/
[25] http://www.adrreports.eu

Details of recommendations made by the PRAC about signals are published monthly. When there is a recommendation for a change to product information the changes are translated into all official EU languages and published by the EMA as a service the Member States and to industry.

The outcomes of **imposed PASS studies** are available in the register on the ENCePP website[26]. Full **RMPs** are not published (although they can be made available via EMA's access to documents policy), but as already mentioned summaries in public-friendly language are being published for new medicines approved since 2014.

Work has also taken place to allow for greater transparency on the outcomes of single-assessment PSURs (PSURs for a group of medicines all containing the same active substance or combination are considered together). The **outcomes of PSURs** for centrally authorised medicines which recommend changes to the marketing authorisation are published on the EMA website as part of each medicine's European Public Assessment Report (EPAR). The outcome for nationally authorised medicinal products included in 'mixed' procedures where centrally authorised products were also involved can be found on the Community register[27] . As of mid-2015, conclusions of PSUR single assessments related to only nationally authorised medicines are also being published[28].

Transparency as an underlying principle of communications

The high degree of transparency about pharmacovigilance issues, in which not only outcomes but processes are communicated, carries some risks of causing alarm amongst medicines users and wider civil society. It is acknowledged that this could have unintended consequences for public health (e.g. patients discontinuing beneficial medicines). Interaction with stakeholders is therefore crucial in ensuring that risks are communicated clearly, accurately and proportionately and in the context of the potential benefit.

In the long-run trust in the regulatory system requires this transparency, which forms part of a **wider transparency agenda** in which European legislators and regulators are playing a leading role; ever more of the clinical evidence on which decisions about medicines are made is becoming publicly available. The greater transparency and communication brought about by the new legislation in terms of pharmacovigilance fosters an environment in which transparency is seen as a norm. This encourages openness and communication about other regulatory processes.

SYSTEMS AND SERVICES IMPROVEMENT

The role of the EMA includes the provision of some of the systems and services needed for the pharmacovigilance network to function. The new legislation has required the development of some new systems and services and enhancement or simplification of others. Member States and key stakeholders including the pharmaceutical industry have had an important input to the design and development of these systems.

The revised legislation foresees that pharmacovigilance activities conducted at EU level for human medicinal products should be financed by **fees** paid by marketing authorisation holders[29].

[26] http://www.encepp.eu/encepp_studies/indexRegister.shtml
[27] http://ec.europa.eu/health/documents/community-register/html/index_en.htm
[28] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000620.jsp&mid=WC0b01ac0580902b8d
[29] Regulation (EU) No 658/2014 of the European Parliament and of the Council of 15 May 2014 on fees payable to the European Medicines Agency for the conduct of pharmacovigilance activities in respect of medicinal products for human use, OJ 189, 27.6.2014, p.112.

These additional resources will be used to remunerate the national competent authorities of the Member States for the pharmacovigilance assessments they carry out as rapporteurs for the PRAC and to contribute to the pharmacovigilance-related costs of the EMA, including the system improvements described in this section of the report. The Article 57 database referred to below supports routine pharmacovigilance business processes, as well as the collection of pharmacovigilance fees.

Article 57 database

A **database** of all authorised medicines (both centrally and nationally authorised) in the EU has been developed over the reporting period, as originally envisaged in **Article 57** of Regulation (EC) No 726/2004 and developed in the updated pharmacovigilance legislation. Maintaining this information in a single location is intended to reduce duplication of effort and costs, and improve the efficiency of database and systems communication within the network, with international partners, and with the industry. It will allow identification of products and substances in reports of suspected side effects, in referral procedures and PSURs, and is used to support collection of pharmacovigilance fees from the industry.

It is envisaged that this database will eventually support the provision of information to patients and the public via a medicines web-portal.

The development of the Article 57 database and collecting and maintaining the medicinal product entries received from the marketing authorisation holders, has been a considerable undertaking, requiring close co-operation between the EMA and the industry. The database represents information on over 580 000 medicines from nearly 4 300 marketing authorisation holders. The information was updated by submissions from the companies during 2014, and the database started to enter routine use and maintenance in 2015.

EudraVigilance enhancements[30]

The legislation requires enhancement of EudraVigilance to support simplified reporting, better search, analysis and tracking functions, and improved data quality. The database needs to support the Member States in their requirement to monitor reports of suspected side effects and to support industry in monitoring the safety of its products. The enhancements will include compliance with various international data standards, which will facilitate data exchange. Significant progress on enhancing the EudraVigilance database has been made during the reporting period including the launch of the ADR website, the support to signal detection activities through production and distribution to the Member States of data outputs from the system, and in the planning and building of the enhanced system with its new functionalities and new data structure. At the time of reporting the development of the system is on track to undergo in early 2018 the audit foreseen in the legislation.

Literature monitoring service

The EMA is required to monitor selected medical literature for reports of suspected side effects to certain active substances, and enter them into the EudraVigilance database as ICSRs[31]. This

[30] Further information on the EudraVigilance database is available in the annual report foreseen under Article 24(2) of Regulation (EC) No 726/2004 (http://www.ema.europa.eu/docs/en_GB/document_library/Report/2016/03/WC500203705.pdf)

[31] Article 27 of Regulation (EC) No 726/2004.

should enhance the quality of the safety information available, and it is hoped will reduce the administrative burden on the industry for reporting for the relevant substances. Preparation of the EudraVigilance system to perform this service was completed in 2014 and the service was launched in June 2015.

PSUR repository

The legislation creates a legal requirement to set up a repository for all PSURs[32] and their assessment reports. This will considerably simplify the submission process for the pharmaceutical industry and provide ready access by regulators via a user interface that will allow search and retrieval of documents.

The repository has been developed during the reporting period, with system feedback supplied by Member State and industry users, and the repository was made available and audited for functionality during 2015. Use of the repository for the submission of PSURs will become compulsory in mid-2016.

COOPERATION AND COORDINATION WITH REGULATORS

Within the EU network

The EU regulatory network requires close co-operation and co-ordination between over 30 national competent authorities, the EMA and the European Commission. The updated legislation has aimed to facilitate this by strengthening the network, reducing duplication, and clarifying roles and responsibilities.

The PRAC is an important pillar of this improved system, with its members working at the European level but supplying knowledge and perspectives developed within their national agencies.

Improved and co-ordinated communication, including the Early Notification System and the use of lines-to-take, has helped to ensure that the system speaks coherently to external stakeholders, so patients and the public receive consistent messages about the safety of their medicines across the EU, and that Member States are made aware of developing issues in one country that may lead to media interest in another. The development of improved systems and services over the reporting period, in which Member State input has been crucial, should allow further improvement.

International regulators and ICH

The EU pharmacovigilance system exists in the context of global safety monitoring and as part of a tradition of long-standing cooperation between regulators and harmonisation of guidelines and practices. The EMA acts as a central point of contact with other major regulators, in particular the US Food and Drug Administration (FDA), Health Canada and the Japanese regulatory authorities. Confidentiality arrangements between regulators permit sharing of critical data and expertise related to safety issues and product assessments, and assist timely and co-ordinated communication about relevant issues (for example, by giving early warning of safety-related communications that may generate public concern or media enquiries). Based on the successful product-related collaboration, the system has also concluded on strengthened strategic collaboration with the FDA, via the so-called international pharmacovigilance cluster[33]. The EU

[32] Article 25a of Regulation (EC) No 726/2004.

[33] European Medicines Agency/FDA/ Guiding principles for the international pharmacovigilance cluster, 22 May 2015. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/12/WC500179390.pdf.

network's best practice have been shared with external regulators via training courses and workshops.

The members of the EU regulatory network play a key role in developing harmonised guidelines for human medicines regulators through the Association of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (**ICH**). ICH brings together the regulatory authorities of Europe, Japan, the United States, Canada and Switzerland, and experts from the pharmaceutical industry, with the aim of agreeing common approaches and requirements where possible for the authorisation of medicines. The membership in the ICH Association is expected to increase further.

An important outcome during the reporting period was the adoption by ICH of a new guideline on the format and content of periodic benefit-risk evaluation reports[34], based on the approach for PSURs brought in by the new EU pharmacovigilance legislation.

COOPERATION AND COORDINATION WITH STAKEHOLDERS

Patients and healthcare professionals

Patients and healthcare professionals are key stakeholders in the revised European pharmacovigilance system, since they are the people actually prescribing, dispensing and using medicines. The PRAC membership therefore includes representatives of these groups, who have input to all the activities of the Committee, and supply relevant perspectives to all aspects of its work. Broader consultations with patient and healthcare professional organisations may form part of referrals and a patient representative is included in scientific advisory groups (SAGs), expert groups convened to supply specialist input. Patient and healthcare professional representatives also review relevant safety communications. Work has also been undertaken in preparing for future public hearings in the context of referral procedures.

The importance of involving these critical stakeholders is illustrated by the review of valproate and related substances in pregnant women, an Article 31 referral which began in October 2013.

Case study: Valproate and related substances, Article 31 referral

What **was the reason for the referral?**

Valproate and related medicines are nationally authorised medicines that have been used for many years to treat epilepsy and bipolar disorder, and in some Member States are also authorised to prevent migraine. It has been known for many years that use in pregnant women increases the risk of certain birth defects in children, and evidence has also built up that they may result in a delay in the child's development. In October 2013, the UK requested a review of these medicines following the publication of new studies suggesting that in some children effects on development, which could include autism, might be long-lasting.

What evidence was reviewed?

The PRAC reviewed available studies and reports providing the most recent evidence on harms, including both congenital malformations and long-lasting developmental disorders, and importantly, consulted representatives of patients and families who had been affected as well as a group of experts and specialists in fields such as neurology, child development and obstetrics. Patient representatives were thus actively involved in the process and had significant input into

[34] ICH guideline E2C (R2) on periodic benefit-risk evaluation report.

the development of risk minimisation measures.

What were the recommendations of the scientific review?

The PRAC recommended a strengthening of warnings in the product information to ensure that healthcare professionals and patients were aware of the risks and that patients were prescribed valproate only when clearly necessary. Educational materials were recommended so that women and healthcare professionals were better informed about the risks of valproate exposure in the womb and of the need for effective contraception while using it, and it was advised that treatment should be regularly reviewed by doctors, including at puberty and when a woman wished to become pregnant.

What was the outcome?

Since these medicines were all authorised nationally, the recommendations were sent to the CMDh which endorsed them by consensus in November 2014, and they were implemented by the Member States according to an agreed timetable.

Conclusions

The referral shows the way in which the regulatory system can incorporate the experiences and concerns of patients and sufferers from adverse reactions into a rigorous and timely review process, resulting in better information for users of the medicines and more appropriate use of a valuable but potentially problematic treatment for these serious conditions.

The EMA interactions with patient and healthcare professional representatives are managed in line with an agreed framework for interaction designed to minimise conflicts of interest.

At the Member State level many interactions also take place between the various national medicines regulators and national patient and healthcare professional organisations. A survey of national competent authorities carried out in January 2015 by the Working Group of Communication Professionals (representing the Member States) and the EMA found that 85% of respondents had formal or semi-formal interactions with patient groups and representatives. This has been particularly true in the area of side effect reporting where some Member States work directly with patient organisations to facilitate side effect reporting, and 13 of them work with patients or patient representatives to user-test side effect reporting forms.

Following the establishment of the PRAC and the bedding in of the new legislation, improved procedures for drafting and reviewing safety communications to healthcare professionals (DHPCs) were also developed, to ensure that these were appropriately reviewed by members of the relevant committees and their content was clear.

Academia

Academia plays a significant role in generating the evidence on which regulators rely to make judgements about the benefits and risks of medicines. In pharmacovigilance, the EU network has engaged actively with academia, most notably through the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Engagement has also occurred through regulatory science projects, particularly the Innovative Medicines Initiative (IMI) funded EU PROTECT[35] project on pharmacovigilance methods.

[35] Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium.

The industry

The pharmaceutical industry is a key actor in pharmacovigilance. Individual marketing authorisation holders have specific responsibilities under the legislation in terms of running a system of pharmacovigilance, monitoring and reporting for their products. The EU network has strengthened its communication and consultation with industry on draft guidance and through a regular 'Industry Platform' where representatives of EU industry associations meet with regulators.

The media

Press and communication departments of the national competent authorities and of the EMA interact regularly with local and international media to encourage side-effect reporting and disseminate important safety-related messages and outcomes of regulatory processes as described under *Communications*, above.

The national regulators, with their close understanding of the healthcare and media environment within their own countries, play a key role in ensuring safety-related messages are clearly understood and disseminated in each Member State in appropriate ways. Timely provision of lines-to-take and safety communications to the Member States is important in supporting this work.

Press releases and communications strategies are developed for areas of particular public interest, including referrals such as those related to hormonal contraceptives or the medicine Diane 35 (cyproterone and ethinyloestradiol, a hormonal combination approved for the treatment of women with severe acne). The network works to ensure that strategic messages and important issues are communicated appropriately to the media.

PHARMACOVIGILANCE AND PUBLIC HEALTH

While medicines save lives and prevent suffering, the burden of adverse drug reactions is considerable: some 5% of hospital admissions in the EU and around 197 000 deaths per year have been thought to be due to adverse reactions to medicines[36].

Experience to date suggests that the revised pharmacovigilance system now in place in the EU is resulting in more timely and consistent outcomes to optimise the safe and effective use of medicines. This is based on risk-proportionate scientific decisions made on the basis of the best available evidence. Fast and robust detection of issues, decision-making and communication to users of medicines allows those users to make informed decisions and reduces risks from the use of the medicines, thus benefiting public health. Furthermore, efficiencies gained by working in a network can make more efficient use of resources.

The existence of reliable systems for monitoring drug safety and pro-active planning of data collection and ways to minimise those risks in the form of RMPs and post-authorisation studies is important in supporting authorisation of new and innovative medicines.

Work is ongoing to develop better measurements for the impacts of pharmacovigilance including health outcomes and the PRAC strategy on health impact measurement was published in 2016[37]. It is expected that the strategy will support the collection of more data relevant to the health impact of the EU pharmacovigilance system which can be relevant for subsequent reports.

[36] Annex 2 of the Report on the impact assessment of strengthening and rationalising EU Pharmacovigilance, Commission of the European Communities, Sept 2008.

[37] European Medicines Agency, PRAC strategy on health impact measurement, EMA/790863/2015, 11 January 2016.

CONTINUING AND FUTURE DEVELOPMENT OF THE NETWORK

Training

The national competent authorities of the Member States and the EMA offer programmes of internal and external training on the infrastructure and procedures required for pharmacovigilance. This has included training to familiarise regulators, industry and other stakeholders with the details of the revised legislation, the guidelines on good pharmacovigilance practices, and the updated processes for data submission and analysis. For example, in 2014 alone, 24 training sessions on EudraVigilance data submission, 11 training sessions on the medicinal product dictionary used by EudraVigilance (xEVMPD) and two introductory sessions to EudraVigilance took place, along with access to the xEVMPD e-learning platform by 250 users.

Measures have been put in place during the period covered by the report to improve training within the network, in the form of a joint initiative between the EMA and the Member States to develop an **EU Network Training Centre** (EU NTC). The initiative was agreed in 2014, and is intended to ensure that the best scientific and regulatory practices are spread across the network, through the provision of high quality and relevant training materials shared through the EU NTC platform. In addition to ensuring harmonised standards and providing professional development for regulatory staff, it should reduce duplication of effort and thus ensure that resources available for training are used most effectively.

Process improvement

Based on the experience of the first years of operation of the new EU pharmacovigilance legislation and in dialogue with stakeholders, the EU network is putting effort into increasing both the efficiency and effectiveness of pharmacovigilance processes. This can be seen through revised processes, revisions to guidelines on good pharmacovigilance practice and through the development of systems and services such as medical literature monitoring and the PSUR repository. Further processes improvement will be a focus for the next period, based both on experience and the results of regulatory sciences.

Building capacity and improving regulatory science

A number of projects have been initiated during the reporting period to improve the science and practice of pharmacovigilance, and so enable future improvements in the system.

The Strengthening Collaboration for Operating Pharmacovigilance in Europe (**SCOPE**) Joint Action will run from 2013 until 2016. It is an EU-funded 'Joint Action' with contributions from the involved Member States, designed to understand how regulators in EU countries run their national pharmacovigilance systems. Using this information, SCOPE will develop and deliver guidance and training in key aspects of pharmacovigilance, along with tools and templates to support best practice[38]. Survey data from the Member States obtained under the auspices of SCOPE has been used in the preparation of this report.

Work to encourage the conduct of high quality, multi-centre, independent post-authorisation studies is also ongoing within the context of the European Network of Centres in Pharmacoepidemiology and Pharmacovigilance[39]. This is a partnership involving 147 centres across Europe that brings together expertise and resources in pharmacoepidemiology and pharmacovigilance. The EU register of these studies is available from its website. It also develops methodological standards and governance principles for such studies.

[38] Progress in the various work packages that constitute the project is reported on a dedicated website: http://www.scopejointaction.eu/.
[39] http://www.encepp.eu/index.shtml

The **PROTECT** project (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium)[40] was a public-private partnership co-ordinated by the EMA which looked at ways to strengthen safety surveillance and the monitoring of the benefit-risk of medicines in Europe. This was to be achieved by developing new tools and methods for early detection and assessment of adverse drug reactions, and finding improved ways to present data on benefits and risks. These methods were tested in real-life situations in order to provide all stakeholders with accurate and useful information supporting risk management and continuous benefit-risk assessment. The project finished in 2015 and assessment of outputs for implementation into routine practice is now underway, with new tools already being implemented in guidance and systems (e.g. EudraVigilance).

Other regulatory science projects initiated during this period include WebRADR[41] which aims to investigate apps for side-effect reporting and the role of social media data in this area of pharmacovigilance and ADVANCE (Accelerated development of vaccine benefit-risk collaboration in Europe)[42] which aims to establish a blueprint for a sustainable system for vaccine benefit-risk monitoring in the EU. The EU invested 31.7 million euros into pharmacovigilance research under the 7th Research Framework Programme, which ended in 2013.

CONCLUSIONS

The European pharmacovigilance network represents an example of successful co-operation at the European level, to the benefit of EU citizens. The networked system allows all participants to share in the best available expertise and evidence and co-ordinate the regulatory actions required, producing more efficient and consistent outcomes for everybody. The regulatory tools made available under the revised legislation, including risk management plans, post-authorisation studies, signal detection and management at EU level, PSUR assessment and referrals, represent an increasingly proactive approach to medicines safety, complemented by improvements in regulatory action and communication when safety concerns are identified.

The system operates with high transparency, necessary to develop the trust of the society it serves. Engagement of key stakeholders such as patients and healthcare professionals is embedded in the system, and the perspectives they provide contribute significantly to the decision-making process. For the future, deepening involvement is foreseen, including the holding of public hearings for critical safety issues.

Work is proceeding on the infrastructure and procedures needed to support further development of the system, and to simplify and streamline existing processes where possible so that the regulatory burden is minimised for all stakeholders. Delivery of the medical literature monitoring service, of the new EudraVigilance system and of the PSUR repository and full use of the Article 57 EU medicinal product database will increase efficiency and deliver simplification for stakeholders. Work continues to complete the development and implementation of other systems such as centralised ADR reporting through the EudraVigilance database. Ongoing research in the field of regulatory science, will also support future improvements.

The work to implement the revised legislation and the increased level of transparency and communication it brings has been challenging for all parties, but is now well established and has opened new ways of communicating on medicines which are helping to set the tone for increased communication and transparency in medicines regulation in general.

[40] http://www.imi-protect.eu/
[41] http://web-radr.eu/
[42] http://www.advance-vaccines.eu/

ABBREVIATIONS

ADR	adverse drug reaction (side effect)
ADVANCE	Accelerated Development of VAccine beNefit-risk Collaboration in Europe, a project to improve assessment of benefits and risks of vaccines
Art. 107i	Article 107(i) of Directive 2001/83/EC. It applies when, on the basis of concerns resulting from the evaluation of data from pharmacovigilance activities, a Member State or the European Commission considers: – suspending or revoking a marketing authorisation (MA); – prohibiting the supply of a medicinal product; – refusing the renewal of a MA; – is informed by the marketing authorisation holder that, on the basis of safety concerns, he has interrupted the placing on the market of a medicinal product or has taken action to have a MA withdrawn, or intends to take such action or has not applied for the renewal of a MA.
Art. 20	Article 20 of Regulation (EC) 726/2004. It applies when a referral procedure is initiated as a result of the evaluation of data relating to pharmacovigilance of medicinal product(s) authorised via the centralised procedure only.
Art. 31	Article 31 of Directive 2001/83/EC. It applies where the interests of the Union are involved. When a referral procedure is initiated as a result of the evaluation of data relating to pharmacovigilance of an authorised medicinal product(s) the issue is referred to the Pharmacovigilance Risk Assessment Committee.
ANSM	Agence Nationale de Sécurité du Médicament et des Produits de Santé, the French medicines regulator
CAP	centrally authorised product, a medicine for human use authorised by the European Commission based on an evaluation by EMA
CHC	combined hormonal contraceptive
CHMP	Committee for Medical Products for Human Use
CMDh	Co-ordination Group for Mutual recognition and Decentralised procedures – human
DHPC	direct healthcare professional communication
EC	European Commission
EEA	European Economic Area
EMA	European Medicines Agency
ENCePP	European Network of Centres in Pharmacoepidemiology and Pharmacovigilance, a partnership involving 147 centres across Europe

ENS	early notification system
EPAR	European public assessment report, a dossier of public information relating to the approval of a medicine
EU	European Union
EURD	List of European Union reference dates and frequency of submission of periodic safety update reports (a list of active substances for which PSURs must be submitted and the dates and frequencies at which this should occur)
EV	EudraVigilance, the database for collating suspected side-effect reports that is maintained by EMA
G-CSF	granulocyte colony stimulating factor, a protein that stimulates white blood cell production
GVP	good pharmacovigilance practice, guidelines on how pharmacovigilance activities should be carried out
HCP	healthcare professional
ICH	Association of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICSR	individual case safety report, a standardised report of a suspected side effect
IMI	Innovative Medicines Initiative, a public-private initiative aiming to speed up the development of better and safer medicines for patients
IT	information technology
LMS	lead Member State, a Member State who acts on behalf of the network in assessing pharmacovigilance data for a particular active substance
MAH	marketing authorisation holder, the company marketing a medicine
MHRA	Medicines and Healthcare products Regulatory Agency, the UK medicines regulator
NAP	nationally authorised product, a medicine evaluated and approved by national regulators
NCA	National Competent Authority, a national medicines regulator
NTC	Network Training Centre
PAES	post-authorisation efficacy study
PAS	post-authorisation study
PASS	post-authorisation safety study
PhV	pharmacovigilance
PRAC	Pharmacovigilance Risk Assessment Committee
PROTECT	Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium, a public-private partnership to examine ways

	to strengthen safety surveillance and the monitoring of the benefit-risk of medicines in Europe
PSUR	periodic safety update report
PSUSA	periodic safety update – single assessment
RMP	risk management plan
SAG	Scientific Advisory Group
SAR	serious adverse reaction
SCOPE	Strengthening Collaboration for Operating Pharmacovigilance in Europe, an EU-funded Joint Action project involving regulators from many EU Member States plus Norway and Iceland
VTE	venous thromboembolism (a blood clot obstructing a vein)
WebRADR	a consortium developing a mobile app to report suspected adverse drug reactions, and investigating the potential for publicly available social media data for identifying drug safety issues
xEVMPD	eXtended EudraVigilance Medicinal Product Dictionary

ANNEXES – technical data

The following annexes present the detailed numerical data which supports the text and figures in the report. It has been collected by the Member States and the EMA, as detailed in the section *Sources of data* at the start of the report. The data should be read in conjunction with the explanations and clarifications in the text of the report.

ANNEX 1

1. SIDE EFFECT REPORTING

1a. Number of individual case-safety reports (ICSRs) European Economic Area (EEA)

Postmarketing ADR reporting (EEA)		2011	2012	2013	2014
		January-December	January-December	January-December	January-December
Healthcare professionals (HCP)	CAPs	115 130	121 219	140 729	148 579
	Non CAPs	83 582	82 337	89 519	87 694
	Total	198 712	203 556	230 248	236 273
Patients	CAPs	7 302	10 103	16 227	17 697
	Non CAPs	5 373	8 326	15 783	15 595
	Total	12 675	18 429	32 010	33 292
Patients and HCPs	CAPs	10 637	11 976	12 766	14 208
	Non CAPs	5 223	5 587	4 708	4 672
	Total	15 860	17 563	17 474	18 880
Other sources*	CAPs	467	403	342	514
	Non CAPs	737	793	383	483
	Total	1 204	1 196	725	997
Total no. of ICSRs received (EEA)	CAPs	133 536	143 701	170 064	180 998
	Non CAPs	94 915	97 043	110 393	108 444
	Total	228 451	240 744	280 457	289 442
No. ICSR reported which have been identified as subject to medication error (EEA)	CAPs	1 723	1 928	2 636	3 429
	NAPs	2 353	2 593	3 121	3 649
	Total	4 076	4 521	5 757	7 078

*Please note that 'Other sources' were combined with 'Healthcare professionals' for charts on p. 10 - 11

1b. Number of individual case-safety reports (ICSRs) non European Economic Area

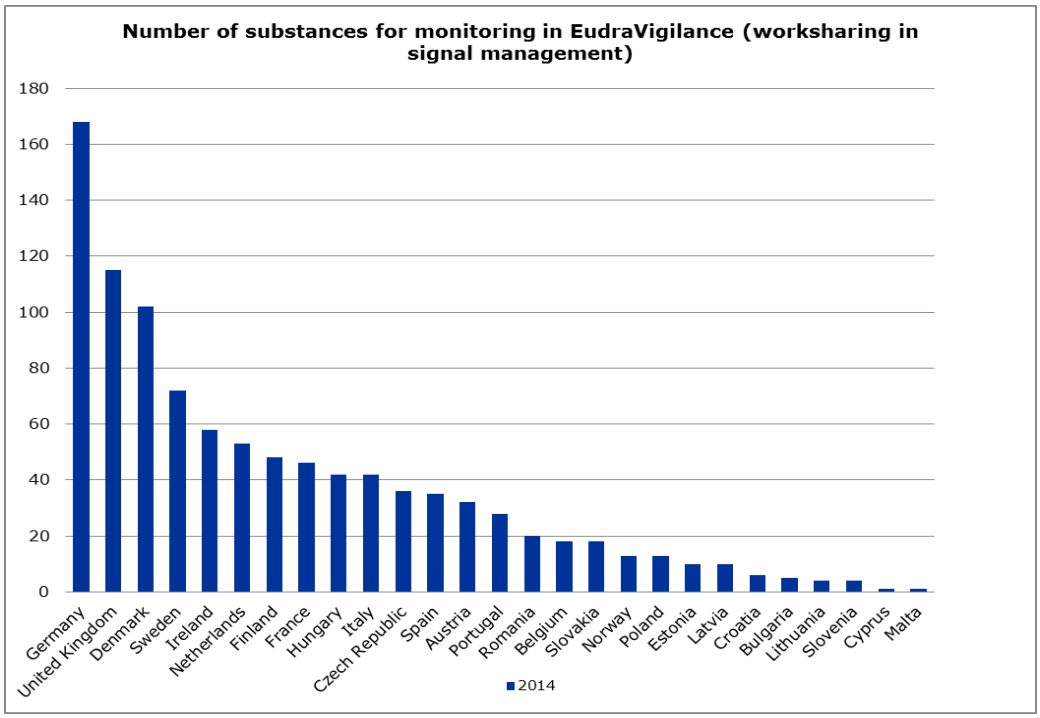
ADR reporting (non EEA)	2011	2012	2013	2014
Healthcare professionals	258 879	324 089	332 291	363 704
Patients	46 502	143 257	212 777	210 179
Other sources*	11 555	11 714	11 935	17 310
Patients and HCPs	100 980	134 532	156 794	174 361

*Please note that 'Other sources' were combined with 'Healthcare professionals' for charts on p. 10 - 11

ANNEX 2

2. SIGNALS

2a. Worksharing in signal management



2b. Numbers of signals

Signal reference data		2012	2013	2014
		July-December	January-December	January-December
No. of signal validated (total)	CAPs	43	63	55
	Non CAPs	19	29	16
	Total	62	92	71
No. of signal validated by NCA	CAPs	15	22	23
	Non CAPs	18	28	16
	Total	33	50	39
No. of signal validated by EMA	CAPs	28	41	32
	Non CAPs	1	1	0
	Total	29	42	32
No. of signal confirmed (total)	CAPs	33	54	47
	Non CAPs	18	27	15
	Total	51	81	62
No. of EMA signal confirmed	CAPs	24	34	27
	Non CAPs	1	1	0
	Total	25	35	27
No. of NCA signal confirmed	CAPs	9	20	20
	Non CAPs	17	26	15
	Total	26	46	35
No. of signal not confirmed (total)	CAPs	10	9	8
	Non CAPs	1	2	1
	Total	11	11	9
No. of EMA signal not confirmed	CAPs	4	7	5
	Non CAPs	0	0	0
	Total	4	7	5
No. of NCA signal not confirmed	CAPs	6	2	3
	Non CAPs	1	2	1
	Total	7	4	4

2c. Signal detection by lead Member State

Member State	Number of substances for signal detection (lead Member State – LMS)		
	2012	2013	2014
Germany (DE)	152	152	168
United Kingdom (UK)	114	114	115
Denmark (DK)	111	111	102
Sweden (SE)	54	54	72
Ireland (IE)	60	60	58
Netherlands (NL)	52	52	53
Finland (FI)	51	51	48
France (FR)	48	48	46
Hungary (HU)	42	42	42
Italy (IT)	34	34	42
Czech Republic (CZ)	79	79	36
Spain (ES)	35	35	35
Austria (AT)	27	27	32
Portugal (PT)	18	18	28
Romania (RO)	24	24	20
Belgium (BE)	19	19	18
Slovakia (SK)	19	19	18
Norway (NO)	13	13	13
Poland (PL)	13	13	13
Estonia (EE)	10	10	10
Latvia (LV)	15	15	10
Croatia (HR)	0	0	6
Bulgaria (BG)	5	5	5
Lithuania (LT)	4	4	4
Slovenia (SI)	5	5	4
Cyprus (CY)	1	1	1
Malta (MT)	1	1	1
TOTAL	1 006	1 006	1 000

3. RISK MANAGEMENT PLANS

3a. Number of Risk Management Plans

No. of Risk Management Plans submitted	2012 June-December	2013 January-December	2014 January-December
PRAC (CAPs)	48	637	597
National competent authorities (NAPs)	3 553	7 356	8 992

For distribution of the RMPs for the NAPs authorised by Member State, *see* *Annex 10*.

3b. Public Assessment reports as a measure of new approvals

No. of Public Assessment Reports published on EMA's web-portal for CAPs	2012	2013	2014
New applications	81	94	89
Extension of indications	50	50	51
RMP summaries (from Apr 2014)	N/A	N/A	54

4. ROUTINE BENEFIT RISK MONITORING (PERIODIC SAFETY UPDATE REPORTS)

4a. Number of PSURs

	2012	2013	2014
	July-December	January-December	January-December
PSURs reviewed at PRAC for CAPs only	20	430	426
PSURs reviewed at PRAC for CAPS and NAPS	0	6	45
Total number of PSUR reviewed at PRAC (CAP/NAP)	20	436	471
PSURs submitted to an NCA for assessment at national level only (NAP)	5 093	3 726	3 310

For distribution of the PSURs for the NAPs authorised by individual Member State, *see* *Annex 10*.

4b. PSUR worksharing

	2012	2013	2014
	July-December	January-December	January-December
No. of PSURs in which one NCA acted as lead Member State	62	151	116

4c. Medicines under additional monitoring as of December 2014

List			Annexes		List + Annexes		
CAPs	NAPs	Total	No. annexes	NAPs	Total CAPs	Total NAPs	Total - All
193	8	201	12	1 269	193	1 277	1 470

ANNEX 5

5. REFERRALS

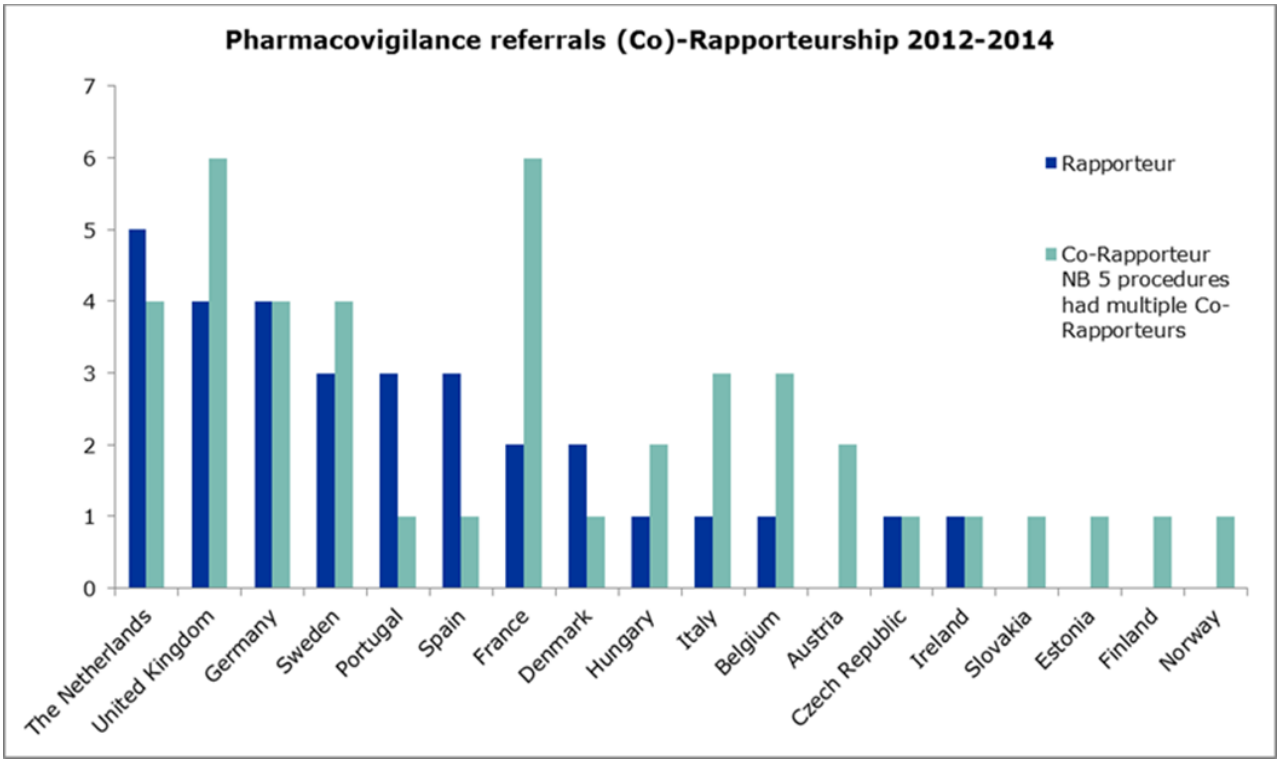
5a. Table of referral procedures, 2012-2014

Procedure name	INN (for overview)	Art.	Started	Triggered by	Outcome
2012					
Codeine	codeine	31	Oct-12	UK	V
Diclofenac	diclofenac	31	Oct-12	UK	V
SABA (Short Acting Beta Agonists)	terbutaline, salbutamol, hexoprenaline, ritodrine, fenoterol	31	Nov-12	HU	V,R
HES (Hydroxyethyl starch solutions)	hydroxyethyl starch	31	Nov-12	DE	V
Almitrine	almitrine	31	Nov-12	FR	R
Diacerein	diacerein	31	Nov-12	FR	V
2013					
Tredaptive	nicotinic acid/laropiprant	20	Jan-13	EC	S
Trevaclyn	nicotinic acid/laropiprant	20	Jan-13	EC	S
Pelzont	nicotinic acid/laropiprant	20	Jan-13	EC	S
Tetrazepam	tetrazepam	107i	Jan-13	FR	S
Cyproterone, ethinylestradiol - DIANE 35 & other medicines containing cyproterone acetate 2mg and ethinylestradiol 35 micrograms	cyproterone/ethinylestradiol	107i	Feb-13	FR	V
Combined hormonal contraceptives	desogestrel, gestodene, norgestimate, etonogestrel, drospirenone, dienogest, chlormadinone, norgestimate, nomegestrol acetate/estradiol, norelgestromin/ethinylestradiol	31	Feb-13	FR	V
Flupirtine	flupirtine	107i	Mar-13	DE	V
Domperidone	domperidone	31	Mar-13	BE	V,R
Nicotinic acid and related substances - acipimox, xantinol nicotinate	nicotinic acid, acipimox, xantinol nicotinate	31	Mar-13	DK	V
Kogenate Bayer/Helixate NexGen	octocog alfa	20	Mar-13	EC	V

Procedure name	INN (for overview)	Art.	Started	Triggered by	Outcome
Renin-angiotensin system (RAS)-acting agents	captopril, imidapril, zofenopril, candesartan, delapril, telmisartan, aliskiren, moexipril, enalapril, valsartan, fosinopril, irbesartan, perindopril, quinapril, ramipril, eprosartan, olmesartan, trandolapril, losartan, azilsartan, lisinopril, spirapril, benazepril, cilazapril	31	May-13	IT	V
Protelos/Osseor	strontium ranelate	20	May-13	EC	V
NUMETA G13%E, NUMETA G16%E emulsion for infusion and associated names	glucose, lipids, amino-acids and electrolytes	107i	Jun-13	SE	V,S
Zolpidem-containing medicinal products	zolpidem	31	Jul-13	IT	V
Hydroxyethyl starch (HES) - containing medicinal products	hydroxyethyl starch	107i	Jul-13	UK	V
Bromocriptine-containing medicines	bromocriptine	31	Sep-13	FR	V
Valproate related substances	valproate	31	Oct-13	UK	V
Iclusig	ponatinib	20	Dec-13	EC	V
2014					
Testosterone	testosterone	31	Apr-14	ET	V
Codeine for cough in paediatric population	codeine	31	Apr-14	DE	V,R
Ambroxol/Bromhexine	ambroxol/bromhexine	31	Apr-14	BE	V
Methadone	methadone	107i	Apr-14	NO	V,S
Hydroxyzine	hydroxyzine hydrochloride	31	May-14	HU	V
Corlentor and Procoralan	ivabradine	20	May-14	EC	V
Ibuprofen and dexibuprofen	ibuprofen and dexibuprofen	31	Jun-14	UK	V

Key to outcomes: **V**=variation of marketing authorisation; **S**=suspension of marketing authorisation (can be lifted if new evidence is presented by marketing authorisation holder); **R**=revocation of marketing authorisation (permanent). A referral of a group of medicines may result in differing outcomes for different medicines.

5b. Distribution of rapporteurships for referrals by Member State



ANNEX 6

6. POST-AUTHORISATION STUDIES

6a. Post-authorisation safety studies

	2012	2013	2014
	July-December	January-December	January-December
No. of imposed non interventional PASS protocols for CAPs reviewed at PRAC	4	11	23
Nationally imposed PASS	5	6	6

6b. Post-authorisation efficacy studies

	2014
CHMP imposed	14
National	1

7. INSPECTIONS

7a. Number of inspections

	2012	2013	2014
No. of pharmacovigilance inspections performed (CHMP mandated)	9*	6	13**
No. of pharmacovigilance inspections performed (CAP programme)	26	37	48
No. of pharmacovigilance inspections performed (EU total)	207	195	167

*7 from July-December 2012

**including 3 sites inspected for conduct of a PASS

7b. Master file and logbook

	2012	2013	2014
No. of occasions when the MAH to submit a copy of the PhV system master file	9	6	10

7c. Imposed penalties on marketing authorisation holders

	2012	2013	2014
	July-December	January-December	January-December
No. penalties to MAHs regarding noncompliance with their PhV obligations	0	4*	1

*includes one local infringement notice issued

ANNEX 8

8. MEDICATION ERRORS

8a. Individual case safety reports (ICSRs) related to medication errors

		2012	2013	2014
		July-December	January-December	January-December
No. ICSR reported which have been identified as subject to medication error (EEA)	CAPs	1 173	2 636	3 429
	NAPs	1 374	3 121	3 649
	Total	2 547	5 757	7 078
Total no. of ICSRs received (EEA)	CAPS	76 833	170 064	180 998
	Non-CAPs	51 669	110 393	108 444
	Total	128 502	280 457	289 442

ANNEX 9

9. PHARMACOVIGILANCE ACTIVITIES BY THE PRAC

9. Items on PRAC Agenda

Workload	2012 (Jul-Dec)	2013	2014
Art.31 referrals	7	54	34
Art.107i referrals		16	5
Art.5(3) referrals		3	1
Signals	51	127	118
RMPs	48	637	597
PSURs	20	438	470
PASS Protocols	5	91	137
PASS Results		13	51
Renewals, Conditional Renewals and Annual Reassessments		104	56
Pharmacovigilance Inspections	11	14	10
Other safety issues - CHMP	12	29	19
Other safety issues – Member State	5	8	23
Total items	159	1 534	1 521

10. PHARMACOVIGILANCE ACTIVITIES BY MEMBER STATES AT NATIONAL LEVEL

Question\MS-->	AT	BE	BG	CY	CZ	DE-Bfa	DE-PEI	DK	EE	ES	FI	FR	GR	HR	HU	IE	IT	LT	LV	MT	NL	NO	PL	PT	RO	SE	SI	SK	UK	Totals
1. RMPs	213	139	2001	965	280	545	63	0	426	3579	70	0	0	349	564	147	1327	1922	47	37	1085	421	66	1557	1539	250	492	1026	791	***19901***
2012 Jul-Dec	27	14	436	146	51	5	12	n/a	71	793	4	n/a	n/a	76	81	24	243	398	2	15	237	65	2	286	248	39	75	203	n/a	3553
2013	105	44	747	380	80	158	24	n/a	138	1187	34	n/a	n/a	127	246	69	503	712	15	9	392	146	1	625	624	105	152	437	296	7356
2014	81	81	818	439	149	382	27	n/a	217	1599	32	n/a	n/a	146	237	54	581	812	30	13	456	210	63	646	667	106	265	386	495	8992
2. PSURs	1492	108	0	519	1204	2827	157	366	45	872	43	250	0	26	50	432	403	54	553		1094	12	328	27	7	432	6	0	822	***11307***
2012 Jul-Dec	481	32	0	164	218	2074	47	232	4	213	25	21	n/a	n/a	13	234	97	13	218	n/a	414	6	84	n/a	1	156	5	n/a	341	4752
2013	436	38	0	281	346	491	75	86	13	340	13	109	n/a	n/a	27	127	164	21	230	n/a	412	2	148	5	2	165	0	n/a	195	3531
2014	575	38	0	74	640	262	35	48	28	319	5	120	n/a	26	10	71	142	20	105	n/a	268	4	96	22	4	111	1	n/a	286	3024
3. PASS	2											12		1	1			1												***17***
2012 Jul-Dec	0	0	0	0	n/a	n/a	0	n/a	0	0	n/a	4	0	0	0	0	0	1	0	0	n/a	0	0	0	0	n/a	0	0	0	5
2013	1	0	0	0	n/a	n/a	0	n/a	0	0	n/a	5	0	0	0	0	0	0	0	0	n/a	0	0	0	0	n/a	0	0	0	6
2014	1	0	0	0	n/a	n/a	0	n/a	0	0	n/a	3	0	1	1	0	0	0	0	0	n/a	0	0	0	0	n/a	0	0	0	6
4. PAES																	1													***1***
2014 May-Dec	0	0	0	0	n/a	0	0	n/a	0	n/a	n/a	n/a	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1
5. Penalties																	4												1	***5***
2012 Jul-Dec	0	0	0	0	n/a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	n/a	0	0	0	0	0	0	0	0	0
2013	0	0	0	0	n/a	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	n/a	0	0	0	0	0	0	0	1	3
2014	0	0	0	0	n/a	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	n/a	0	0	0	0	0	0	0	0	1

Table shows entries for activity at purely national level for each EEA country participating in the pharmacovigilance network, except for Luxembourg, Iceland and Liechtenstein for which no data were available.

Two sets of figures are shown for Germany, which has two NCAs (BfArm – the Federal Agency for Medicines and Health Products and PEI – the Paul-Ehrlich-Institute, Federal Institute for Vaccines and Biomedicines).

Where the data were not available this is indicated by n/a.

1