

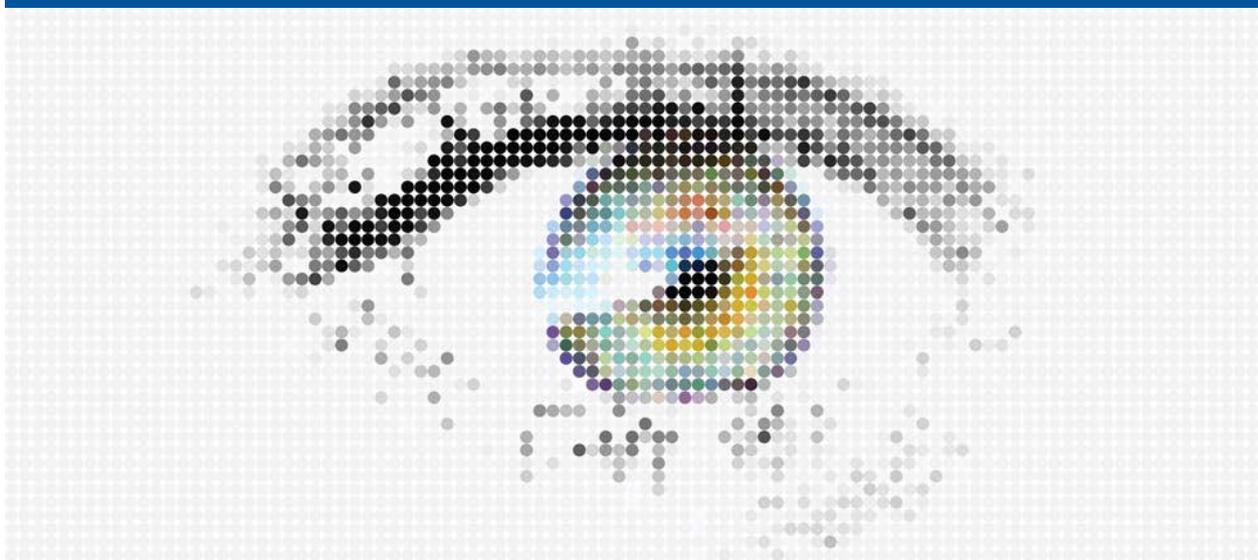


EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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Pharmacovigilance Department

# One-year report on human medicines pharmacovigilance tasks of the European Medicines Agency

Reporting period: 2 July 2012 to 1 July 2013



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# 1. Summary and Key Findings

## 1.1. European Union's new pharmacovigilance legislation

The European Union's (EU's) new pharmacovigilance (PhV) legislation, which applied from July 2012, offers better promotion and protection of public health through more clearly defined roles and responsibilities for the many stakeholders involved, simplified tasks, decreased duplication of effort, and targeted administrative simplification. The legislation was the biggest change to the regulation of human medicines in the EU since 1995 and had significant implications for applicants and for holders of EU marketing authorisations (MAs). The European Medicines Agency (the Agency/EMA) is responsible for implementing much of the new legislation, in collaboration with the national competent authorities and the European Commission.

Implementation of the new PhV legislation has been a complex process with the Agency's responsibilities significantly changed. Priorities for implementation of new PhV legislation, agreed by the EMA Management Board, have been and remain firstly public health activities, secondly transparency and communication activities and thirdly simplification activities. Based on this prioritised implementation, most of the new PhV legislation provisions are now fully operational, however, further implementation is required.

Based on the performance indicator evidence collected between 2 July 2012 and 1 July 2013 the Agency has demonstrated positive results in delivering its' PhV tasks since the start of operation of the new PhV legislation.

## 1.2. Collection of key information on medicines

- Better planning is evident – risk management plans are now routine and proportionate to the level of risk of the product and delivered for 100% of new centrally authorised product applications.
- The role of Periodic Safety Update Report (PSUR) assessment in public health impact is becoming clearer and examples have shown rapid and timely risk minimisation including restriction of indications.
- Posting of 135 Post-Authorisation Safety Studies (PASS) studies on the EU PAS (Post-Authorisation Studies) register has increased transparency of studies for patients and healthcare professionals.
- Adverse Drug Reaction (ADR) reporting has increased since implementing the new PhV legislation with over 9000 more patient reports received and approximately 175,000 more Individual Case Safety Reports (ICSRs) received in the EudraVigilance (EV) post marketing module (pre-duplicate removal) in the reporting period.
- With the launch of <http://www.adrreports.eu/> ADR data are more accessible to the public.

## 1.3. Analysis and understanding of data and information

- 47% of confirmed signals detected through the Agency's signal detection activities led to label changes during the data lock period (between 2 July 2012 and 1 July 2013).
- 9.3% of signals led to referral procedures (e.g. codeine overdose in children treated for pain, and hydroxy-ethyl starch infusions associated with fatal outcomes).

- Following the selection of the black-triangle as the black symbol by the Commission, the Additional Monitoring list was launched by the Agency in 2013. By August 2013 there were 119 listed medicines.
- The Agency provided the format and information technology (IT) tool for industry to submit structured information on medicines and received 337,751 submissions by September 2013.
- Requirements for EV and PSUR repositories and literature monitoring are being finalised<sup>1</sup>.

#### **1.4. Regulatory action to safeguard public health**

- The Pharmacovigilance Risk Assessment Committee (PRAC) was established on schedule with civil society representation completed in 2013. It has an increasing workload which is greatest for Risk Management Plans (RMPs), PSURs, and referrals.
- More timely decision-making has been delivered:
  - Article 31 referrals have been finalised in less than 8 months as compared to less than 15 months in previous years,
  - Article 107i referrals have been finalised in 3 months.
- Better evidence is being produced in support of regulatory decision-making e.g. routine identification of data needs for referrals.
- Major public health reviews have been initiated including those on:
  - all combined hormonal contraceptives and venous thrombo-embolism,
  - Diane-35 (and generics) and venous thrombo-embolism,
  - tetrazepam (and generics) and serious and fatal skin reactions,
  - diclofenac (including generics and products without prescription) and cardiovascular risk,
  - codeine-containing products (including generics) and overdose in children.

This will change the labelling and use of medicines taken by millions of EU citizens.

#### **1.5. Communicating with stakeholders**

Greater transparency of decision-making has been delivered in the form of agendas, minutes, and signal assessment outcomes from PRAC being posted on the Agency web site.

- The Agency website has been designated as the European medicines web portal for legal compliance.
- Better information is available for therapeutic decision-making including information about:
  - additional monitoring, e.g., use of the black triangle to draw attention to products under additional monitoring, and the web-posted additional monitoring list,
  - the Agency's withdrawn products procedure which clarifies the responsibility of industry and increases awareness of products withdrawn from the market,
  - ADR reporting by patients,

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<sup>1</sup> *Post report note*: the functionalities to be audited for the EV and PSUR repositories were adopted at the December 2013 EMA Management Board

- Signals mentioned in web posted highlights from PRAC meetings,
- outcomes of referral procedures and other safety issues through coordinated Community warnings.
- The Agency issued 70 'Lines to Take' to the Network between 2 July 2012 and 1 July 2013.
- The Agency issued 197 Notifications to Member States (MSs) regarding safety announcements between 2 July 2012 and 1 July 2013.
- Good Vigilance Practice (GVP) modules on core processes were delivered on schedule by June 2012.
- The US Food and Drug Administration (FDA)-EMA multi-lateral PhV cluster with Japan and Canada as observers started in 2013.
- The Agency has trained approximately 10,400 individuals in PhV over the past years and in 2013 developed and published a catalogue containing all the training material prepared in the context of the implementation of the PhV legislation.

### ***1.6. Monitoring of regulatory actions and related activities including process improvement***

- PhV inspection and compliance monitoring are achieving performance targets:
  - 100% of inspections have been conducted in accordance with the risk-based programme for routine PhV inspections of Market Authorisation Holders (MAHs) with centrally authorised products (CAPs),
  - Cases of MAH non-compliance identified during PhV inspections and non-compliance issues reported by the MAH to the regulatory authorities were discussed at PRAC.
- There is on-going process improvement through leveraging developments in regulatory science and experience using the new legislation:
  - Evidence-based recommendations for the design, conduct and analysis of PASS studies to improve their quality, validity and value,
  - Evidence-based recommendations on the choice and application of methods to increase the effectiveness of signal detection from spontaneous reports and electronic health records has increased the capacity for signal detection,
  - Evidence-based guidance and public internet-based demonstration tool on methods for the assessment and visualisation of the benefit-risk of medicinal products,
  - Revisions of relevant regulatory and scientific guidelines including GVP Modules VIII (PASS) and IX (Signal Management), Guideline on the use of statistical signal detection methods in the EV data analysis system, Checklist for Study protocols, European Network for Centres of Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide for methodological standards in pharmacoepidemiology.

### ***1.7. Continuous improvement***

Implementation of the new PhV legislation, based on the legal requirements, is on track, e.g., GVP, PRAC, revised procedures, etc. As implementation has progressed, the Agency and stakeholders have reflected on the experience with the new PhV legislation. The data in this report support the

expectation that the main objectives of the new PhV legislation are being achieved, e.g., improved timeliness of procedures, greater transparency, etc. Implementation of PhV legislation will continue through 2014 according to the prioritised implementation plan with further reflection on measuring performance especially as relates to behaviour change and impacts on public health and industry needed as the remaining elements of the new PhV legislation become operational.

The EU is seen as a global leader in PhV, an example being the leadership shown by the ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) guideline development around extending PSURs to provide greater emphasis on cumulative benefit and risk knowledge regarding medicines, by establishing the multi-lateral EMA-FDA PhV Cluster initiative, by requests to lead harmonisation activities by fellow medicines regulators, and by the date in the PSUR-EURD (EU Reference Date) list followed by some foreign regulators beyond the EU.

Throughout the first year of operation of the new PhV legislation, the Agency has engaged with a large number of stakeholders through open dialogue and exchange, recognising the roles and responsibilities of each party in the PhV activities for medicines authorised in the EU. The Agency will continue to collect, monitor and use the data to identify and implement possible administrative and scientific improvements, with the intention to facilitate the highest quality PhV and to remove any unnecessary burdens. In the spirit of continuous quality improvement, the Agency has identified various improvement actions to be implemented.

### ***1.8. Major change delivered toward goals of increased trust and transparency***

The Agency has shown leadership in putting into operation its PhV tasks through collaboration, consultation and concentration on PhV activities. There is concrete evidence that major change has been delivered which should lead to better public health. This is shown by strengthened clarity of roles and responsibilities of parties involved in PhV activities in the EU, greater transparency of information about safety of medicines, improved timeliness of procedures, etc. Changes brought about by the new PhV legislation, such as increased transparency of scientific committee proceedings and decision-making are increasing the understanding and trust of patients and health care professionals in the safe use of medicines in the EU.

## **2. Introduction**

- Pharmacovigilance

Before a medicine is authorised for use, evidence of its safety and efficacy is 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. Once a product has been authorised and marketed in the European Union (EU), the European Medicines Agency plays a key role in the ongoing pharmacovigilance (PhV). PhV, as defined by the World Health Organization (WHO), is - the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem. The aims of PhV are to enhance patient care and patient safety in relation to the use of medicines; and to support public health programmes by providing reliable, balanced information for the effective assessment of the risk-benefit profile of medicines. Some side effects or 'adverse reactions' (ARs) may not be seen until a very large number of people have received the medicine and used it over longer time periods in real life use often in more diverse populations/subpopulations and with more concomitant medications than used in clinical trials. The real

life use of medicines only happens once healthcare professionals begin prescribing/dispensing. It is therefore vital that the safety of all medicines is monitored throughout their use in healthcare practice.

In terms of a burden to society, 5% of all hospital admissions are due to an Adverse Drug Reaction (ADR). 5% of patients in hospitals suffer an ADR with ADRs being the 5th most common cause of hospital death. It is estimated that 197,000 deaths per year in the EU are caused by ADRs and that even small improvements in the PhV system will have a major impact on public health and society<sup>2</sup>.

- Objective of this report

The objective of this report is to present the European Commission (EC) with the first year experience with the Agency's PhV tasks subsequent to application of the new PhV legislation. The report aims to summarise the initial measurement of structural and process performance indicators (PIs).

The Agency is hereby providing a report on the its' PhV tasks as the report referenced in the new PhV legislation. Article 29 of Regulation (EC) No 726/2004<sup>3</sup> as amended by Regulation (EU) No 1235/2010<sup>4</sup> states, "The Commission shall make public a report on the performance of pharmacovigilance tasks by the Agency on 2 January, 2014 at the latest and subsequently every 3 years thereafter".

#### Objectives of this report on the Agency's pharmacovigilance tasks

1	Present a summary of the initial structural and process performance indicators used in the measurement of the Agency's PhV tasks
2	Provide a summary of the Agency's PhV tasks (Section 3)
3	Provide an overview of the elements of the new PhV legislation introduced to date and what is left to be done (Section 4)
4	Provide results of indicator data on the Agency PhV tasks for the first year of operation of the new PhV legislation from 2 July 2012 to 1 July 2013 (Section 6)

### 2.1. Reporting Period

This report mainly captures information from the period 2 July 2012 to 1 July 2013 ("reporting period"). Data from previous years, data from before the operation of the new PhV legislation, as well as key implementation milestones, e.g., publication of ADR data and of the format and information technology tool (Article 57 database) for MAHs to facilitate provision of medicinal product information to the Agency, have been included where available and relevant. Reference to other differing reporting periods are duly noted in the report.

### 2.2. Data Sources used for this report

Various data sources were used in this report, including Agency databases, as well as data collection by Agency scientific committee secretariats such as the Pharmacovigilance Risk Assessment Committee

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<sup>2</sup> European Commission, Staff Working Document, Impact Assessment, SEC(2008) 2670 Volume I, Accompanying Document to the Proposal for a Regulation amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 and the Proposal for a Directive amending, as regards pharmacovigilance, Directive 2001/83/EC

<sup>3</sup> 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, 30.04.2004, p.1)

<sup>4</sup> Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 10 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 advance therapy medicinal products (OJ L 348, 31.12.2010, p.1)

(PRAC). Information provided has not been collected from or confirmed with any organisation outside of the Agency. Where available, already produced summary reports have been used as source information for comparisons. The precision or level of detail of the data measured by each indicator and the differing record system on which they may be based may vary, e.g., electronic databases versus spread sheets, data collections from projects necessary to the operation of the new PhV legislation, etc.

### **2.3. Performance Indicators included in this report**

This report provides measures of the performance of the Agency's PhV tasks using process and structural types of indicators to focus performance measurement across the range of Agency pharmacovigilance tasks. The report includes quantitative and qualitative information and examples about the Agency's PhV tasks (Coglianese, 2012<sup>5</sup>), (EMA, 2012<sup>6</sup>), (EC, 2009<sup>7</sup>), (EC, 2008<sup>8</sup>), (EMA, 2010<sup>8,9</sup>). Several of these indicators have been used as part of programme governance by the Agency for some time while others have been developed to be more reflective of specific outputs subsequent to the application of the new PhV legislation. Some represent basic workload measurement, e.g., counts of numbers of PhV procedures or submissions; numbers of Agency peer-reviews or scientific committee discussions on various procedures. Others are Key Performance Indicators (KPIs), defined as the limited set of indicators most important to a strategic understanding of the Agency's functioning.

### **2.4. Outside of the scope for this report**

The data elements used in preparing this report may not be all inclusive of the Agency's tasks that are related to PhV of Human Medicines, e.g., all policy development and all International Relations workload and resource expenditures are not captured in this report. This report is also not intended to be an impact evaluation as regards the new PhV legislation. Outcome indicators such as for assessing behaviour change and health system or industry outcomes and impacts are outside the scope of the current report. The PhV tasks of National Competent Authorities (NCAs) and MAHs are also outside the scope of this report.

### **2.5. Compliance Management Objectives**

The Commission Implementing Regulation (EU) No 520/2012<sup>10</sup> Section 3, Article 15 outlines certain Compliance Management Objectives. A summary of how the Agency's performance of its PhV tasks fulfils these objectives is in section 6.2.

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<sup>5</sup> Coglianese, C., Measuring Regulatory Performance – Evaluating the impact of regulation and regulatory policy, OECD, August 2012

<sup>6</sup> European Medicines Agency, Guideline on good pharmacovigilance practices (GVP), Module I – Pharmacovigilance systems and their quality systems.

([http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2012/06/WC500129132.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129132.pdf) )

<sup>7</sup> European Commission, Impact Assessment Guidelines, SEC(2009) 92, 2009

<sup>8</sup> Road Map to 2015 – European Medicine's Agency's contribution to Science, Medicines and Health, EMA Management Board, December 2010 @ [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2011/01/WC500101373.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/01/WC500101373.pdf)

<sup>9</sup> Implementing the European Medicines Agency's Roadmap to 2015: The Agency's contribution to Science, Medicines, and Health "From Vision to Reality", @

[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2011/10/WC500115960.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/10/WC500115960.pdf)

<sup>10</sup> 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, 10.06.2012, p. 5)

## 3. Overview of Agency pharmacovigilance tasks

- The Agency operates a PhV system which interconnects with the European Commission and the systems operated by each National Competent Authority (NCA), together forming the PhV pillar of the EU regulatory network

### 3.1. Stakeholders

The Agency plays a key role in coordinating activities relating to the authorisation and supervision of medicines, including safety monitoring and other PhV tasks, across the EU network.

### 3.2. Pharmacovigilance System

To fulfil the extensive requirements of the new PhV legislation, the Agency has established a matrix managed PhV System within the Agency, with the Agency's PhV tasks integrated into the lifecycle management of medicines which is performed in several divisions. The Agency also carries out PhV tasks as part of the EU PhV regulatory network with NCAs of EU Member States (MSs).

### 3.3. Agency pharmacovigilance tasks and related objectives

The list of EMA Pharmacovigilance tasks for centrally authorised products and nationally authorised products, where applicable, is based both on the pharmacovigilance activities included in the EU pharmacovigilance legislation and the Good pharmacovigilance practice (GVP) modules. These tasks are also listed in the Agency's Pharmacovigilance System Manual. The Manual is intended to be made public. This list of tasks is not intended to be a fulsome list of all Agency PhV activities related to the PhV tasks since it would be too lengthy to include in this report, e.g., for PSURs this list could include activities such as preparing the list of harmonised submission dates, preparation of PRAC advice and updated EURD list following MAH request, validation of PSURs, preparation of data for the rapporteur from the EV database, preparation of PRAC, Committee for Medicinal Products for Human Use (CHMP)/Coordination Group for Mutually Recognised and Decentralised Procedures (human) (CMDh) outcomes, etc. The principal Agency pharmacovigilance tasks include the following:

1. EMA Pharmacovigilance system delivering the requirements of the quality system (based on GVP Module I) – *maintenance of system and audit of system*
2. Pharmacovigilance inspections (based on GVP Module III) - *coordination*
3. Risk Management Systems (based on GVP Module V) – Risk Management Plan (*RMP*) *coordination*
4. Adverse Drug Reaction (*ADR*) Case Report Management (based on GVP Module VI), including ADR collection and management as well as provision of data support and analysis – *facilitation of ADR reporting by MAHs and patients/health care professionals, literature monitoring*
5. Periodic Safety Update Reports (*PSURs*)(based on GVP Module VII), including management of EURD list – *coordination*
6. Post-Authorisation Studies (*PAS*) (based on GVP Module VIII) – coordination regarding Post-Authorisation Safety Studies (*PASS*) and Post-Authorisation Efficacy Studies (*PAES*)
7. Signal Management (based on GVP Module IX)
8. Emerging Safety Issues (based on GVP Module IX) and Incident Management (see Section 12 of PhV System Manual) - *management*

9. Management of list(s) of products, including products under additional monitoring (GVP Module X) as well as list of withdrawn products
10. Safety Communications (based on GVP Module XV) – *coordination of publication of PhV information*
11. Pharmacovigilance referrals - *coordination*
12. Guidance coordination (including GVP development) and standards for the system
13. Training and capacity building, including European Network for Centres of Pharmacoepidemiology and Pharmacovigilance (*ENCePP*)
14. Monitoring the compliance of Marketing Authorisation Holders (*MAHs*)
15. Coordination of stakeholders' (pharmacovigilance) enquiries

Related activities include:

- PhV Information Technology (*IT*) systems development and maintenance
- Scientific committees and decision-making, e.g., PRAC, (CHMP), (CMDh) regarding PhV issues
- International harmonisation activities regarding PhV, e.g., regarding ADR data collection and Individual Case Safety Reports (ICSR) coding standards, e.g., Medical Dictionary for Regulatory Activities (MedDRA), etc.
- Stakeholder relations/consultations including organisation and use of public hearings, and responding to PhV Helpdesk enquiries
- Process Improvement (e.g., Best evidence development leveraging ENCePP, IMI-PROTECT [Innovative Medicines Initiative - Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium], and Drug Utilisation Studies [DUS] for addressing data gaps in pharmacovigilance issues assessments)
- Performance measurement and use of results in governance (Structure/Process, Behaviour Change, and Outcomes measurement).

## 4. New pharmacovigilance legislation

### 4.1. Background

The EC began a review of the European system of safety monitoring in 2004 including an independent study sponsored by the EC and extensive public consultation in 2006 and 2007. The new PhV legislation was adopted by the European Parliament (EP) and Council of Ministers in December 2010 and was applied from July 2012. The new legislation amends existing PhV legislation contained in Directive 2001/83/EC<sup>11</sup> and Regulation (EC) No. 726/2004<sup>3</sup>. The legislation was further amended in 2012 (see Section 4.6.). The Agency works with the EC, NCAs in MSs, and a wide range of stakeholders including patients, healthcare professionals and industry, to ensure effective implementation and operation of the new PhV rules. There are other general legislative references pertaining to reporting requirements, concerning operation of PhV tasks and procedures<sup>12, 13, 14</sup>

<sup>11</sup> 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)

<sup>12</sup> Title III Placing on the Market, Chapter 4 Mutual recognition and decentralized procedure - Article 38 – (1) Agency shall publish an annual report on the procedures laid down in this Chapter and shall forward that report to the European Parliament and the Council for information; (2) At least every ten years the Commission shall publish a report on the experience acquired on the basis of the procedures described in this Chapter and propose any amendments which may be necessary to improve those procedures

## **4.2. Goals of the new pharmacovigilance legislation for EU citizens**

For EU citizens, the new PhV legislation had a number of goals:

- to strengthen patient involvement in the monitoring of medicines;
- to reduce the burden of ADRs;
- to inform and engage them on the benefit-risk aspects of taking a medicine;

## **4.3. Operational objectives of the new pharmacovigilance legislation**

The legislation aimed to:

- make roles and responsibilities clearer;
- minimise duplication of effort;
- free up resources by rationalising and simplifying reporting of periodic safety update reports (PSURs) and ADRs;
- establish a clear legal framework for post-authorisation monitoring;
- strengthen reporting systems for collection of high-quality data on the safety of medicines;
- provide a more rigorous, science-based approach that integrates the concepts of benefit-risk balance and risk management planning;
- increase engagement of patients and healthcare professionals;
- enable provision of more and better information to the public, with greater transparency of the decision making processes.

It was estimated that these measures could save up to approximately 5,000 lives, while providing savings to society of some €2.5 billion per year in the EU<sup>2, 15</sup>.

## **4.4. Orientation to the new pharmacovigilance legislation**

The legislation's initiatives can be grouped as actions in the following topic areas reflecting the overall process for safety monitoring in the EU:

### **4.4.1. Collection of key information on medicines**

- Risk management plans (RMPs) with proportionate risk management
- Periodic safety update reports (PSURs)
- Post-authorisation safety and efficacy studies (PASS/PAES)
- Electronic submission of information on medicines

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<sup>13</sup> Title IX Pharmacovigilance , Chapter 5 Implementation, Delegation and Guidance - Article 108b – The Commission shall make public a report on the performance of pharmacovigilance tasks by the Member States on 21 July 2015 at the latest and every 3 years thereafter

<sup>14</sup> Title V General and Final Provisions – Article 86 – At least every 10 years, the Commission shall publish a general report on the experience acquired as a result of the operation of the procedures laid down in this Regulation, in Chapter 4 of Title III of Directive 2001/83/EC and in Chapter 4 of Title III of Directive 2001/82/EC

<sup>15</sup> European Commission, Staff Working Document, Annexes, SEC(2008) 2670 Volume II, Accompanying Document to the Proposal for a Regulation amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 and the Proposal for a Directive amending, as regards pharmacovigilance, Directive 2001/83/EC

- Adverse drug reaction reporting by patients and healthcare professionals

#### **4.4.2. Analysis and understanding of data and information**

- Strengthened signal detection in EudraVigilance
- Additional monitoring of medicines
- Enhanced PhV IT (information technology) systems

#### **4.4.3. Regulatory action to safeguard public health**

- Changes in scientific committees and decision-making
- Strengthened referral procedures

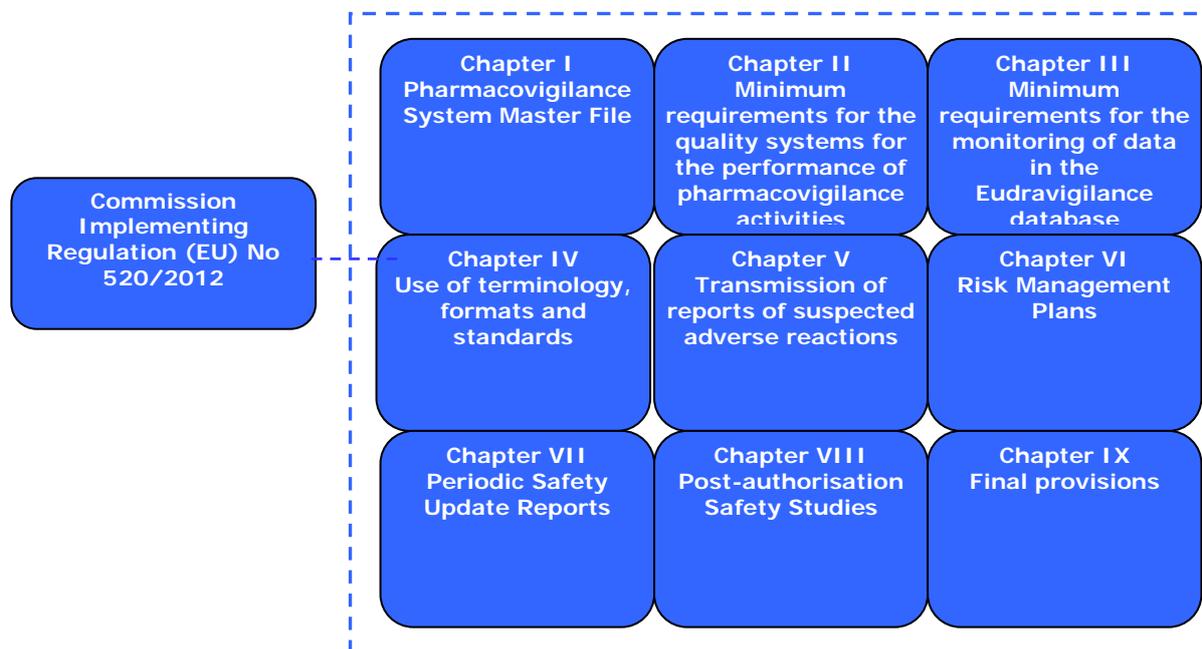
#### **4.4.4. Communicating with stakeholders**

- Publishing of information on medicines
- Coordination of safety messages
- Public hearings

#### **4.5. Structure of the implementing regulation**

In order to set uniform conditions regarding the implementation of certain aspects of the new PhV legislation, the implementing regulation (Commission implementing regulation No 520/2012<sup>10</sup>) of 19 June 2012 was adopted. This is a legally binding act of the European Commission (EC) that provides details on the operational aspects for the new legislation. The implementing regulation was structured into chapters as illustrated in [Figure 1.](#) :

**Figure 1.** Implementing regulation structure



#### **4.6. Amendments to new pharmacovigilance legislation in 2012**

The new PhV legislation was further amended in October 2012 by Regulation (EU) No 1027/2012<sup>16</sup>, which applied as of 5 June 2013 and Directive 2012/26/EU<sup>17</sup>, which applied as of 28 October 2013. The amendments further strengthened the protection of patient health with the following measures.

##### **4.6.1. Strengthened requirements for notification of cessation of marketing and withdrawal**

Marketing-authorisation holders of human medicines have to notify the EU regulators of any action to withdraw a product from the market (to suspend marketing, to withdraw from market, to request withdrawal of a market authorisation, or not to apply for a renewal of a market authorisation), together with the reason for this action, no less than two months before the interruption. The MAH shall also make the notification in cases where the action is taken in a third country. Each year the Agency shall make public a list of the medicinal products for which the market authorisation has been refused, revoked or suspended in the Union, whose supply has been prohibited or which have been withdrawn from the market, including the reasons for such action.

##### **4.6.2. Changes to referral procedures**

Article-107*i* (Urgent Union) referral procedures are now triggered automatically if a MS or the EC, as a result of the evaluation of data resulting from PhV activities, suspends or revokes a marketing authorisation (MA), prohibits the supply of a medicinal product or refuses a renewal of a MA or 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 marketing

<sup>16</sup> Regulation (EU) No 1027/2012 of the European Parliament and of the Council of 25 October 2012 amending Regulation (EC) No 726/2004 as regards pharmacovigilance (OJ L 316, 14.11.2012, p.38)

<sup>17</sup> Directive 2012/26/EU of the European Parliament and of the Council of 25 October 2012 amending Directive 2001/83/EC as regards pharmacovigilance (OJ L 299, 27.10.2012, p.1)

authorisation withdrawn, or that he intends to do so or has not applied for the renewal of a marketing authorisation.

For Article-31 referral procedures, when the EC or a MS considers urgent action is necessary to protect public health, they may suspend or prohibit the use of a medicine at any stage of the procedure, as a temporary measure until a definitive decision on the referral is adopted. The amendments also stipulate that for procedures covering a range of medicines, centrally authorised medicines shall be included in the procedure whether the grounds for the procedure are based on safety, efficacy or quality issues.

### **4.6.3. Translation exemptions**

To facilitate the availability of medicines across the EU, the 2012 amendments of the pharmacovigilance legislation have extended the scope of translation exemptions to include cases of severe issues of availability, including shortages of medicines. In these cases, the marketing-authorisation holder can request an exemption to translate the package leaflet, and now also the labelling, of the medicine into the official languages of the Member State concerned. Prior to these amendments, translation exemptions already applied to medicines intended for the treatment of rare conditions and medicines that are administered by healthcare professionals only.

### **4.6.4. Extended scope of additional monitoring**

The mandatory scope of the medicines subject to additional monitoring has been extended to include medicines given conditional approval or authorised under exceptional circumstances, medicines authorised with specific obligations on the recording or monitoring of suspected adverse drug reactions, and medicines for which the MAH is required to carry out a PASS.

## ***4.7. Prioritised implementation of the new PhV legislation***

Many of the new PhV legislation provisions are now fully operational, however, further implementation is required, particularly for those processes, assessments, services and information technology developments subject to resource constraints. Priorities for implementation of new PhV legislation are, firstly public health activities, secondly transparency and communication activities and thirdly simplification activities.

## **5. Milestones in implementing new pharmacovigilance tasks**

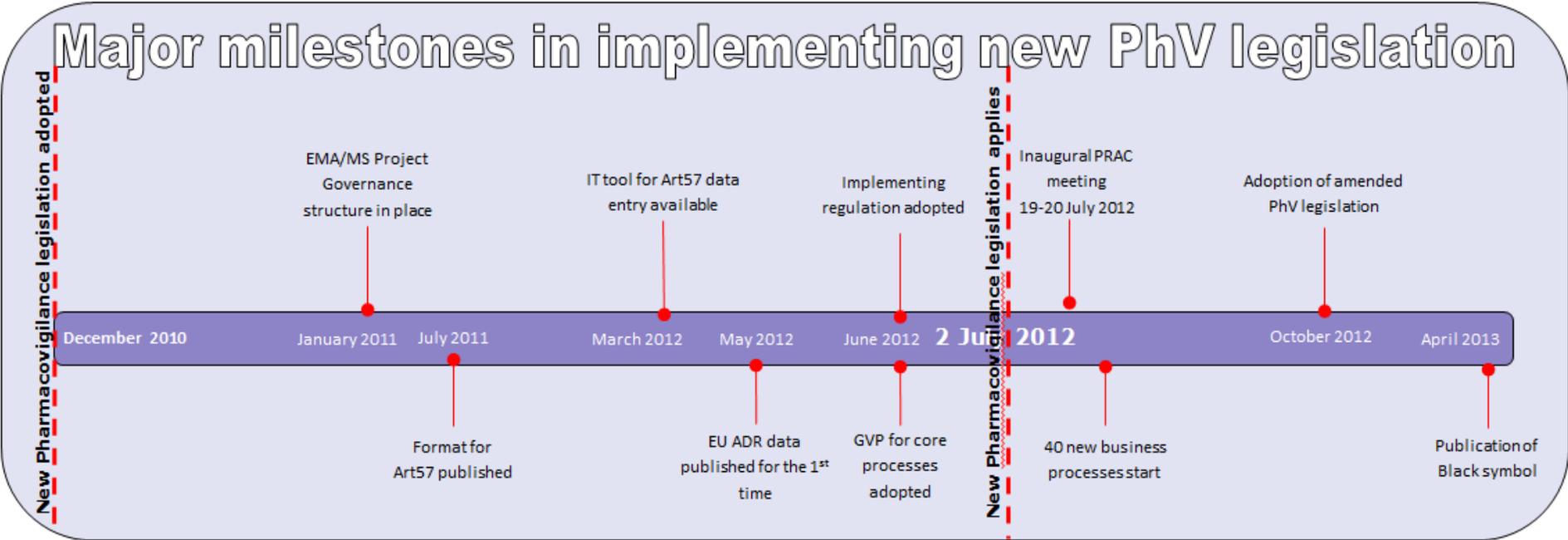
### Highlights

- Pharmacovigilance Risk Assessment Committee (PRAC) met first in July 2012
- All core process Good Vigilance Practice (GVP) chapters/modules were delivered on schedule

### ***5.1. Timeline chart for major milestones***

Key timelines for delivering on the new PhV legislation in the data collection period for this report are shown in the below [Figure 2.](#) and in the [Table 1.](#) titled "Progress report table on operation of the new Phv legislation at the Agency (data lock point 1 July 2013)" for a more inclusive list:

Figure 2. Timeline chart - major milestones



**Table 1.** Progress report table on operation of the new Phv legislation at the Agency (data lock point 2 July 2013)

Implemented  On-going implementation  Not started/not ready 				
COLLECTION OF KEY INFORMATION ON MEDICINES				
1.	Risk Management Plans (RMPs)	2012	2013	Progress
	Establishment of operation of new procedure for requesting and assessing RMP			<ul style="list-style-type: none"> <li>Started July 2012</li> <li>Templates for industry (Oct 2012)</li> <li>Format compulsory (Jan 2013)</li> </ul>
2.	<b>Periodic Safety update Reports (PSURs)</b>			
	<ul style="list-style-type: none"> <li>Operation of new procedures related to PSURs for CAPs</li> </ul>			<ul style="list-style-type: none"> <li>Started July 2012</li> </ul>
	<ul style="list-style-type: none"> <li>Development, maintenance and publication of harmonized birthdates to support PSUR submission</li> </ul>			<ul style="list-style-type: none"> <li>First list published Oct 2012 (monthly updates)</li> </ul>
	<ul style="list-style-type: none"> <li>Handling of PSURs for active substances contained in both CAPs and NAPs in accordance with European Union Reference Date (EURD) list</li> </ul>			<ul style="list-style-type: none"> <li>Started June 2013</li> </ul>
	<ul style="list-style-type: none"> <li>Delivery of PSUR repository and single PSUR assessment process for NAPs allowing centralized reporting for industry and faster warnings for NAPs</li> </ul>			<ul style="list-style-type: none"> <li>Functionalities to be audited agreed at December 2013 EMA Management Board. Repository available to industry in 2015.</li> </ul> 
3.	<b>Post-Authorization Safety and Efficacy Studies (PASS/PAES)</b>			
	<ul style="list-style-type: none"> <li>Implementation of the PASS procedure for protocols approval and results management for CAPs</li> </ul>			<ul style="list-style-type: none"> <li>Started July 2012</li> </ul>
	<ul style="list-style-type: none"> <li>PAES: Public consultation on delegated act on PAES by EC</li> </ul>			<ul style="list-style-type: none"> <li>From 28/11/2012 to 18/02/13</li> </ul>
	<ul style="list-style-type: none"> <li>PASS: Operate the procedure for initial protocol and protocol amendment endorsement and results</li> </ul>			<ul style="list-style-type: none"> <li>Started 2013</li> </ul>

Implemented 		On-going implementation 		Not started/not ready 	
	management for NAPs				
	<ul style="list-style-type: none"> <li>PASS: Establish a procedure to encourage MAHs to collaborate on PASS affecting multiple medicinal products</li> </ul>				
	<ul style="list-style-type: none"> <li>PAES: Deliver scientific guidance on methodological aspects (expert workshop)</li> </ul>				<ul style="list-style-type: none"> <li>PAES expert workshop held 24/10/13-25/10/13</li> </ul>
<b>4.</b>	<b>Electronic submission of core medicine information by MAHs ('Article 57')</b>	<b>2012</b>	<b>2013</b>	<b>Progress</b>	
	<ul style="list-style-type: none"> <li>Start validation of received information</li> </ul>				
	<ul style="list-style-type: none"> <li>Initiate limited quality assurance of data being submitted on medicinal products authorized in EU</li> </ul>				
	<ul style="list-style-type: none"> <li>Achieve an agreement with industry on submission of varied marketing authorizations in view of operating the process for submission of maintenance data at later stage</li> </ul>				<ul style="list-style-type: none"> <li>Last workshop with industry representatives held 22/05/13</li> </ul>
	<ul style="list-style-type: none"> <li>Updates (variations) to data can be submitted and data fully used to support regulation, safety and stakeholder needs</li> </ul>				<ul style="list-style-type: none"> <li>ICT development in progress</li> <li>Variations to start 2014</li> </ul> 
<b>5.</b>	<b>Reporting by patients</b>				
	<ul style="list-style-type: none"> <li>Cooperation with MS to provide information to patients on direct reporting</li> </ul>				<ul style="list-style-type: none"> <li>Core data fields agreed by MS (June 2012)</li> </ul>
	<ul style="list-style-type: none"> <li>Prepare guidance on patient reporting in cooperation with MS</li> </ul>				<ul style="list-style-type: none"> <li>Draft guidance available and undergoing consultation with the Member States</li> </ul>
<b>6.</b>	<b>List of medicines withdrawn for safety reasons</b>				
	<ul style="list-style-type: none"> <li>Develop business process for establishing, maintaining and publishing such list</li> </ul>				<ul style="list-style-type: none"> <li>Based on 2012 changes to PhV legislation</li> <li>Process start October 2013</li> </ul>

Implemented		On-going implementation		Not started/not ready	
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7.	<b>Literature monitoring</b>			
	<ul style="list-style-type: none"> <li>EMA service to industry for population of Eudravigilance with case reports of old substances</li> </ul>			<ul style="list-style-type: none"> <li>Service available to industry in 2015</li> </ul> 

### BETTER ANALYSIS/UNDERSTANDING OF DATA AND INFORMATION

1.	Eudravigilance and signal detection	2012	2013	Progress
	<ul style="list-style-type: none"> <li>Operation of revised signal detection process for CAPs</li> </ul>			<ul style="list-style-type: none"> <li>Started July 2012</li> </ul>
	<ul style="list-style-type: none"> <li>Support MS to operate the new EU signal detection processes for NAPs</li> </ul>			<ul style="list-style-type: none"> <li>Started July 2012</li> <li>Signal work-sharing list published Oct 2012</li> </ul>
	<ul style="list-style-type: none"> <li>Start of signal management through PRAC</li> </ul>			<ul style="list-style-type: none"> <li>Started Sept 2012</li> </ul>
	<ul style="list-style-type: none"> <li>Continuation of maintenance work for current EV system including data quality</li> </ul>			<ul style="list-style-type: none"> <li>As planned</li> </ul>
	<ul style="list-style-type: none"> <li>Implementation of web-publishing of adverse reaction data (further to EV Access Policy)</li> </ul>			<ul style="list-style-type: none"> <li>Delivered May 2012 for CAPs</li> </ul>
	<ul style="list-style-type: none"> <li>Perform analyses of EV data for NAPs (in collaboration with MS Competent Authorities through work-sharing)</li> </ul>			<ul style="list-style-type: none"> <li>Operational 2012</li> </ul>
	<ul style="list-style-type: none"> <li>Delivery of enhanced functionalities and IT system audit results in centralized reporting for industry</li> </ul>			<ul style="list-style-type: none"> <li>Agreement on the functionalities to be audited at December 2013 EMA Management Board. Simplification delivered to industry 2016/17</li> </ul> 
2.	<b>Additional monitoring</b>			
	<ul style="list-style-type: none"> <li>Develop and publish list of medicines with additional monitoring status</li> </ul>			<ul style="list-style-type: none"> <li>Initial list published 25/04/13</li> </ul>

Implemented 		On-going implementation 		Not started/not ready 	
	<ul style="list-style-type: none"> <li>Monitor that product information for relevant CAPs is updated to reflect this status</li> </ul>				<ul style="list-style-type: none"> <li>First Black Triangles starting to appear Q4 2013</li> </ul>
<b>3.</b>	<b>Medication errors</b>				
	<ul style="list-style-type: none"> <li>Establish guidance/best practice considerations on medication error prevention and reporting</li> </ul>				<ul style="list-style-type: none"> <li>Stakeholder workshop held 28/02/13-01/03/13</li> <li>Heads of Medicines Agencies consulted Q4 2013</li> </ul>
<b>REGULATORY ACTION TO SAFEGUARD PUBLIC HEALTH</b>					
<b>1.</b>	<b>Scientific committees and decision-making</b>	<b>2012</b>	<b>2013</b>	<b>Progress</b>	
	<ul style="list-style-type: none"> <li>Establishment and running of new committee (PRAC) and responsibilities for CMD(h)</li> </ul>			<ul style="list-style-type: none"> <li>Established July 2012</li> </ul>	
	<ul style="list-style-type: none"> <li>PRAC outputs: establish a strategy for supporting PRAC assessments and recommendations with 'best evidence', including aspects of effectiveness of risk minimization/impact on regulatory action</li> </ul>			<ul style="list-style-type: none"> <li>Monthly 'best evidence' meetings held to support PRAC</li> <li>Strategy document under development</li> </ul>	
	<ul style="list-style-type: none"> <li>Implement risk-based system for measuring effectiveness of risk minimization measures</li> </ul>			<ul style="list-style-type: none"> <li>In the 2014 EMA work programme</li> </ul> 	
<b>2.</b>	<b>Strengthening referral procedures</b>				
	<ul style="list-style-type: none"> <li>Operation of new referral procedure (Urgent Union Procedure)</li> </ul>			<ul style="list-style-type: none"> <li>First referral launched in Oct 2012</li> </ul>	
	<ul style="list-style-type: none"> <li>Redesign the 2012 implemented procedures and business processes to include 2012 changes</li> </ul>			<ul style="list-style-type: none"> <li>Delivered 2013</li> </ul>	
<b>3.</b>	<b>Pharmacovigilance inspections</b>				
	<ul style="list-style-type: none"> <li>Develop and implement a revised process for coordination of PhV inspections</li> </ul>			<ul style="list-style-type: none"> <li>SOPs under finalization</li> </ul>	

Implemented  On-going implementation  Not started/not ready 

**COMMUNICATION WITH STAKEHOLDERS**

1.	Online publishing of information	2012	2013	Progress
	<ul style="list-style-type: none"> <li>Publication(on EMA website) of agendas, minutes, assessments, approvals, recommendations, opinions, and decisions of PRAC, CMD(h), and CHMP</li> </ul>			<ul style="list-style-type: none"> <li>Started July 2012 for PRAC agendas and minutes</li> <li>CMDh PhV items in agendas and minutes public from 2012</li> <li>Publish agendas and minutes of CHMP meetings (Q4 2013)</li> </ul>
2.	<b>Coordination of safety messages</b>			
	<ul style="list-style-type: none"> <li>Operation of the coordination of MS' safety announcements for non-CAPs</li> </ul>			<ul style="list-style-type: none"> <li>Started July 2012</li> </ul>
3.	<b>Public hearings</b>			
	<ul style="list-style-type: none"> <li>Develop concept of public hearings (including criteria and methodologies)</li> </ul>			<ul style="list-style-type: none"> <li>Public consultation launched Q4 2013</li> </ul>
	<ul style="list-style-type: none"> <li>Introduction of public hearings in the context of Urgent Union Procedure</li> </ul>			<ul style="list-style-type: none"> <li>First public hearing following EMA Management Board endorsement of the modalities in 2014</li> </ul>
4.	<b>Risk Management Plan Summaries</b>			
	<ul style="list-style-type: none"> <li>Agree modalities to publish summary information for RMPs</li> </ul>			
	<ul style="list-style-type: none"> <li>Publish RMP first summaries</li> </ul>			<ul style="list-style-type: none"> <li>To start Q1 2014</li> </ul>
5.	<b>European Medicines web-portal</b>			
	<ul style="list-style-type: none"> <li>Initiate research and design work</li> </ul>			

## 6. One year of data collection and monitoring of Agency pharmacovigilance tasks

- The Agency has implemented the majority of elements of the new PhV legislation
- The Agency's pharmacovigilance tasks have been comprehensively measured and reported against
- Structure and process tasks have been measured in this data collection for the first year of operation since implementation of the new PhV legislation
- Behaviour change and outcome measures of impacts will be collected from 2014

### 6.1. Orientation to the monitored performance indicators in this report

The performance indicators used in this report are described in Section 2.3 above.

### 6.2. Compliance Management Objectives

- The Agency has achieved 7 of 8 relevant Compliance Management Objectives and the implementation of the last objective, literature monitoring, is progressing in line with planning

Evidence of the Agency achieving the key Compliance Management Objectives for the new PhV legislation as laid down in Commission Implementing Regulation (EU) No 520/2012<sup>10</sup> Section 3 (Minimum requirements for the quality systems for the performance of pharmacovigilance activities by national competent authorities and the Agency), Art 15, paragraphs 1, 2 and 3, is summarised in the Table 2. ). The Compliance Management Objectives for the Agency are:

- ensuring evaluation of the quality, including evaluating quality and completeness of PhV data submitted
- ensuring assessment of PhV data and its processing within timelines
- ensuring independence in the performance of PhV tasks
- ensuring effective communication among NCAs and between NCAs and the Agency as well as with patients, healthcare professionals, MAHs and the general public
- ensuring that NCAs and Agency inform each other and EC of their intention to make announcements relating to the safety of a medicinal product authorized in several MS or an active substance contained in such a medicinal product
- conducting inspections, including pre-authorisation inspections and
- implementing procedures for monitoring of medical literature (being developed and should be operational by end of 2014).

**Table 2.** Assessment table regarding Compliance Management Objectives

#### Commission Implementing Regulation (EU) No 520/2012 Section 3, Art 15 – Compliance Management Objectives – actions fulfilling objectives

No.	Objective	Agency PhV task data demonstrating achievement of objective
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**Commission Implementing Regulation (EU) No 520/2012 Section 3, Art 15 – Compliance Management Objectives – actions fulfilling objectives**

<p><b>1a</b></p>	<p>Ensuring evaluation of the quality, including completeness, of PhV data submitted</p>	<ul style="list-style-type: none"> <li>• Duplicates management and ICSR recoding (for further info please see @ <a href="http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/07/WC500146607.pdf">http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/07/WC500146607.pdf</a>);</li> <li>• Number of organizations subject to EV data quality review by Agency (235 at the data lock point)</li> <li>• Patient reporting, see section 6.3.1.6. ;</li> <li>• Signal management including signal confirmation, see section 6.3.2.1. ;</li> <li>• Additional Monitoring List, see section 6.3.2.3.</li> <li>• Enabling more precise coding of suspected ADRs for increased quality through increased precision in coding guidance and terminology, e.g., Patient Support Programmes/Market Research Program guidance (please see @ <a href="http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2013/06/event_detail_000723.jsp&amp;mid=WC0b01ac058004d5c3">http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2013/06/event_detail_000723.jsp&amp;mid=WC0b01ac058004d5c3</a>) and Medication error workshop, see section 6.3.2.4.</li> </ul>
<p><b>1b</b></p>	<p>Ensuring assessment of PhV data and its processing within timelines provided by Dir 2001/83/EC and Reg (EC) No 726/2004</p>	<ul style="list-style-type: none"> <li>• ICSR processing, EV Annual Report (for further info please see @ <a href="http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/07/WC500146607.pdf">http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/07/WC500146607.pdf</a>);</li> <li>• RMP, PSUR, Signal management, PASS/PAES assessment, Referral Management, PRAC outputs, see section 6.3.3.</li> </ul>
<p><b>1c</b></p>	<p>Ensuring independence in the performance of PhV tasks</p>	<ul style="list-style-type: none"> <li>• PRAC civil society membership (see section 6.3.4.3. );</li> <li>• Conflict of Interest Declarations by Agency staff, external experts and Committee members (for further information please see @ <a href="http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/document_listing/document_listing_000178.jsp&amp;mid=WC0b01ac0580029338">http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/document_listing/document_listing_000178.jsp&amp;mid=WC0b01ac0580029338</a>);</li> <li>• Oversight of Agency finances by Management Board (for further information please see @ <a href="http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000098.jsp&amp;mid=WC0b01ac0580028c2f">http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000098.jsp&amp;mid=WC0b01ac0580028c2f</a>)</li> </ul>
<p><b>1d</b></p>	<p>Ensuring effective communication among NCAs and between NCAs and the Agency as well as with patients, healthcare professionals, MAHs and the general public</p>	<ul style="list-style-type: none"> <li>• Number of organizations reporting to EV, see section 6.3.1.6. ;</li> <li>• EPITT (European Pharmacovigilance Issues Tracking Tool) use in signal management;</li> <li>• SMART (Signal Management Technical Working Group) Signal Management Work Sharing;</li> <li>• PhV Stakeholder meetings (please see @ <a href="http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2013/10/event_detail_000794.jsp&amp;mid=WC0b01ac058004d5c3">http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2013/10/event_detail_000794.jsp&amp;mid=WC0b01ac058004d5c3</a>);</li> <li>• Incident Management Plan decision communication (please see @</li> </ul>

## Commission Implementing Regulation (EU) No 520/2012 Section 3, Art 15 – Compliance Management Objectives – actions fulfilling objectives

		<a href="http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000544.jsp&amp;mid=WC0b01ac05805b713e">http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000544.jsp&amp;mid=WC0b01ac05805b713e</a> ); <ul style="list-style-type: none"> <li>• PRAC civil society membership, see section 6.3.4.3. (Topics other than GVP);</li> <li>• PRAC and CMDh transparency, web posting of agendas and minutes, see section 6.3.4.1.;</li> <li>• PRAC, CMDh and CHMP transparency through use of web posted 'highlights';</li> <li>• Additional Monitoring, see section 6.3.2.3.</li> <li>• Sharing of Lines to Take with Network partners</li> </ul>
1e	Guaranteeing that NCAs and Agency inform each other and EC of their intention to make announcements relating to the safety of a medicinal product authorized in several MS or an active substance contained in such a medicinal product in accordance with Art 106a of Dir 2001/83/EC	<ul style="list-style-type: none"> <li>• Incident Management Plan decision communication, (please see @ <a href="http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000544.jsp&amp;mid=WC0b01ac05805b713e">http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000544.jsp&amp;mid=WC0b01ac05805b713e</a>);</li> <li>• # of Lines to Take =70 (between 2 July 2012 and 1 July 2013);</li> <li>• # of Notifications to MSs regarding safety announcements = 197 (between 2 July 2012 and 1 July 2013)</li> </ul>
1f	Conducting inspections, including pre-authorization inspections	<ul style="list-style-type: none"> <li>• PhV Inspections, see section 6.3.5.1.</li> </ul>
2	In addition to procedures referred to in para 1, NCAs shall establish procedures for collecting all suspected adverse reactions that occur in their territory	<ul style="list-style-type: none"> <li>• N/A (NCAs)</li> </ul>
3	Agency shall establish procedures for monitoring of medical literature in accordance with Art 27 of Regulation (EC) No 726/2004	<ul style="list-style-type: none"> <li>• Post 2013 work</li> </ul>

### 6.3. Results of review of data collection on Agency pharmacovigilance tasks

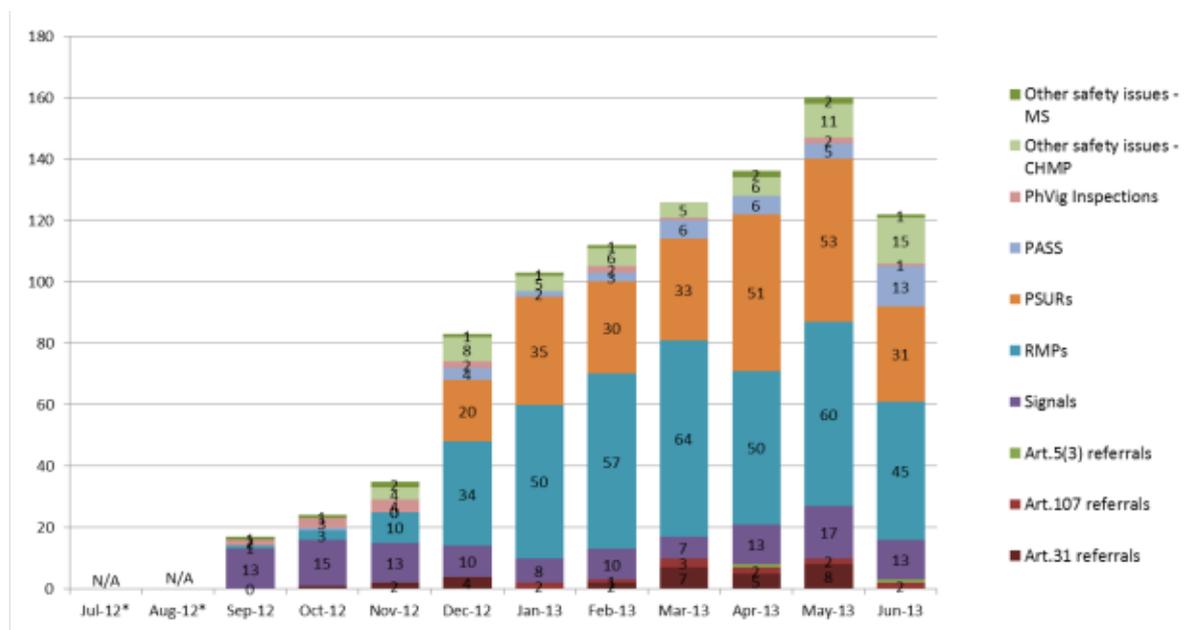
#### 6.3.1. Collection of key information on medicines

Collecting key information on the safety of a medicine is critical to ensuring its safe and effective use. The Agency has implemented a number of new activities described below to ensure that data- and information-collection procedures provide a solid foundation for protection of public health.

- ADR reporting in EEA increased by 51,215 and for non-EEA reports by 124,152 since implementing the new PhV legislation
- PRAC assessments of RMPs are available to CHMP in 100% of marketing authorisation applications (MAAs)
- Risk proportionate and systematic planning of data collection is enabled by routine RMPs
- PSUR review resulted in rapid and timely risk minimisation (e.g. Protelos/Osseor [strontium ranelate]) – clarifies importance of PSURs in public health
- 40 PASS procedures were handled by PRAC during the one year period of data collection
- Posting of 135 PASS studies on EU PAS register has increased transparency for patients and

**Figure 3.** PRAC work volume (July 2012 to July 2013)

Figure 3 gives the monthly number of procedures by activity type



### 6.3.1.1. Risk management plans (RMP)

The new PhV legislation strengthens procedures for the submission of RMPs to the Agency. In the EU, companies submit a RMP when applying for a marketing authorisation. The plan includes commitments on how the medicine will be monitored for safety during its lifetime, and on risk-minimisation activities. The Agency has established a new procedure for requesting and assessing RMPs from industry, and, in June 2012, published a module (V) on RMPs as part of the guideline on good pharmacovigilance practice (GVP). From 2014, the Agency will establish targeted monitoring of the effectiveness of key risk-management measures<sup>18, 19</sup>.

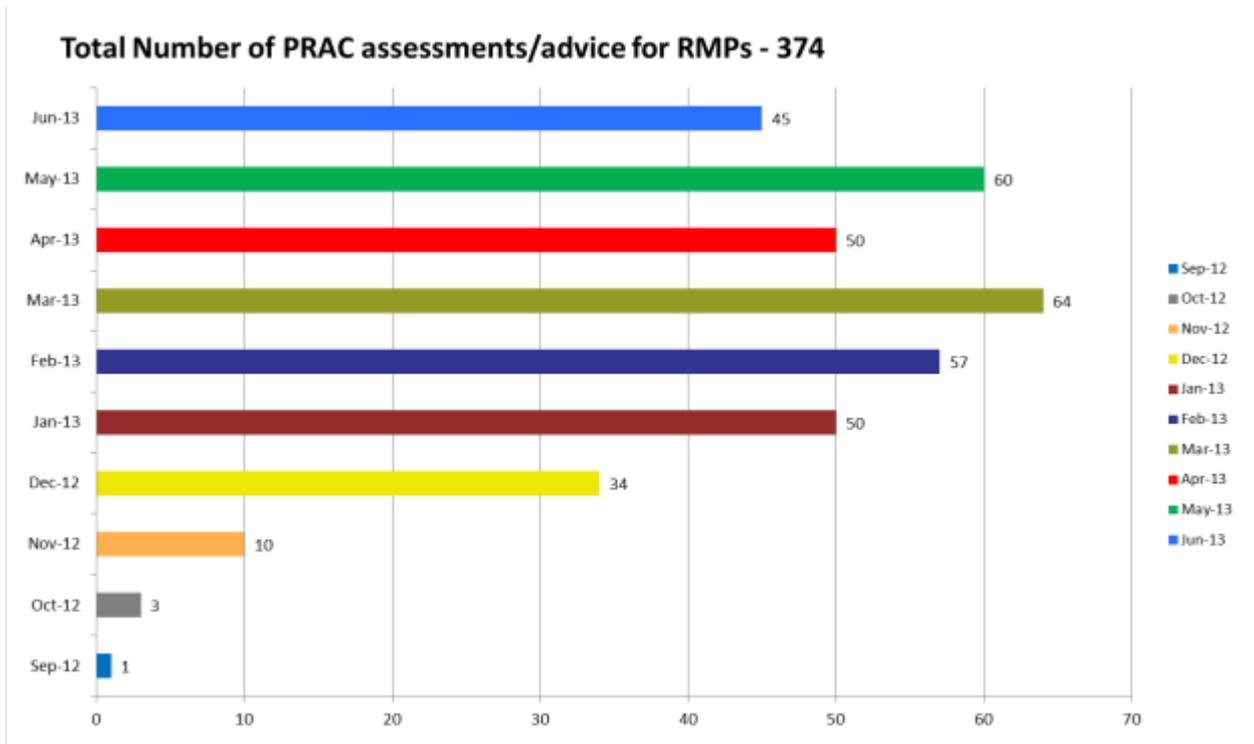
There were 374 RMP assessments procedures handled by PRAC during the one year period of data collection. This accounted for 19% of PRAC Plenary discussion time. For centrally authorised products (CAPs) RMPs have been assessed as part of 100% of Market Authorisation Applications (MAA) and in 100% of variations and line extensions resulting in a significant change in Market Authorisation (MA). PRAC assessments of RMPs for MAA and line extensions have been timely and available to CHMP in 100% of occasions prior to adoption of a final opinion. In recognition of the need to optimise the work process for shared efficiencies, collaborative work continues to simplify RMP templates and assessment report formats. Since RMPs are now routine, risk-proportionate and more systematic planning of data collection and better risk minimisation has been delivered.

The following Figure 4. shows monthly number of PRAC assessments for RMPs while Figure 5. divides these RMP assessments by phase of regulatory oversight (pre-authorisation and post-authorisation).

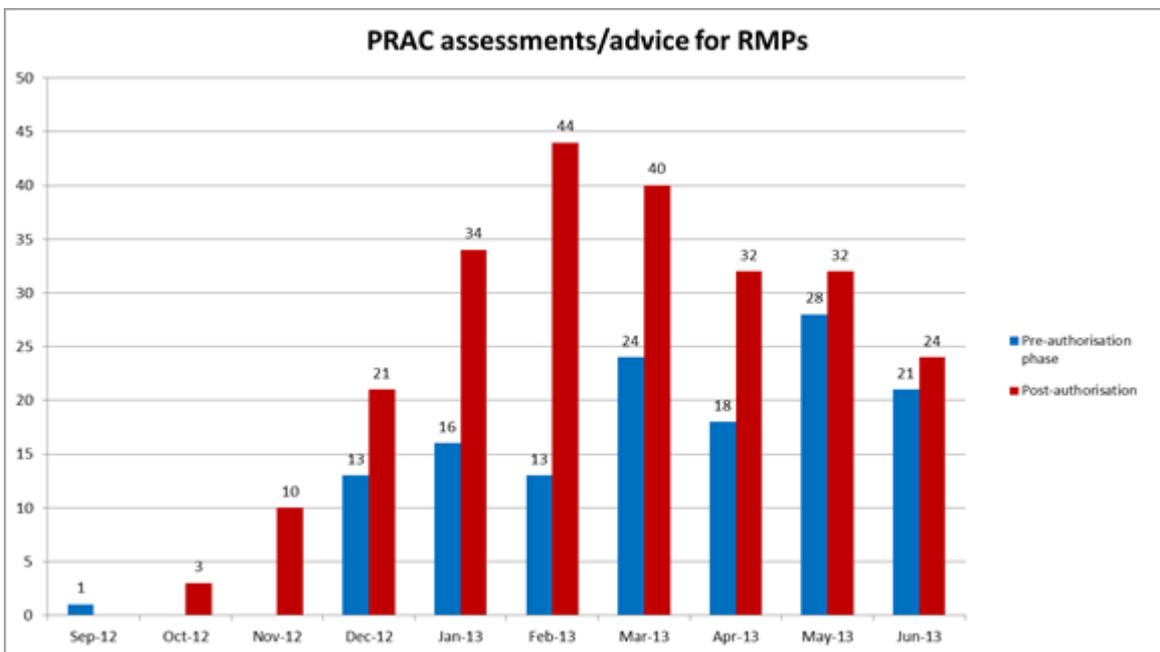
<sup>18</sup> Rednelli, C., Fritsch, O., Measuring Regulatory Regulatory Performance – Evaluating Regulatory management tools and programmes, OECD, July 2012

<sup>19</sup> Prieto, L., et al, Evaluation of effectiveness of risk minimization measures, *Pharmacoepi and Drug Safety*, 21: 896-899, 2012

**Figure 4.** PRAC Assessments for RMPs



**Figure 5.** PRAC assessments/advice for RMPs



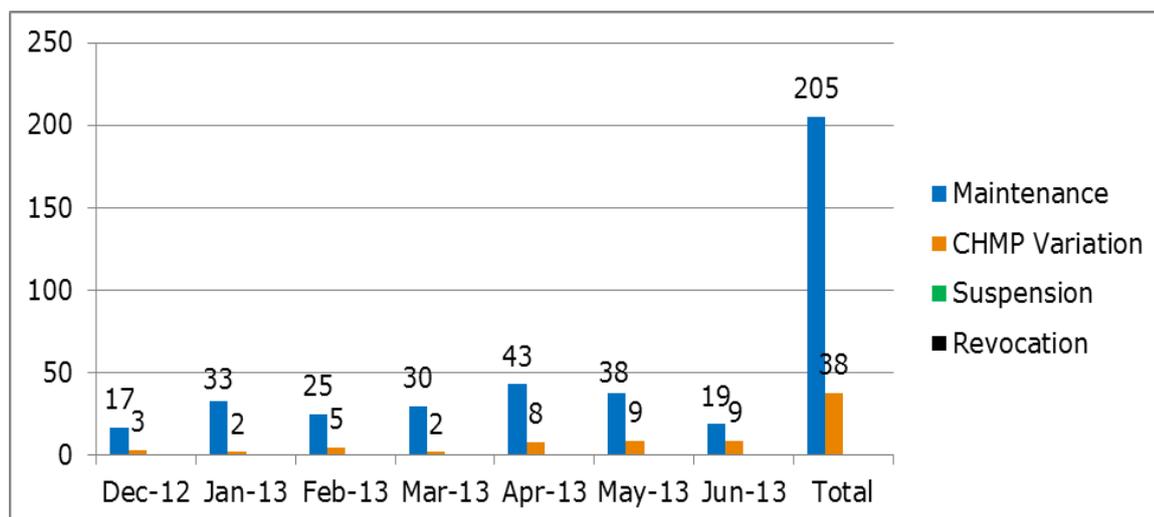
### 6.3.1.2. Periodic safety update reports (PSURs)

PSURs provide an evaluation of the benefit-risk balance of a medicine and are submitted by marketing-authorisation holders at defined periods during the post-authorization phase. The Agency published a module (VII) on PSURs as part of the GVP guideline in June 2012. It has also implemented new

procedures relating to PSURs for CAPs and single assessments for substances contained in at least one CAP, and published a list of Union reference dates for the preparation and submission of PSURs (EURD). This list is updated on a monthly basis. From 2014, work will concentrate on introduction of PSURs for Nationally Authorised Products (NAPs), where CAPs are not part of the assessment, while there will still be work on CAPs and CAPs plus NAPs.

There were 253 PSUR assessment procedures handled by PRAC during the one year period of data collection. This accounted for 16% of PRAC plenary discussion time. PSUR recommendations have been adopted according to required timelines. 16% of PSUR assessments have resulted in label changes. No revocations or suspensions have resulted from PSUR assessments. An increasing number of PSUR procedures result in MA variation, and there is an increased efficiency and faster decision-making on these safety issues, since there is no need for follow-up variation for centrally authorised products. This results in rapid implementation of the changes in the product information (PI) and delivers warnings and restrictions to patients faster in the interest of public health. The impact of PSUR assessment on MAs is becoming better understood in terms of its impact on public health due to examples such as Protelos/Osseor (strontium ranelate) where significant and timely narrowing of the indication occurred as a direct result of PSUR assessment. See Figure 6. for PSUR outcomes by month.

**Figure 6.** PSURs – Outcomes at PRAC



- 243 PSUR PRAC recommendations (single CAPs) from Dec 2012 till June 2013
- 38 (16%) PRAC recommendations to vary MA
- No suspensions, no revocations

For more information please see @

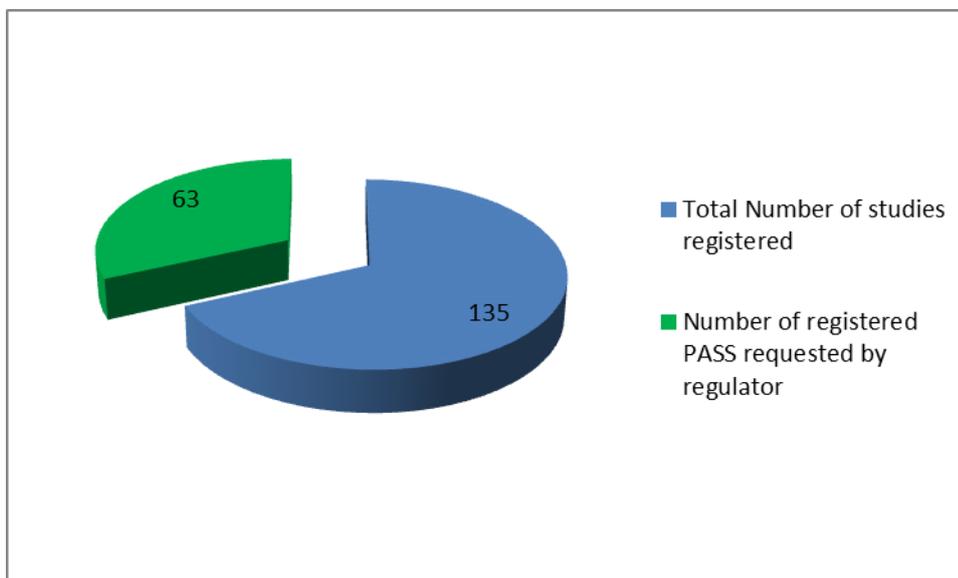
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### **6.3.1.3. Post-authorisation safety and efficacy studies (PASS/PAES)**

A PASS is a study of an authorised medicine that identifies, characterises or quantifies a safety hazard, confirms the safety profile of the medicine, or measures the effectiveness of risk-management activities during the product's lifetime. A PAES is a study aimed at verifying the efficacy of a medicine on the market, including efficacy in everyday medical practice. The purpose of the information derived from a PASS/PAES is to support decision-making on the safety and benefit-risk profile of a medicine, and thereby to enhance its safe and effective use. The Agency published a GVP module (VIII) on PASS in June 2012, and is preparing a separate guideline on methodological aspects of PAES to become available in 2014. A key task of the Agency's PRAC is to approve new non-interventional PASS

protocols and reports. The ability to require and enforce PASS/PAES studies is becoming part of the competent authorities' toolkit for improving the benefit-risk monitoring of medicines.

**Figure 7.** Registered studies on EU PAS Register



There were 40 PASS procedures handled by PRAC during the one year period of data collection (both imposed and non-imposed, RMP contained). This accounted for 4% of PRAC plenary discussion time. 100% of imposed PASS protocols were assessed within the legal timeframe. 25 CAPs had a total of 37 PASS imposed in the one year period of data collection with 28 as an Annex II obligation to conduct post-authorisation measures (PAMs). From the 37 PASS, 35% were interventional studies. Nine imposed non-interventional PASS protocols were reviewed by PRAC and all were assessed within the legal timeframe of 60 days. Twenty-seven non-imposed PASS protocols were reviewed by PRAC within the allocated timeframe which was 60 days or below in 63% of cases. Five imposed PASS protocols and 6 imposed PASS reports were assessed by PRAC within the allocated 60 day timeframe.

There were 135 studies registered in the publically accessible EU PAS register. 47% (63 studies) were requested by competent authorities of which 8% (5 studies) were imposed. Posting on the EU PAS register increased the transparency of studies for stakeholders.

#### **6.3.1.4. Electronic submission of core medicine information on medicines by MAHs, i.e., Article 57(2) database**

The industry is required to provide the Agency key information on all authorised human medicines in the EU using, in line with Article 57 of the amended Regulation (EC) No 726/2004<sup>3</sup>, a dedicated format for the electronic submission of information. The format for MAHs to use when submitting core information on medicinal products was developed as planned by the Agency in 2011 with an IT tool available in early 2012. MAHs were required to electronically submit information on medicinal products for human use authorised or registered in the Union to the Agency, at the latest by 2 July 2012. These provisions apply independent of the authorisation procedure of the medicinal product. 337,751 Medicinal Product presentations have been submitted. This information has undergone quality checks and will be used by the Agency and the EU network to support all activities related to the safety monitoring of medicines. In 2014 the Agency will go live with the processes to allow updates and information relating to variations, renewals, etc., to data in the Article 57 database.

For more information see @

[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2012/03/WC500123661.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/03/WC500123661.pdf)

#### **6.3.1.5. IT systems development/management**

New IT systems are required to be developed and audited to support certain provisions in the legislation, notably a repository for periodic safety update reports (PSURs) and enhancements to the EudraVigilance database. The development of the required IT systems, in coordination with EU medicines regulatory authorities and the pharmaceutical industry, will continue during 2014.

#### **6.3.1.6. ADR reporting, monitoring and management (EudraVigilance)**

The new PhV legislation included a strengthened role for the EudraVigilance database as the single point of receipt of all suspected ADRs by MSs and industry directly to the EV database, allowing all NCAs to simultaneously have access and share PhV information for medicinal products for human use authorised in the EU. This centralisation of reporting by MAHs will only come into effect when the new EudraVigilance functionalities, referred to in section 6.3.1.5, have been audited and delivered. The new PhV legislation further requires EV be fully accessible to all NCAs, the Agency and the EC and MAHs to the extent necessary to comply with their PhV obligations. EV also has to be appropriately accessible to healthcare professionals and the public while guaranteeing personal data protection. The Agency is obligated to operate procedures that ensure the quality and integrity of the information collected in EV, including the use of standard web-based structured ADR report forms. For further information please see @ [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2013/07/WC500146607.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/07/WC500146607.pdf).

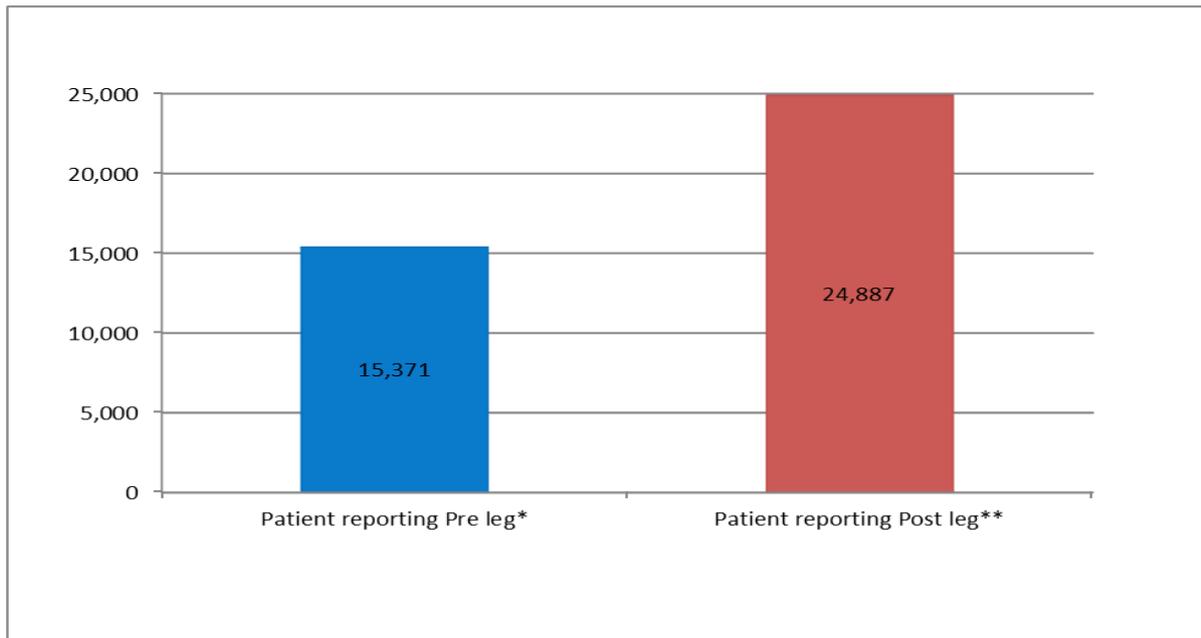
A significant increase in numbers of submitted individual case safety reports (ICSRs) has been observed, in keeping with international trends. In the reporting period there were 1,080,755 ICSRs submitted. There was an absolute increase of approximately 51,000 European Economic Area (EEA) reported post-marketing ICSRs received in the data collection period compared to approximately 169,000 ICSRs received in the same period the year before the new PhV legislation was implemented. Non-EEA post-marketing ICSR reporting increased by approximately 124,000 over the approximately 367,000 non-EEA ICSRs reported during the same period the year before the new PhV legislation was implemented.

There have been continued improvements in EV Data Quality Management with over 87,000 ICSRs recoded, over 100,000 duplicate cases removed from the system, and over 242 EV data quality assessments performed.

#### **Reporting by patients**

The legislation introduced a right for individual European citizens to report suspected side effects of medicines directly to national medicines regulatory authorities. There was an absolute increase in spontaneous ADR reporting by patients in the EEA in the one year reporting period of over 9000 reports, giving a total of approximately 25,000 compared to approximately 15,000 in the previous year. This is an approximately 60% increase from the year prior to the implementation of the new pharmacovigilance legislation. **Figure 8.** and **Figure 9.** show ADR reporting by patients and healthcare professionals in EEA for the one year period before and after implementation of the new legislation.

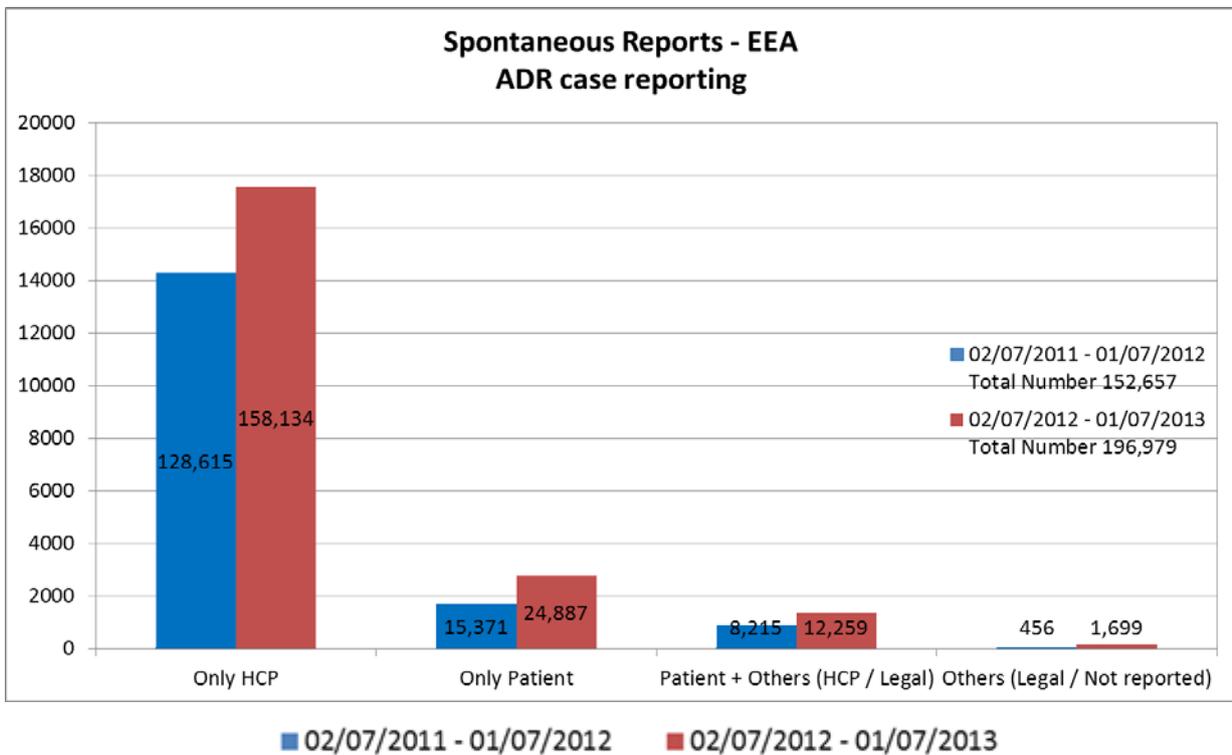
**Figure 8.** Spontaneous ADR cases reporting by patients (EEA)



\* Pre legislation data period - 02/07/2011 - 01/07/2012

\*\* Post legislation data period - 02/07/2012 - 01/07/2013

**Figure 9.** Spontaneous Reports - ADR case reporting totals (EEA)



### 6.3.2. Analysis and understanding of data and information

The ability to query, analyse and understand data is essential for proper monitoring of the safety and of the benefit-risk profile of a medicine. As part of its implementation of the new EU PhV legislation, the Agency is working to ensure support for better analysis and understanding of data and information on medicines. The Agency is continuing to invest in signal detection processes and tools.

- 47% of signals detected by the Agency resulted in label changes; 27 are under further evaluation
- 8 signals (9.3%) resulted in referral procedures
- The Additional Monitoring list was launched by the Agency in 2013 with a maximum of 119 listed medicines as of August 2013

#### 6.3.2.1. Signal detection in EudraVigilance

The new legislation requires the Agency, in collaboration with MSs, to monitor the data in EV to determine whether there are new risks or whether risks have changed and whether these risks impact on the benefit-risk balance of certain medicines. EMA leads on CAPs and NCAs on NAPs. The PRAC is responsible for initial analysis and prioritisation of signals. The implementing regulation establishes procedural steps for signal management, including validation, confirmation, prioritisation, assessment and recommendation.

Since July 2012, the Agency has been operating a revised signal-detection process for CAPs, and supporting the EU MSs in the operation of their signal detection processes for NAPs. Overall signal management through the PRAC, together with the sources of information (other than the EV system) used to assess the safety of medicines, is described in the GVP module (IX) on signal management, and published in June 2012.

- Signal management data

Between July 2012 and September 2013, there were 2,213 signals evaluated by the Agency. Approximately 44% were signals of disproportionate reporting. 92 signals were validated and confirmed. 54 signals (59%) concerned CAPs only, 29 signals (31%) NAPs only and 9 (10%) both CAPs and NAPs. Of these 92 signals, 51 had EV as the data source. Other sources were national reviews for 19, literature for 9, studies for 5, the USA Food and Drug Administration (FDA) or Pharmaceuticals and Medical Devices Agency (PMDA) notifications for 4, and historical issues of the Agency's Pharmacovigilance Working Party (PhVWP) for 4. There was a 44% increase year on year for signal confirmation in the network signal tracking system, European Pharmacovigilance Issues Tracking Tool (EPITT), with a median time between EPITT entry and PRAC discussion of 45 days. 49 signals (53%) were validated by the Agency and 43 (46%) by MSs. Eight signals (9.3%) resulted in EU referral procedures. 44(47%) signals resulted in label change(s). 100% of CAPs were monitored at least monthly by the Agency.

- Signals and PRAC workload

There were 119 signal assessment procedures handled by the PRAC between 2 July 2012 and 1 July 2013 relating to the 92 individual signals. This accounted for 10% of PRAC plenary discussion time. Signal descriptions and summary tables are being web-posted monthly.

- For more information see @ [http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document\\_listing/document\\_listing\\_000375.jsp&mid=WC0b01ac0580727d1c](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000375.jsp&mid=WC0b01ac0580727d1c)

- [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2013/10/WC500150868.xls](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/10/WC500150868.xls)

### 6.3.2.2. Literature monitoring

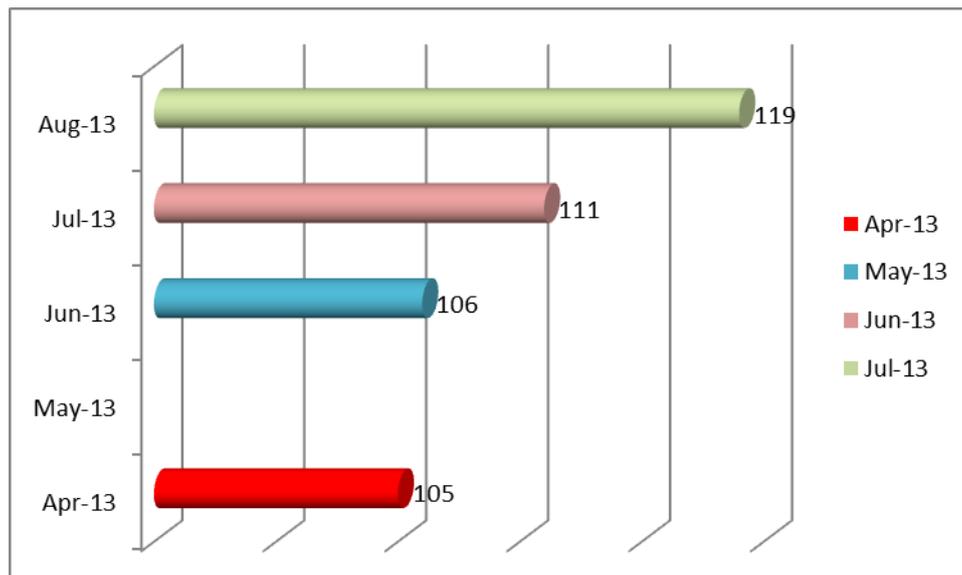
The Agency is required to monitor scientific and medical literature for authorised medicinal products. This relieves the pharmaceutical industry of the burden of such monitoring and data entry into the EV system. A defined list of medical and scientific literature will be monitored for certain listed active substances. The new legislation requires the Agency to publish and monitor this list. Preparation is underway and Agency will start these literature-monitoring activities from the end of 2014.

### 6.3.2.3. Additional monitoring of medicines, management and list

As mentioned above in section 4.6.4., the 2012 amendments to the pharmacovigilance legislation extended the scope of additional monitoring. Some medicinal products such as new active substances and bio-similar biologicals are authorised subject to additional monitoring, and competent authorities may require additional monitoring for products that are subject to post-authorisation study, conditions or restrictions that are specified in the RMP, products for paediatric use and for a significant change in the marketing authorisation, including a new manufacturing process of a biotechnologically-derived medicinal product. The new legislation requires that products subject to additional monitoring are included in an up-to-date, publicly available list and are identified by a black symbol with an appropriate standardised explanatory sentence in the summary of product characteristics and package leaflet.

The Agency, in collaboration with the MSs, published in April, 2013 the first list of medicines subject to additional monitoring. This list is publicly available, and is maintained on a monthly basis. The list and the subsequent changes to package leaflets for medicines on it, i.e., a 'black symbol', a specific statement and a standardised explanatory sentence, encourages the reporting of suspected side effects and increases transparency for patients on medicines that are being closely monitored. The highest number of products on the list as of August 2013 was 119.

**Figure 10.** Additional Monitoring List statistics



The number of the additionally monitored drugs – 119 (published 9 August 2013)

For more information see @

- [http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document\\_listing/document\\_listing\\_000366.jsp&mid=WC0b01ac058067c852](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000366.jsp&mid=WC0b01ac058067c852)
- [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2013/09/WC500150608.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/09/WC500150608.pdf)

#### **6.3.2.4. Medication errors (MEs)**

Medication errors resulting in harm should be reported to EV and data exchanged at national level between NCAs and patient safety functions. A stakeholders' workshop at which EU and non-EU experts were consulted took place in February 2013 (for more information please see @ [http://www.ema.europa.eu/ema/index.jsp?curl=pages/news\\_and\\_events/events/2012/10/event\\_detail\\_000666.jsp&mid=WC0b01ac058004d5c3](http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2012/10/event_detail_000666.jsp&mid=WC0b01ac058004d5c3)) and resulted in recommendations to strengthen prevention and reporting, as follows:

1. Harmonisation and further development of terminologies and definitions at EU and international level
2. Establishment of collaborative relationships between national patient safety authorities, national regulators, the EMA and the European Commission
3. Development of new methods to identify medication errors from a patient safety and pharmacovigilance perspective through data pooling and analysis
4. Systematic assessment and prevention of the risk of medication errors during the product life-cycle including prior to granting marketing authorisation through the EU risk-management planning process
5. Active engagement and capacity building with patient consumer groups and healthcare professionals to improve safe medication practices
6. Support to research into safe medication practices.

#### **6.3.3. Regulatory action to safeguard public health**

Ensuring that regulators can respond to emerging or urgent health issues in a timely and efficient way is a key deliverable of the new PhV legislation. The new PhV legislation increases the opportunities for quick and robust regulatory action through the creation of a new committee (PRAC), a strengthened CMDh, and new procedures that fast-track the decision-making process when public health is at risk.

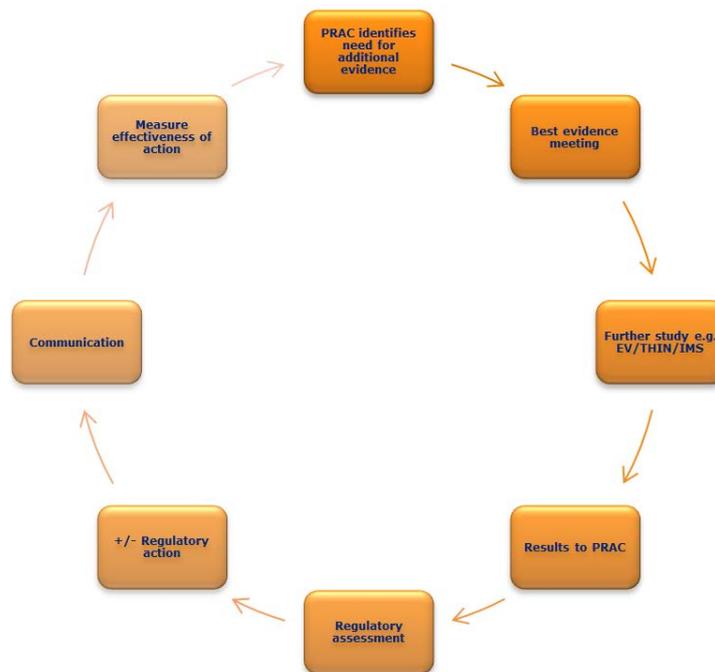
- PRAC dealt with 918 procedures during 11 meetings in the first year of activity
- There is a high rate of acceptance of PRAC recommendations by CHMP/CMDh with 7/9 PRAC recommendations on referrals endorsed with no changes and 2/9 with only minor changes
- Transparency has been strengthened by web posting of PRAC Agenda, Highlights and Minutes
- There is a decrease in time for finalisation of referral procedures from more than 12 months to between 1 and 8 months

Work is on-going to raise the quality of opinions, including the development of benefit–risk methodologies, basing PRAC recommendations on the scientific evaluation of best-evidence and integrating available information from all sources including data analyses by marketing authorisation holders, academics and regulatory agencies, the literature and reports from healthcare professionals

and patients. This also involves stimulating research questions and producing new data in an ‘evidence-decision’ strategy that subsequently may support regulators in decision making. The EMA’s European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) and the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT) programmes are examples of applying the strategy to pharmacoepidemiological research<sup>20</sup>. The core strategy is outlined in Figure 11.

**Figure 11.** EMA Evidence-decision cycle

***Evidence – decision cycle***



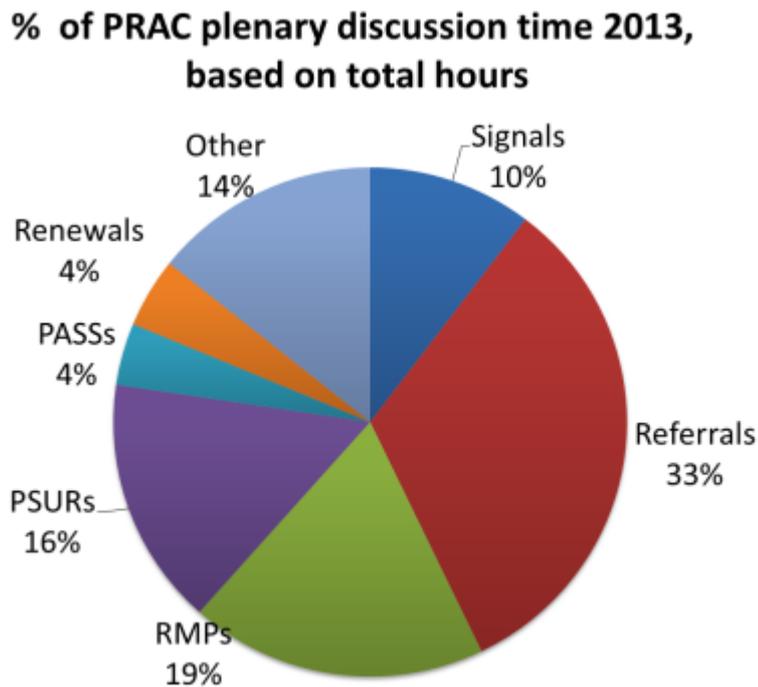
**6.3.3.1. Scientific committees and decision-making**

**Creation of the Pharmacovigilance Risk Assessment Committee (PRAC)**

A new scientific committee, the PRAC, came into existence in July 2012, with monthly meetings being held thereafter. The mandate of the PRAC covers all aspects of the risk management of the use of medicinal products for human use, including the detection, assessment, minimisation and communication relating to the risk of adverse reactions, having due regard to the therapeutic effect of the medicinal product, PhV audits, and the design and evaluation of post-authorisation safety studies. PRAC members include representatives of patient organisations, healthcare professionals, EU MSs and EC appointed experts. The PRAC focuses on assessing and monitoring safety issues relating to human medicines, and its recommendations are used by the Committee for Medicinal Products for Human Use (CHMP) when adopting opinions for substances in at least one CAP and by the CMDh for substances only in nationally authorised medicines. See Figure 12. for PRAC plenary discussion time as divided by topic area/procedure type.

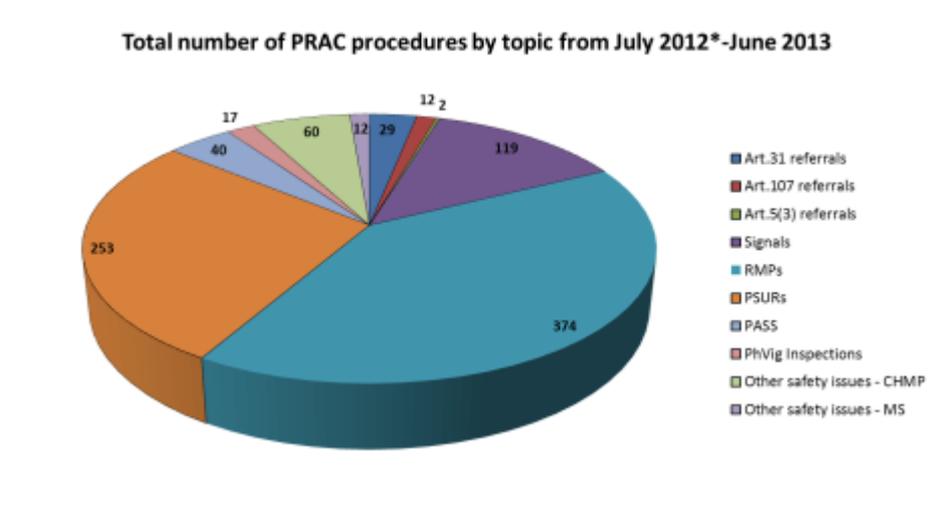
<sup>20</sup> Arlett, P., et al, The European Medicines Agency’s use of prioritised independent research for best evidence in regulatory action on diclofenac, Pharmacoepidemiology and Drug Safety 2014, DOI: 10.1002/pds.3594

**Figure 12.** PRAC discussion time



PRAC met first in July 2012 with an organisational meeting. In the one year of data collection since the July 2012 meeting, PRAC dealt with 918 total procedures, including RMPs: 374, PSURs: 253, Signals: 119 procedures relating to 92 individual signals; PASS: 40; Referrals: 41. There were 11 PRAC meetings during the period of data collection. All PRAC proceedings including votes are conducted according to established rules of procedure. Complete PRAC membership, i.e., representing the civil society, was established by March 2013 when healthcare professionals and patients joined. Procedures are well understood by all parties and improvements have been seen in the quality of procedures and assessments. There is an increased efficiency of handling safety issues due to dedicated procedures, especially as relates to signal management. There is a recognised need for further optimisation and there has been implementation of risk-proportionate criteria for plenary discussions for PSURs, RMPs, renewals and annual reassessments. A continuous quality improvement process in procedures was implemented, e.g., consistency of wording in assessment reports especially as concerns criteria for requests to MAHs for additional information. There has been a high rate of acceptance of PRAC recommendations with CHMP/CMDh, e.g., 7/9 referrals were endorsed with no change and 2/9 referral procedures required very minor changes in product information wording or follow-up requirements with CMDh. See [Figure 13.](#) for a PRAC procedures by topic.

**Figure 13.** PRAC Procedures



### **6.3.3.2. Stronger role for the Coordination Group (CMDh)**

The legislation also revised the mandate of the CMDh, which now takes the lead on decision-making for nationally authorised medicines, based on recommendations from the PRAC. The legislation introduced an opinion-making power, either by consensus or majority vote. In the latter case a binding EC decision is required. This facilitates harmonised implementation of safety recommendations across the EU.

### **6.3.3.3. Referral procedures**

A major new referral procedure, known as the urgent Union procedure, has been implemented. This procedure, which can be initiated by an EU MS or the EC, is specifically designed to rapidly assess significant, emerging safety concerns resulting from the evaluation of data from pharmacovigilance activities linked with a medicine or a class of medicines available in the EU, regardless of its authorisation route (i.e. centralised or national authorisation). In a referral, the Agency is requested to conduct a scientific assessment of a particular medicine or class of medicines on behalf of the EU. A key aspect of the new procedure is the systematic involvement of the PRAC in providing safety expertise to the primary assessment. The PRAC then identifies appropriate regulatory actions, such as amending the product information, restricting the use of the medicine or withdrawing the medicine from the market in the interest of protecting public health. In addition, the Article 20 referrals and Article 31 referral, when they relate to pharmacovigilance, are systematically assessed by the PRAC. The PRAC's recommendations are forwarded to the CHMP or the CMDh for their opinion/decision.

Of 21 referral procedures started in PRAC during the data collection period, 100% were completed according to legal timeframes. During the period, the 21 referrals of all types included: (Article 20 PhV: 5 [3 finalised during the period]; Article 107i: 5 [3 finalised during the period]; Article 31 PhV: 11 [3 finalised during the period]). For 6 of these procedures (29%), an ad-hoc expert working group was organised and a total of 9 of these referrals were finalised during the data collection period. "Finalised" means that a final outcome was obtained at either CHMP, CMDh or with a European Commission decision as indicated. The pharmacovigilance related safety issues raised as referrals have resulted in better information for patients. Examples include variations such as for combined oral hormonal contraceptives, diclofenac (a non-steroidal anti-inflammatory [NSAID]) and flupirtine (an alternative painkiller to NSAIDs and opioids); restrictions of indications, such as for codeine containing

medicines, and suspensions of the marketing authorisation such as for tetrazepam (a benzodiazepine), Numeta G13%E (glucose, lipids, aminoacids and electrolytes - parenteral nutrition solution) and Tredaptive (nicotinic acid/laripiprant).

Seventy-four per cent of the referrals involved more than one MAH and only 1/21 referrals started in the data collection period resulted in a request for a re-examination procedure. These numbers may of course change as the data is evolving and dependent on latest decisions subsequent to the data collection period for this report. There appears to be an increasing involvement of non-MAH stakeholders in Art 107i referral procedures through submissions received due to the new procedures for inviting stakeholder submissions.

Critically there is a decreased total assessment time for Article 31 referrals which is a key result for public health, i.e., total assessment time of Article 31 referrals is 1 to 8 months as compared to 12 to 15 months in previous years.

Overall there continues to be an unpredictable workload for referral procedures as well as an increasing demand for ad-hoc expert meetings, which may require further refinement of process to support the PRAC work. See Figure 14. for a breakdown of PRAC referral procedures; Figure 15. for referral outcomes and Figure 16. for on-going referrals at time of the data lock point for this report.

**Figure 14.** Referral data

Number of Referral procedures (July 2012-July 2013)

Referral type	Started	Finalised
Art. 20	5	3
Art. 107i	5	3
Art. 31	11	3
<b>Total</b>	<b>21<sup>2</sup></b>	<b>9<sup>3</sup></b>

Also includes procedures started and finalised by PRAC in July 2013

<sup>2</sup> In 6 procedures (29%) an ad-hoc expert meeting has been organised

<sup>3</sup> Finalised means final outcome obtained at either CHMP or CMDh

**Figure 15.** Referral outcomes at PRAC vs. CHMP/CMDh (time taken 1-8 mos.)

Procedure name	Article	Finalised	Committee	Grounds	Outcome	EC Decision	Duration (calendar days)
Tredaptive	20	Jan-13	CHMP	B-R	Suspension	Yes	1 month
Trevaclyn	20	Jan-13	CHMP	B-R	Suspension	Yes	1 month
Pelzont	20	Jan-13	CHMP	B-R	Suspension	Yes	1 month
Tetrazepam	107i	Apr-13	CMDh	S	Suspension	Yes	3 months
Cyproterone, ethinylestradiol - DIANE 35 & other medicines containing cyproterone acetate 2mg and ethinylestradiol 35 micrograms	107i	May-13	CMDh	S	Variation	Yes	3 months
Almitrine	31PhV	May-13	CMDh	B-R	Revocation	No	7 months
Codeine-containing medicinal products	31PhV	Jun-13	CMDh	B-R	Variation	No	8 months
Diclofenac-containing medicinal products	31PhV	Jun-13	CMDh	B-R	Variation	Yes	8 months
Flupirtine	107i	Jun-13	CMDh	S	Variation	Yes	6 months

**Figure 16.** On-going Referral procedures to date

Procedure name	INN	Article	Issue
Combined hormonal contraceptives	desogestrel, gestodene, norgestimate, etonogestrel, drospirenone, dienogest, chlormadinone, norgestimate, nomegestrol acetate/estradiol, norelgestromin/ethinylestradiol	31	risk of venous thromboembolism
Domperidone	domperidone	31	adverse heart effects, including QT prolongation and arrhythmias
Substances related to nicotinic acid (acipimox)	acipimox	31	Follow-up procedure to nicotinic acid and laropiprant, where study results higher frequency of non-fatal but serious side effects and a failure to reduce of major vascular events.
Kogenate Bayer/Helixate NexGen	octocog alfa	20	children given 2nd-generation full-length recombinant F-VIII products may develop antibodies than those given 3rd-generation recombinant products; this increase was not seen with other recombinant or plasma-derived F-V.
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	Concerns that the combination use of several RAS-acting agents could increase risk of hyperkalaemia, low blood pressure and kidney failure. The benefits combination use of RAS-acting agents in reducing overall mortality is questioned.
Protelos/Osseor	strontium ranelate	20	increased risk of serious heart problems, blood clots and rare serious skin
Zolpidem-containing medicinal products	zolpidem	31	drowsiness and slower reactions the day after taking the medicine and possible increased risk of accidents during activities that require alertness
Hydroxyethyl starch (HES) - containing medicinal products	hydroxyethyl starch	31	increase risk of mortality and renal replacement treatment/failure: re-examination
Hydroxyethyl starch (HES) - containing medicinal products	hydroxyethyl starch	107i	increase risk of mortality and renal replacement treatment/failure: suspension
Bromocriptine-containing medicines	bromocriptine	31	rare but potentially serious or fatal cardiovascular, neurological and psychiatric effects
Short-acting beta agonists (SABAs)	terbutaline, salbutamol, hexoprenaline, ritodrine, fenoterol, isoxsuprine	31	cardiovascular risk of the medicines when used as tocolytics compared with benefit, particularly if used for a prolonged period (more than 48 hours).
Diacerein	diacerein	31	safety concerns (very frequent digestive disorders, some serious cases of disorders and skin reactions) and also evidence from clinical trials and the literature suggesting that the effectiveness of diacerein in osteoarthritis was

For more information please see @

[http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_000150.jsp&mid=WC0b01ac05800240d0](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&mid=WC0b01ac05800240d0)

### 6.3.4. Communicating with stakeholders

A commitment to openness and transparency is explicit in the new PhV legislation. With new provisions on public access to agendas and minutes of regulatory meetings on safety issues, the new PhV legislation aims to increase public confidence in the safety of the monitoring system for medicines in the EU. The Agency is working to introduce these and other measures to improve its communication with stakeholders and increase the transparency of its operations as part of its implementation of the new PhV legislation.

- GVP modules were delivered on schedule
- The Agency issued 70 Lines to Take (between 2 July 2012 and 1 July 2013)
- The Agency issued 197 Notifications to MSs regarding safety announcements (between 2 July 2012 and 1 July 2013)
- PRAC Agendas, Highlights and Minutes were posted monthly on the Agency's web site. PRAC Signal recommendations were posted monthly from September 2013
- The FDA-EMA multi-lateral PhV cluster with Japan and Canada as observers started in 2013
- The Agency's Withdrawn Products procedure was initiated in October 2013
- The Agency has developed and published a catalogue containing all the training material prepared in the context of the implementation of the PhV legislation

#### **6.3.4.1. Online publishing of information**

In 2012, the Agency began publishing the agendas and minutes of the PRAC and CMDh on its public website. PRAC Signal recommendations were published starting in September 2013. From December 2013, this initiative was extended to cover the agendas and minutes of the CHMP. The Agency, together with the EU MSs, is developing the fully functional European medicines web portal on medicines, with links to the national medicines web portals of all EU MSs. During this development, the Agency's website acts as the European medicines web portal.

There has been significant increase in transparency of decision-making around safety issues with 100% of PRAC agendas being web posted on day 1 of PRAC meetings and meeting highlights published on the Friday of each PRAC meeting week. Communications on PRAC recommendations concerning finalised pharmacovigilance related safety referrals are published on the Friday of PRAC meeting week and finalised minutes are published the following month.

For more information please see @

[http://www.ema.europa.eu/ema/index.jsp?curl=pages/about\\_us/document\\_listing/document\\_listing\\_000353.jsp&mid=WC0b01ac05805a21cf](http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/document_listing/document_listing_000353.jsp&mid=WC0b01ac05805a21cf)

#### **6.3.4.2. Coordination of safety messages**

Building on its existing role in communicating safety issues for CAPs and referral procedures for NAPs, the Agency is required by the new PhV legislation to coordinate the safety announcements by the MSs. The goal is to ensure that the European public receives consistent and coherent safety advice on medicines that are authorised through national procedures but available in more than one MS.

Seventy Lines to Take and 197 Notifications to MSs were issued by the Agency in the one year period for this report. See patient safety information @

[http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/pha\\_listing.jsp&mid=WC0b01ac058001d126](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/pha_listing.jsp&mid=WC0b01ac058001d126). This page lists major changes made to the authorisation of medicines, which have

been recommended by the Agency's CHMP to improve safety for patients and patient safety information from the last two years. For a full list of all changes made to a centrally authorised medicine, the Agency provides access on the EMA web site to the EPAR. For information on referrals, see @

[http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_000150.jsp&mid=WC0b01ac05800240d0](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&mid=WC0b01ac05800240d0).

#### **6.3.4.3. Public participation in Agency activities**

Public participation allows interested citizens and/or civil-society organisations (patients, consumers and healthcare professionals) to engage with the Agency directly on issues that affect them, or which they can affect. It is a tool for collaborative interaction that gives participants the opportunity to share their real-life experiences and provide input to the Agency's activities in a meaningful way, thus creating a vital platform for mutual exchanges of information. Ultimately, this contributes to the quality of the decision-making process, by highlighting the real-life implications of regulatory decisions. It also helps to increase transparency of and trust in the regulatory system and develop mutual respect between regulators and the community.

Examples of patient participation delivered are: membership by patients on PRAC, patient ADR reporting, improved decision-making through better public access to information on medicines, including health care professional use of the additional monitoring list and the black symbol on products to increase awareness of additional monitoring and ADR reporting, etc.

Pursuant to the referral procedure provided for in Articles 107i to 107k of Directive 2001/83/EC<sup>11</sup>, the Agency informs the public on how to submit information. As part of efforts to more fully engage members of civil society in its PhV activities, in 2014 the Agency will start to organise public hearings on issues relating to the safety of individual medicines or classes of medicines in the context of referral procedures.

#### **6.3.4.4. Summaries of RMPs and publication of RMP summaries**

In 2013, the Agency, together with the EU MSs, agreed the modalities for publishing summary information for RMPs.

#### **6.3.4.5. Guidance(s) development/maintenance**

##### Good Vigilance Practice

A key milestone in implementing the new PhV legislation was the development of Good Vigilance Practice (GVP) consisting of chapters that fall into two categories, (1) modules covering major PhV processes and (2) product- or population-specific considerations. Each chapter was developed by a team consisting of experts from the Agency and from EU MSs. The guideline on GVP is a key deliverable of the new PhV legislation and is self-standing guidance on PhV replacing Volume 9A of Eudralex<sup>13</sup>. It is addressed to EU MAHs, NCAs in MSs and the Agency. The procedure for finalising GVP modules allows for 8 weeks of public consultation per chapter with each chapter divided into an introduction, a section on structures and processes and a section on operation of the EU network.

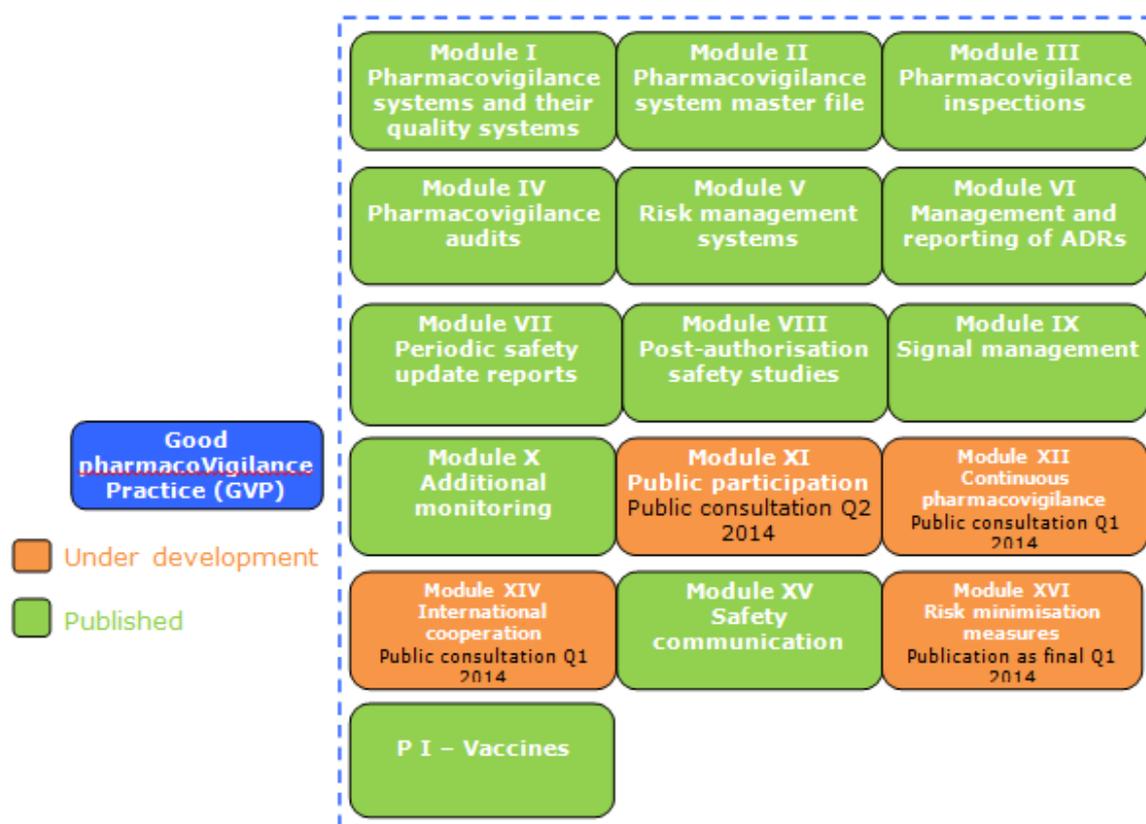
##### Chapter status of GVP

Figure 17. shows the titles of GVP modules and additional information concerning projected dates for publications of certain modules still in development. The chapters or “modules” are colour coded depending on their development status.

For more information see @

[http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document\\_listing/document\\_listing\\_000345.jsp&mid=WC0b01ac058058f32c](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp&mid=WC0b01ac058058f32c)

**Figure 17.** Good vigilance practice



GVP modules were developed on schedule. Further supportive chapters are in development, e.g., Module XI on Public participation, Module XII on Continuous PhV, Module XIV on International Cooperation, and Module XVI on Risk Minimisation Measures. GVP on all core processes were adopted prior to the date of application of the new PhV legislation and the GVP web page was completed on schedule. GVP has been very well received by stakeholders and the review of modules is on-going based on the first year of experience.

#### **6.3.4.6. International harmonisation**

Improving communication between regulatory bodies and public-health bodies to ensure consistency of messages and mutual understanding of respective roles is a priority in the Agency Roadmap to 2015.

The Agency has been collaborating on implementing international standards including ICSRs and the international identification of medicinal products (IDMP). IDMP is one of a group of five standards which together provide the basis for the unique identification of medicinal products. Both sets of standards were adopted by the International Organization for Standardization (ISO) in 2011/2012 and by the European Committee on Standardization.

Implementation of PSUR assessment according to the underpinning ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) guidance E2CR2 is on-going work being done in the context of the new PhV legislation and involving Agency participation in the ICH, as well as the use of ICH products such as MedDRA (Medical Dictionary for Regulatory Affairs).

The September 2013 start of the multi-lateral PhV cluster teleconferences with USA FDA and Health Canada and Japan as observers also enables the international collaborative work with several regulatory agencies in third countries, as well as focussing on product-related consensus building. Since February 2013, the Agency has hosted a Visiting National Expert in PhV on a two year assignment with the goals of increasing the timeliness, efficiency, quality of assessments and collaboration between Health Canada and the Agency in the area of PhV.

#### **6.3.4.7. Products withdrawn for safety reasons**

On the basis of the legislative changes introduced in October 2012, the Agency developed and launched a procedure on 31 October 2013 to collect information on withdrawn products and to support implementation of a list of medicines withdrawn for safety reasons. Information provided regarding the requirements for MAHs to notify NCAs and the Agency about "withdrawn products" included: a Public announcement, Questions and Answers document, Cover letter to be used by MAHs for the notification Excel template to be used by MAHs for the notification.

For more information see @

[http://www.ema.europa.eu/ema/index.jsp?curl=pages/news\\_and\\_events/news/2013/10/news\\_detail\\_001920.jsp&mid=WC0b01ac058004d5c1](http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/10/news_detail_001920.jsp&mid=WC0b01ac058004d5c1)

#### **6.3.4.8. Training**

During the data collection period, the Agency has carried out training for the full scope of its internal and external stakeholders with approximately 30 training sessions, in addition to 2 EudraVigilance Data Analysis System (EVDAS) training sessions per year and MS Assessor training sessions. During the reporting period, the following numbers of participants attended the sessions: 415 to EV case reporting, 40 to EV Introduction, 551 to EV Information Days, 92 to Excellence in PhV, 66 to EV Medicinal Products Dictionary and "extended" version (XEVMPD), 377 to XEVMPD e-learning, 93 to EVDAS (EV Data Analysis System), and 128 to MedDRA training.

The Agency has developed the second edition of a PhV Handbook for staff as a tool to guide operation of PhV tasks. As well, the Agency has developed and published a catalogue containing all the training material prepared in the context of the implementation of the PhV legislation, both for internal (regulatory network) and external (industry, patients, SMEs, healthcare providers, general public) use. The catalogue is in the form of an excel spread sheet and importantly includes links to the corresponding presentations, videos, webinars, etc., as well as the dates when the training sessions took place to give an idea of how current the training material was at the time of presentation.

#### **6.3.4.9. Stakeholder relations/Helpdesk/consultations**

Helpdesk statistics continue to show significant levels of stakeholder interest in PhV issues. Pharmacovigilance Help Desk (P-PV) queries average 200 per month with eighty per cent of these queries being answered within a performance target of 15 days. Seven PhV stakeholder forums have been held since 2011 with the 6<sup>th</sup> held during the reporting period and 7 consultations on GVP modules occurring during the reporting period.

## 6.3.5. Monitoring of regulatory actions and related activities

### 6.3.5.1. PhV inspections and compliance monitoring

100% of inspections have been conducted in accordance with the risk-based programme for routine pharmacovigilance inspections of marketing authorisation holders with centrally authorised products. Figure 18. indicates the pharmacovigilance inspections requested/conducted in 2013 in the context of the programme for pharmacovigilance inspection of companies with CAPs.

**Figure 18.** Human pharmacovigilance inspections requested in 2013 in the context of the programme for pharmacovigilance inspection of companies with CAPs\*

	QPPV (MAH) site	Global PhV site	QPPV Subcontractor site	Subcontractor /Licensing partner site	Affiliate site	Total
CHMP Requested	3	1	1	0	0	5**
National Inspection Programmes	26	1	15	0	1	43
Total	29	2	16	0	1	48***

\* In contrast to the July 2012 to July 2013 data lock for most of the processes in this report, these data relate to the calendar year 2013

\*\* Two of the site inspections were requested by the CHMP in 2013 but will be conducted in 2014

\*\*\* It should be noted that these totals are just a subset of the total number of pharmacovigilance inspections conducted in 2013 in EU/EEA, which is usually over 150 (final number for 2013 is to be confirmed with NCAs) inspections for human medicinal products

Six cases of MAH non-compliance identified during PhV inspections and one non-compliance issue reported by the MAH to the regulatory authorities were referred to PRAC for discussion and recommendation.

In addition, to support further harmonisation for the mutual recognition of pharmacovigilance inspections within the EU, in 2013 the Pharmacovigilance Inspectors Working group, in collaboration with assessors when applicable, focused on the preparation of the following Union procedures:

- Union procedure on the coordination of EU pharmacovigilance inspections;
- Union procedure on the preparation, conduct and reporting of EU pharmacovigilance inspections;
- Union procedure on the management of pharmacovigilance inspection findings which may significantly impact the benefit/risk profile of the concerned medicinal products;
- Union procedure on sharing of pharmacovigilance inspection information;
- Union recommendations on training and experience of inspectors performing pharmacovigilance inspections;
- Union guidance on document retention and record keeping for PhV inspections

#### **6.3.5.2. Audit of PhV System and components**

The new PhV legislation established legal requirements for the Agency to perform audits of its PhV System, including risk based audits of its quality system. Similar legal requirements apply to NCAs in MSs and MAHs.

Past and planned PhV Agency audits include:

- EV related processes audit – 6-20 July 2009
- Signal detection audit – 1-15 March 2010
- Signal management audit – November 2013
- Agency PhV System audit – Planned 2014

#### **6.3.5.3. Performance Management (Process, Behaviour Change, Outcomes measurement)**

The first year since implementation of the new PhV legislation has focused on structure and process measurement of operations. Planning is underway to address the need to measure behaviour change and other outcomes such as impacts on health systems and the pharmaceutical industry.