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REPORT FROM THE COMMISSION

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

{SWD(2016) 284 final}

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1. INTRODUCTION

In the European Union (EU) medicinal products for human use are subject to strict testing and assessment of their quality, efficacy and safety before being authorised either at Member State or EU level. Once placed on the market they continue to be monitored through pharmacovigilance activities.

Pharmacovigilance, as defined by the World Health Organisation (WHO), is 'the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem'.

Some side effects or 'adverse reactions' may not be seen until a large number of people have in real-life use received the medicine. It is therefore vital that the safety of all medicines is monitored throughout their use in healthcare practice.

The EU legal framework of pharmacovigilance for medicinal products for human use is provided for in Regulation (EC) No 726/2004[1] and Directive 2001/83/EC[2]. The legislation was amended in 2010[3] and 2012[4].

Article 29 of Regulation (EC) No 726/2004 and Article 108b of Directive 2001/83/EC require regular reporting on the performance of pharmacovigilance tasks by the European Medicines Agency (EMA) and the Member States respectively.

This report and the accompanying Staff Working Document[5] describe the activities of the EU's networked and collaborative system for monitoring and controlling the safety of human medicines and is focused on activities since the start of operation of new legislation in 2012 until the end of 2014, but also includes information on some tasks and processes initiated up to July 2015.

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1 Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, OJ L 136, 30.4.2004, p. 1.

2 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.

3 Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) No 1394/2007 on advanced therapy medicinal products, OJ L 348, 31.12.2010, p.1 and Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use, OJ L 348, 31.12.2010, p. 74.

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

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2. STRONG COLLABORATION BETWEEN EUROPEAN REGULATORY AUTHORITIES

Ensuring that regulators can respond to emerging or urgent health issues in a timely and efficient way is a key deliverable of the new pharmacovigilance legislation. For that purpose the medicines regulatory authorities in 31 European Economic Area (EEA) countries, the EMA and the European Commission closely collaborate and work in partnership as a network to discuss and deal swiftly with any emerging problem in the interest of patients' access to safe and efficacious medicines[6]. The ability to take quick and robust regulatory action was enhanced through the legislation by: the creation of the Pharmacovigilance Risk Assessment Committee; strengthening of the Co-ordination group for Mutual recognition and Decentralised procedures – human and the introduction of new procedures to fast-track decision-making when public health is at risk.

2.1. The role of Member States

The individual Member States of the EEA power the entire pharmacovigilance system. They provide much of the resource and knowledge for assessing signals of possible emerging side effects and take the lead in evaluating and analysing data when a safety issue is assessed at a European level. They maintain the inspectorates that ensure that medicines marketed in the EU are manufactured appropriately and are of suitable quality, and that the pharmacovigilance systems of industry are working as they should.

The legislation gives the Co-ordination group for Mutual recognition and Decentralised procedures – human (CMDh)[7], a body representing the national regulators of the EEA, the mandate to lead on decision-making when no centrally authorised medicines are involved.

2.2. The role of the European Medicines Agency

The EMA has a central role in the EU system co-ordinating its activities and providing technical, regulatory and scientific support to the Member States and industry.

The new scientific committee, the Pharmacovigilance Risk Assessment Committee (PRAC), came into existence in July 2012. PRAC's mandate covers all aspects of risk management of medicinal products for human use. PRAC members include experts in pharmacovigilance and regulation from EU Member States as well as scientific experts and representatives of healthcare professionals and patient organisations appointed by the European Commission. Figure 1 in the annex presents the relative frequency of the main pharmacovigilance-related activities on the PRAC agenda between July 2012 and December 2014.

2.3. The role of the Commission

The European Commission is the competent authority for centrally authorised medicines and supplies the legal authority that underpins the EU pharmacovigilance system.

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6 European Medicines Agency, The European regulatory system for medicines and the European Medicines Agency, EMA/437313/2014.

7 Further information on the role and activities of CMDh is available on the following webpage: http://www.hma.eu/cmdh.html.

3. MAIN PHARMACOVIGILANCE RELATED TASKS AND ACTIVITIES

The entire pharmacovigilance process—from systems that monitor for and detect possible adverse effects through to regulatory action to mitigate risks—is highly co-ordinated across the regulatory network, the pharmaceutical industry and health systems. The system receives a wide range of input including that from non-EU regulators, academia, health professionals and patients.

The pharmacovigilance process can be broken down into the following key tasks:

- **Risk management planning** - assessing the risks of each new medicine and developing plans to collect data and minimise those risks. PRAC reviewed 48 risk management plans (RMPs) in July–December 2012, 637 in 2013 and 597 in 2014. The Member States, collectively, received around 3 500 (2012), 7 500 (2013), and 9 000 (2014) RMPs for nationally authorised medicines.

- Collecting and managing case reports of possible side effects (**adverse drug reactions** (ADR)). Figure 2 in the annex presents the reports of serious adverse events between 2011 and 2014.

- **Signal detection and management -** analysing reports of suspected side effects to identify signals. Some 193 unique signals were evaluated by PRAC between September 2012 and December 2014. Figure 3 in the annex presents the number of discussions in PRAC concerning either new signals or follow up discussions and Figure 4 gives an overview of the regulatory action following signal assessment.

- Routine benefit-risk monitoring of medicines via **periodic safety update reports** (PSURs) and maintaining the list (EURD list) of schedules for submitting PSURs. The number of PSURs reviewed by PRAC was 20 (July-December 2012), 436 (2013) and 471 (2014). Figure 5 in the annex gives an overview of the regulatory action following PSUR assessment. In addition, the number of PSURs submitted to national competent authorities in the Member States for purely national assessments were around 5 000 in 2012, 3 500 in 2013 and 3 000 in 2014 with an additional 62, 151 and 116 PSUR worksharing procedures for purely nationally authorised medicines during the same periods.

- **Referrals** - Europe-wide reviews of important safety and benefit-risk issues. Between July 2012 and December 2014, 31 safety referrals were sent to the PRAC. Nine of these referrals involved centrally authorised medicines, the remainder dealt solely with nationally authorised products. (See Figure 6 in the annex). Some additional concerns at a national level were also discussed by the CMDh to decide on whether an assessment at EU level was required but did not ultimately trigger a referral. Such CMDh discussions were held on 2 occasions in 2013 and 6 in 2014.

- Managing information on products subject to **additional monitoring**, and products that have been **withdrawn**. At the end of 2014, the list of medicines under additional monitoring included 193 centrally authorised medicines and 8 substances in 1 269

nationally authorised products. During 2014 EMA received 132 notifications of withdrawal of products.

- Assessing and co-ordinating studies after marketing through **post-authorisation safety studies and post-authorisation efficacy studies**. Between July 2012 and December 2014, PRAC reviewed protocols for 38 imposed non-interventional post-authorisation safety studies (PASSs). Member States evaluated an additional 17 PASS protocols for nationally authorised medicines.

- Carrying out **inspections** to ensure company pharmacovigilance systems comply with good pharmacovigilance practice. The number of inspections undertaken was 207 (2012), 195 (2013) and 167 (2014) with 26, 37 and 48 respectively for centrally authorised medicines.

- **Communicating about safety-related issues**, and interacting with and engaging with relevant stakeholders. The agendas, highlights and minutes of the PRAC meetings are published as well as public safety communications on relevant issues. There were 14 public safety communications issued in the second half of 2012, 78 in 2013 and 57 in 2014.

- **Development of systems and guidelines**, and promotion of research to address gaps in knowledge.

- **Monitoring performance of the system**, including compliance with legal obligations and standards.

- **Training and capacity building**.

4. SYSTEMS AND SERVICES IMPROVEMENT

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

- The **Article 57 database**[8] of all authorised medicines (both centrally and nationally authorised) in the EU with information on over 580 000 medicines from nearly 4 300 marketing authorisation holders.

- **Literature monitoring service** - EMA is required to monitor selected medical literature for reports of suspected side effects to certain active substances and enter them into the EudraVigilance database as individual case safety reports. The service was launched in June 2015.

- The **PSUR repository** was developed and made available during the reporting period with its functionality successfully audited in 2015.

[8] Article 57(1)(l) of Regulation (EC) No 726/2004.

- The legislation requires enhancement of **EudraVigilance database** to support simplified reporting, better search, analysis and tracking functions, and improved data quality. Progress has been made on enhancements during the reporting period including the launch of the ADR website and support to signal detection activities. The final audit of the updated system is expected to be completed in early 2018[9].

5. COOPERATION AND COORDINATION

As well as co-ordination among the network of over 30 national competent authorities, the Commission and the EMA work closely with other international regulators through bilateral arrangements and through multilateral fora such as the Association of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) to promote common approaches and standardised requirements for the authorisation of medicines.

Good pharmacovigilance relies on co-operation among the stakeholders and this has been encouraged by the legislation. The input of patients and healthcare professionals throughout the authorisation of medicines and pharmacovigilance is vital. This is provided through civil society representatives being members of PRAC and specifically consulted for certain types of referrals.

6. CONTINUING AND FUTURE DEVELOPMENT OF THE NETWORK

Over the period of the report and beyond, the pharmacovigilance network is focusing on training to develop understanding of pharmacovigilance and regulatory science to enable sharing of best practice, improving the efficiency and effectiveness of the processes, and building capacity.

The Member States and EMA offer extensive training for regulatory staff and for relevant external stakeholders. The efficiency and effectiveness of pharmacovigilance processes have improved. Projects have been initiated to improve the science and practice of pharmacovigilance including: the Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Joint Action; the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP); and, the PROTECT project[10]. Outcomes from these initiatives are already starting to inform further process development and updates to guidelines.

7. CONCLUSIONS

The European pharmacovigilance network represents an example of successful co-operation at the European level, to the benefit of EU citizens. The networked system allows participants to share in the best available expertise and evidence and co-ordinate the regulatory actions, producing more efficient and consistent outcomes for everybody. The regulatory tools made

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

[10] Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium, an Innovative Medicines Initiative public-private funded project.

available under the revised legislation, including risk management plans, post-authorisation studies, signal detection and management at EU level, periodic safety update reports assessment and reviews of medicines through referrals, represent an increasingly proactive approach to medicines safety, complemented by improvements in regulatory action and communication when safety concerns are identified.

The system operates with high transparency, necessary to develop the trust of the society it serves. Mechanisms have been put in place to ensure that accurate safety information reaches the EU public in a timely manner. Engagement of key stakeholders such as patients and healthcare professionals is embedded in the system including through patient reporting of suspected side effects. For the future, deepening involvement is foreseen, including the holding of public hearings for critical safety issues.

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

Abbreviations

ADR	adverse drug reaction
CHMP	Committee for Medicinal Products for Human Use
CMDh	Co-ordination Group for Mutual Recognition and Decentralised procedures—human
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
EURD	list of European Union reference dates and frequency of submission of periodic safety update reports
ICSR	individual case safety report
PASS	post-authorisation safety study
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	periodic safety update report
RMP	risk management plan

ANNEX — Figures and Tables

Figure 1: Number of items on the Pharmacovigilance Risk Assessment Committee (PRAC) agenda July–December 2012, January–December 2013 and January–December 2014

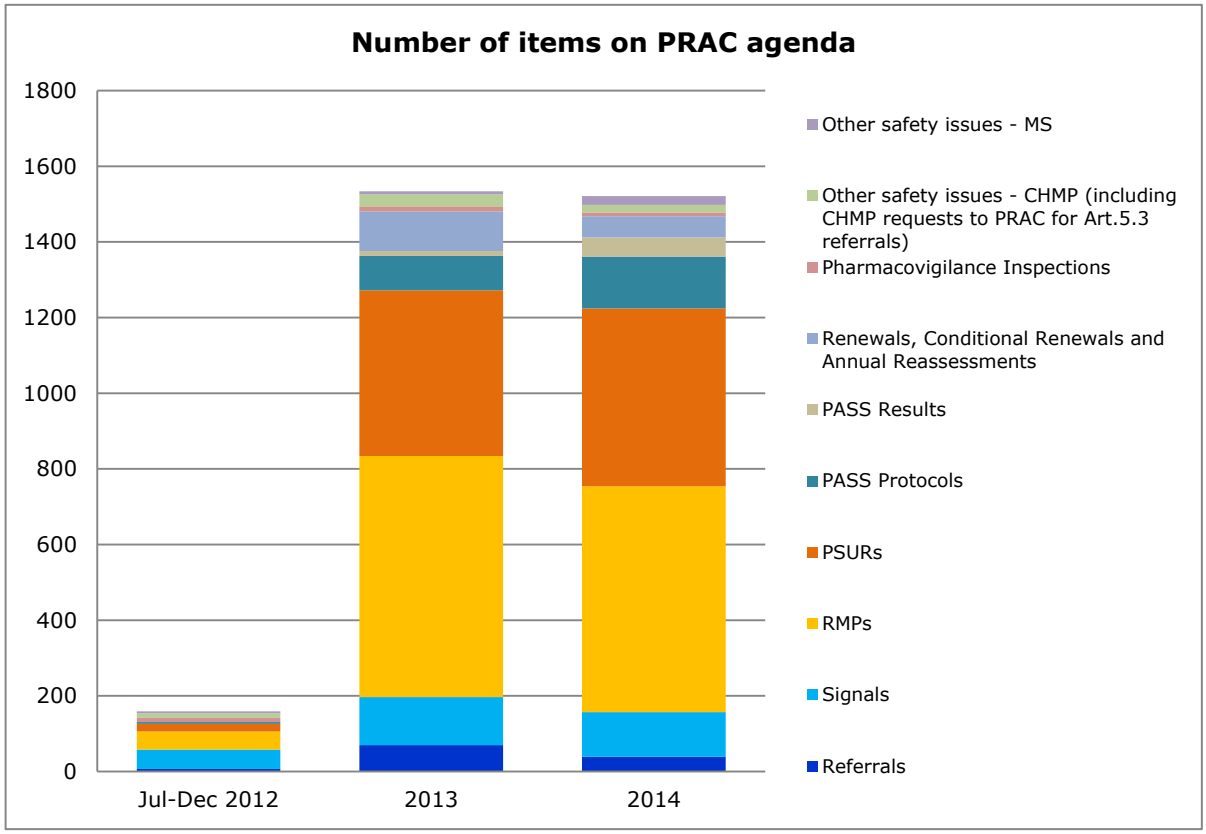
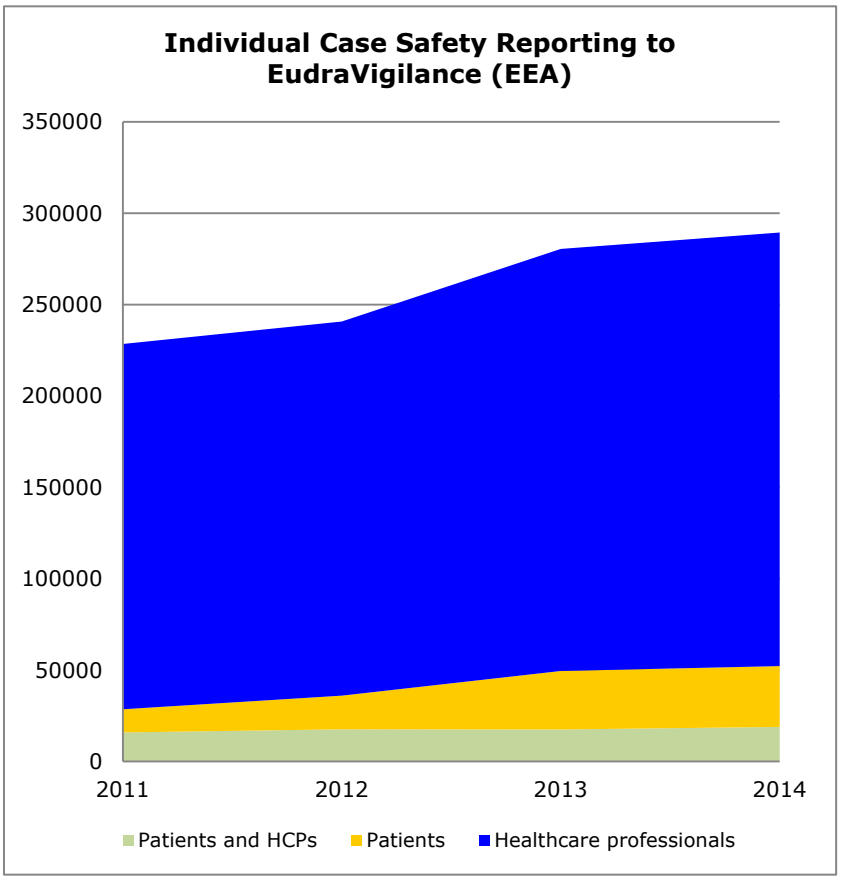
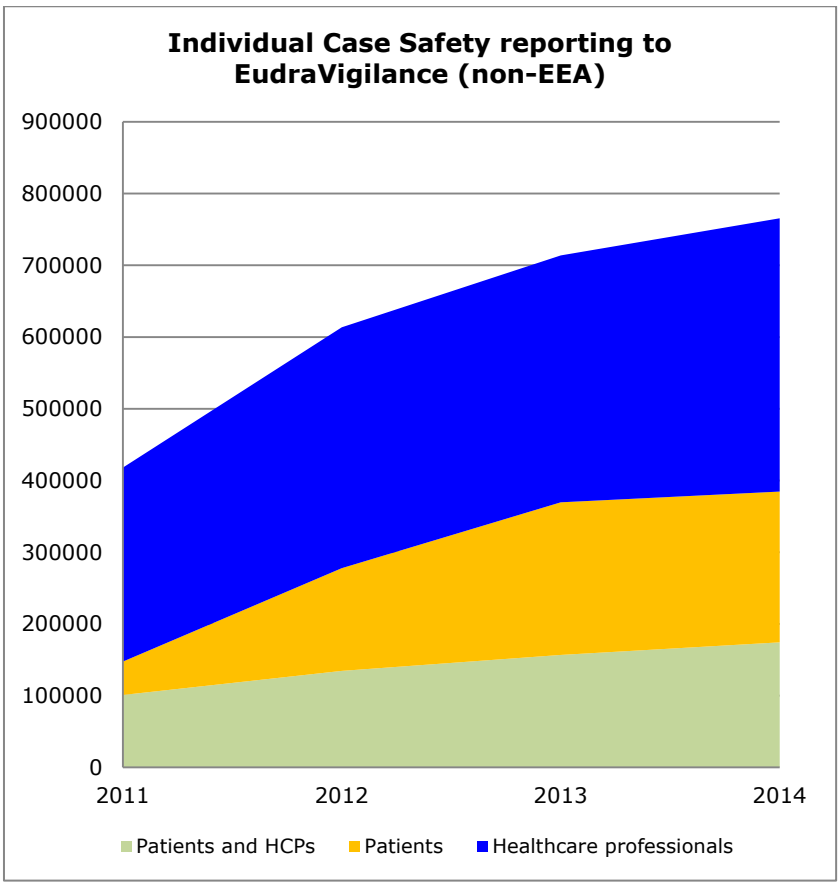


Figure 2 Reporting of individual case safety reports to the EudraVigilance database from European Economic Area countries or non-European Economic Area countries 2011–2014





HCPs - Healthcare professionals

Figure 3: Number of signal related discussions, initial and follow up, in the Pharmacovigilance Risk Assessment Committee (PRAC) September 2012 to December 2014

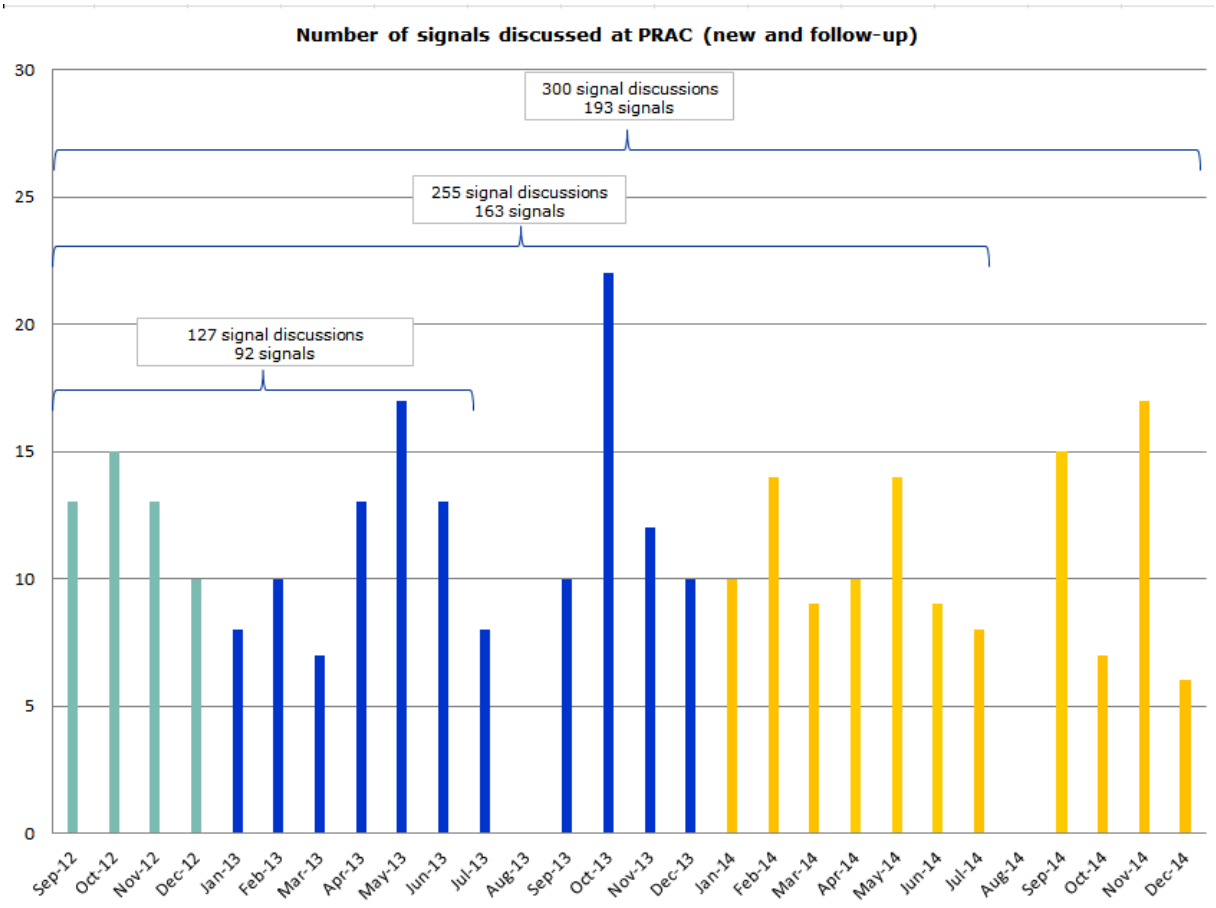


Figure 4: Type of regulatory action following signal assessment by the Pharmacovigilance Risk Assessment Committee (PRAC) September 2012 to December 2014

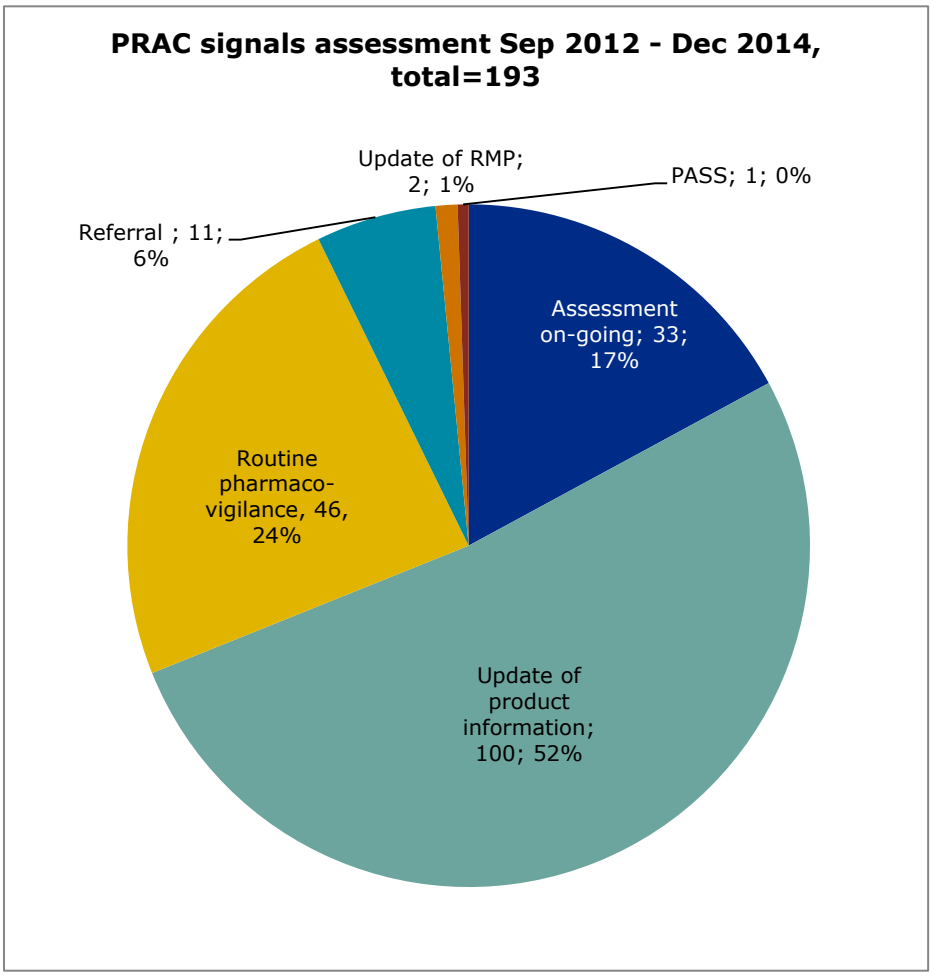
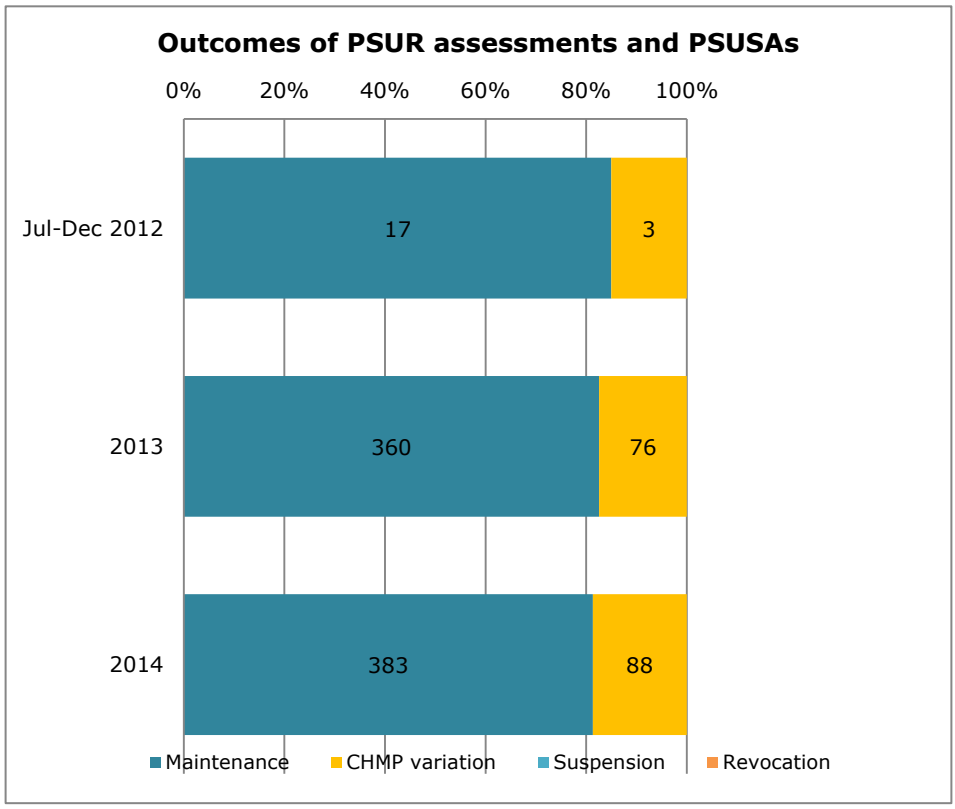


Figure 5: Outcome of the periodic safety update report (PSUR) assessment by the Pharmacovigilance Risk Assessment Committee (PRAC) September 2012 to December 2014



PSUSA – Periodic safety update report – Single assessment

Figure 6: Pharmacovigilance related referral started in 2012, 2013 and 2014

Procedure	Article	Started	Outcome
2012			
Codeine	31	Oct-12	V
Diclofenac	31	Oct-12	V
SABA (Short Acting Beta Agonists)	31	Nov-12	V,R
HES (Hydroxyethyl starch solutions)	31	Nov-12	V
Almitrine	31	Nov-12	R
Diacerein	31	Nov-12	V
2013			
Tredaptive, Trevaclyn, Pelzont (nicotinic acid/laropiprant)	20	Jan-13	S
Tetrazepam	107i	Jan-13	S
Cyproterone, ethinylestradiol - DIANE 35 & other medicines containing cyproterone acetate 2mg and ethinylestradiol 35 micrograms	107i	Feb-13	V
Combined hormonal contraceptives	31	Feb-13	V
Flupirtine	107i	Mar-13	V
Domperidone	31	Mar-13	V,R
Nicotinic acid and related substances - acipimox, xantinol nicotinate	31	Mar-13	V
Kogenate Bayer/Helixate NexGen (octocog alfa)	20	Mar-13	V
Renin-angiotensin system (RAS)-acting agents	31	May-13	V
Protelos/Osseor (strontium ranelate)	20	May-13	V
NUMETA G13%E, NUMETA G16%E emulsion for infusion and associated names (glucose, lipids, amino-acids and electrolytes)	107i	Jun-13	V,S
Zolpidem-containing medicinal products	31	Jul-13	V
Hydroxyethyl starch (HES) - containing medicinal products	107i	Jul-13	V
Bromocriptine-containing medicines	31	Sep-13	V
Valproate related substances	31	Oct-13	V
Iclusig (ponatinib)	20	Dec-13	V

2014			
Testosterone	31	Apr-14	V
Codeine for cough in paediatric population	31	Apr-14	V,R
Ambroxol/Bromhexine	31	Apr-14	V
Methadone	107i	Apr-14	V,S
Hydroxyzine	31	May-14	V
Corlentor and Procoralan (ivabradine)	20	May-14	V
Ibuprofen and dexibuprofen	31	Jun-14	V

Key:

Article 20 referrals – only centrally authorised medicines are concerned
Article 107 referrals – urgent Union interest referrals
Article 31 referrals – Union interest referrals

V – variation of the marketing authorisation
R – revocation of the marketing authorisation
S – suspension of the marketing authorisation