10 December 2019

Report on pharmacovigilance tasks from EU Member States and the European Medicines Agency (EMA), 2015-2018

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Executive summary

- This multi-annual report on pharmacovigilance in the EU summarises the work carried out over the last 4 years by the EU pharmacovigilance network. The network is the cooperative structure formed by the EU Member States and the European Medicines Agency EMA, working in partnership with each other and the European Commission, to support the safe and effective use of medicines in the EU.
- The report is based on data covering the period from January 2015 to December 2018. As well as summarising the extent of the activities carried out during the reporting period, it discusses some initial outcomes of the 2012 pharmacovigilance legislation, viewed in terms of public health, improvement and simplification of the system, and effects on transparency and stakeholder engagement.
- These outcomes include:
  - Establishment by EMA's Pharmacovigilance Risk Assessment Committee (PRAC) of an impact measurement strategy for pharmacovigilance activities.
  - Collaborative research between the EU regulatory network and academic expert centres to evaluate the effectiveness of risk minimisation measures introduced by EU regulators, early results of which suggest that more rapid decisions are being made, based on better evidence.
  - Key system improvements, including:
    - ✓ Important enhancements to the EudraVigilance database, resulting in greatly improved reporting and greater analytical power.
    - ✓ Continued development of the 'Article 57 database' (xEVMPD) which now contains information on more than 800,000 centrally and nationally authorised medicinal products across the EU, and public access to a listing of authorised medicines generated from this source.
    - ✓ Radical simplification and improvement of the way periodic safety update reports (PSURs/PSUSAs) are handled, through creation of a common repository with a single portal for access, together with workflow support and design based on best practice, plus re-use of available data. Importantly, it means MAHs now submit once to the system rather than separately to individual national competent authorities. This has greatly reduced the resource burden of the system.
    - ✓ Establishment and continued development of a centralised platform for regulatory training, notably including pharmacovigilance, thus helping to ensure consistency, increase capacity and spread best practice, while reducing overall cost.
    - ✓ Systematic translation of recommended updates for product information following PRAC signal assessments into all official EU languages, thus facilitating the necessary changes and ensuring consistency.
  - Continued commitment to transparency and stakeholder engagement, including publication of PRAC agendas and minutes and communication on key safety-related outcomes at conclusion of each plenary meeting, and involvement of patients, consumers and healthcare professionals in EMA's management board, as PRAC members, and in working parties and expert groups.

  - Introduction of a formal framework for EMA's interaction with academia, as well as continued academic collaboration in pharmacovigilance and pharmacoepidemiology through the ENCePP network, which celebrated 10 years of existence in 2017.
  - Development of criteria to determine when a public hearing on issues of medicines safety would be of value, and the successful holding of the first such hearings, for valproate-containing medicines in 2017 and for quinolone and fluoroquinolone antibiotics in 2018.

- The third mandate for PRAC commenced in 2018, with the election of a new chair, Dr Sabine Straus, and the appointment by the European Commission of 6 new independent experts to the membership, strengthening the Committee's knowledge in key areas and supplementing new patient and healthcare professional representatives appointed for the second mandate.
- The work of the network continued to grow during the reporting period, with an increased number of items on the PRAC's agenda (particularly relating to ongoing safety monitoring through PSURs and signals, and proactive risk management through the assessment of risk management plans) as well as continued work at Member State level. Among the noteworthy areas are:
  - an enormous increase in suspected adverse reaction reporting to the Member States, due to the go-live of the enhanced EudraVigilance system in November 2017, which was accompanied by a legal requirement to report for the first time all suspected adverse effects in the EEA, including non-serious cases rather than just serious ones. The number of suspected ADRs reported increased by 19% in 2017 from around 1.2 to nearly 1.5 million reports and by a further 37% in 2018 to over 2 million reports, about half of which came from the EEA. Looking at serious reports alone, these also increased over the reporting period from around 1.1 million in 2015 (290,000 from EEA) to about 1.4 million in 2018 (425,000 from EEA).
  - evaluation of nearly 9000 potential signals (information about new or changing safety issues potentially caused by a medicine) by EMA's signal management team over the period of the report, and a similar number at Member State level; about 400 (2%) of these were confirmed and went on to be prioritised and assessed by PRAC, resulting in updates to the product information in about half of the cases, and occasionally in more directed information such as a DHPC, or a wider review at EU level (a referral procedure).
  - proactive measures to manage risk via risk management plans (RMPs) have continued to form an important part of the workload, and can be crucial in allowing patients timely access to innovative treatments such as the new personalised cancer immunotherapies known as CAR-T cell medicines. PRAC assessed more than 500 new or updated plans each year. In addition, nearly 7,000 RMPs were assessed by the Member States for nationally authorised medicines during the reporting period.
  - review by PRAC of more than 150 protocols annually for post-authorisation safety studies (PASS), just under a third of which were for studies imposed on marketing authorisation holders as part of their post-authorisation obligations. In addition, it evaluated results for around 80 to 90 PASS each year. Member States imposed an additional 19 PASS at national level during the reporting period.
  - The number of PSURs/PSUSAs reviewed by PRAC increased steadily from 471 in 2014 to 901 in 2018; about a third of these related to active substances only included in nationally authorised medicines (work which PRAC first took on in 2015). Nearly 5,000 PSURs were submitted to the national competent authorities of the Member States over the period. The introduction of a common PSUR repository has facilitated this work.

  - Some 25 safety referrals had concluded or were ongoing by the end of the reporting period. Although this is fewer than in the period 2012-14, it has included some safety assessments of major importance for public health, including HPV vaccines, retinoids, gadolinium contrast agents, valproate-containing medicines and quinolone and fluoroquinolone antibiotics (the last two of which also incorporated public hearings, so PRAC could hear directly from stakeholders). The outcomes of these referrals included variations of marketing authorisations in 16 cases, suspensions in 4, and permanent revocations in 2 cases. For 4 medicines, PRAC recommended provisional measures as a precaution to protect public health while the referral was ongoing.

- The majority of EU/EEA pharmacovigilance inspections (around 200 to 300 annually, human and veterinary) have continued to be conducted under the national pharmacovigilance inspection programmes. However, EMA's scientific committees also requested between about 10 and 20 pharmacovigilance inspections each year.
- A continued focus on medication errors by the pharmacovigilance system, together with the upgrade to EudraVigilance previously referred to, has improved their reporting from around 8,500 in 2015 to nearly 38,000 in 2018 (of which 24,000 were non-serious). Improvement of reporting is critical so that appropriate action can be taken to minimise such errors and their associated harms. In addition, EMA routinely publishes information on any additional proactive measures put in place during the approval process to prevent medication errors.
- Coordination and collaboration within the network has continued to strengthen with a more mature understanding on all sides of the best ways to implement the legislation in practice. A streamlined EU network governance structure for pharmacovigilance was adopted by in February 2016 which has reinforced the PRAC's role in operational issues and provided a unified Pharmacovigilance Business Team from EMA and the Member States to focus on information systems and to support PRAC where needed. Oversight of the system is provided by an EU Network Pharmacovigilance Oversight Group (EU-POG) which reports to the Heads of Medicines Agencies and the EMA Management Board.
- International collaboration with other regulators, particularly FDA, Health Canada and the Japanese regulatory authorities has continued throughout the period. Additionally, EMA has helped share the network's best practice with external regulators via training courses and workshops, and participation in WHO committees, as well as supporting collaboration on pharmacovigilance through the International Coalition of Drug Regulatory Authorities ICDRA and the development of common standards through ICH.
- Following the UK notification of its intention to withdraw from the EU (Brexit) considerable work has been carried out during the reporting period to mitigate the impacts of the loss of UK expertise and input, including:
  - redistribution of the portfolio of centralised products for which the UK had responsibility by April 2018,
  - gradual disengagement of the UK from (co)rapporteurships at PRAC,
  - redistribution of responsibilities for signal monitoring,
  - work to facilitate knowledge transfer and build capacity in other Member States.
- The early evidence documented in this report shows how the various pharmacovigilance processes have contributed to a robust and effective pharmacovigilance system in the EU. Building on these strengths, future development will entail ever increased engagement with stakeholders, further transparency, evidence-based process improvement, and better use of real-world data and its

analysis to generate real-world evidence. Additionally, earlier engagement of pharmacovigilance and real-world data support to products in development will enable optimised surveillance and risk minimisation as soon as products enter the market. The current strong, effective and efficient EU pharmacovigilance system can thus go from strength to strength, delivering for public health and product innovation.

Introduction

This document is the second triennial report on pharmacovigilance in the EU, prepared for the European Commission by the European Medicines Agency. It has been extended to cover the four years 2015 to 2018 and describes pharmacovigilance activities carried out by the national competent authorities of the EU Member States, Norway and Iceland, and by the European Medicines Agency which also acts as the coordinating body of the EU pharmacovigilance system. It aims to meet the Commission's ongoing obligation to publish a report on those activities, to discuss the potential gains and benefits for public health and EU citizens, to discuss the involvement of various stakeholders in the pharmacovigilance process and to comment on the impact that the legislation is having and will continue to have.

The European system of pharmacovigilance is a strong and adaptable system built on the principles of engagement and collaboration and underpinned by excellent science, robust legal tools, optimal use of resources, and smart processes. European legislation requires that the overall European pharmacovigilance system is underpinned by systems within each of the actors that comprise it. As a result the European Medicines Agency, the national competent authorities, and the marketing authorisation holders for medicines all have their own systems which connect together to build a strong European system. The systems are complemented by standards and guidance, and their quality supported by audit, inspections, transparency and reporting. This report contributes to the transparency and reporting on the European pharmacovigilance system.

Background to this report

This document builds on the first three-year Commission report[1] and accompanying staff working document[2] published in 2016 which provided data on key pharmacovigilance tasks undertaken by the Member States and EMA (including quantitative data from July 2012 to December 2014), and which in turn added to the one-year report on human medicines pharmacovigilance tasks produced by the European Medicines Agency (EMA) in May 2014,[3] which described the initial implementation of the revised pharmacovigilance legislation. The legal basis for these reports is described in Annex 1.

The current report includes data on pharmacovigilance tasks between 2015 and 2018, including quantitative data covering the period 01/01/2015 to 31/12/2018. The period covered by the report saw largely complete implementation of the legislation which first became operational in 2012. Therefore this reporting period is important in providing transparency and accountability for the final implementation of the pharmacovigilance legislation.

The report provides some description and analysis of the impacts on measures of public health, both qualitative and quantitative, of the tools provided by the legislation, and gives an overview of the continuing development and maturation of the system.

Inevitably the report contains a great deal of technical information, but as before, our aim is to make the content as accessible as possible to the non-specialist reader. In order to keep the length of the

[1] European Commission. Monitoring safety of medicines for patients: pharmacovigilance activities related to medicines for human use in the EU. COM(2016) 498. https://ec.europa.eu/health/sites/health/files/files/pharmacovigilance/pharmacovigilance-report-2012-2014.pdf (accessed 01/02/19)

[2] European Commission. Monitoring safety of medicines for patients: pharmacovigilance activities related to medicines for human use in the EU. SWD(2016) 284 https://ec.europa.eu/health/sites/health/files/files/pharmacovigilance/pharmacovigilance-report-2012-2014_annex.pdf (accessed 01/02/19)

[3] EMA. One-year report on human pharmacovigilance tasks by the European Medicines Agency: http://ec.europa.eu/health/files/pharmacovigilance/2014_ema_oneyear_pharmacov_en.pdf (accessed 01/02/19).

document body to a minimum such a reader is referred to the list of abbreviations and definitions included at the end of this document for high level explanations of the main terms and concepts used.

Who is involved?

Responsibility for pharmacovigilance in the EU is distributed via a unique collaborative **network** that promotes and protects human health via a proactive, risk-proportionate, transparent and patient-centred approach.[4]

The **Member States** are key pillars in this EU pharmacovigilance network, particularly in terms of supervising the collection of information on suspected side effects, in the assessment of signals, periodic safety update reports, post-authorisation safety studies and risk management plans, in acting as rapporteurs in the evaluation and analysis of safety issues in referrals, communicating suitably tailored safety messages to their citizens, and maintaining the inspectorates that check that the elements of the system are functioning correctly. The Member States have supplied information and advice for this report.

Experts from the Member States also contribute at the European level through membership of EMA's scientific committees, notably the Pharmacovigilance Risk Assessment Committee (PRAC), primarily responsible for questions of pharmacovigilance and risk management, and the Committee for Medicinal Products for Human Use (CHMP) which is responsible for the overall evaluation and approval of marketing authorisation applications for centrally authorised products (CAPs). In addition, the EU Member States plus Iceland, Liechtenstein and Norway work together through the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which is responsible for ensuring harmonised safety standards for medicines authorised via national procedures.

EMA and its scientific committees coordinate the activities of the network and provide technical, regulatory and scientific support to the Member States and industry, as well as providing essential infrastructure and expertise for various pharmacovigilance tasks. EMA also leads on detecting signals for CAPs and coordinating communication on safety issues at EU level. EMA staff are responsible for assembling the information included here, and drafting the current report.

The **European Commission** oversees the system, and supplies the legal authority that underpins it. It is also the authorising authority for CAPs. This report is provided to the Commission as required by the legislation.

Sources of data

Information regarding Member State activities has been supplied by the national competent authorities of the different countries. Data on centralised activities, particularly those carried out by the PRAC and some other areas such as side-effect reporting, has been collected by EMA in its co-ordinating role within the EU network.

Qualitative information, including descriptive case studies, is included in the report in order to illustrate the way the legislation works at the level of individual issues and to demonstrate the experiences of stakeholders. References to a number of published studies reflecting the impact of the system are also provided throughout.

How was it measured?

[4] Santoro A, Genov G, Spooner A, Raine J, Arlett P. Promoting and protecting public health: how the European Union pharmacovigilance system works. Drug Safety 2017; 40: 855-69.

The quantitative data for the report covers the period from 01/01/2015 to 31/12/2018 (the data lock point). Measures of relevant tasks are provided using a variety of indicators. Some represent basic activity measurements, e.g., simple counts of numbers of procedures or submissions. Others have been used as part of the pharmacovigilance system governance by the Agency, including Key Performance Indicators (KPIs), which have been specifically developed by EMA to measure how well it is carrying out its tasks and to reflect specific outputs required by the new legislation.

Impacts of the legislation

Some key impacts of the 2012 pharmacovigilance legislation, viewed in terms of public health, simplification and transparency, are discussed below.

At the time of the first three-year pharmacovigilance report, the time scale from first implementation of the legislation was too short for much data on its real world impacts to be included. However, a number of studies and initiatives had already been put in place to collect such information. Some of these have since come or are coming to fruition, while others are still ongoing.

How do we measure impact?

A systematic review by Goedecke and colleagues[5] from EMA has looked at the various ways of measuring and analysing the impacts of pharmacovigilance activities and medicines regulation. It pointed out the very variable nature of the methodologies used, and its findings highlighted:

- the need to define measurable public health outcomes, both intended and unintended for regulatory decisions,
- the need for scientific guidance to ensure impact is assessed using robust and appropriate methods,
- the importance of ensuring the results of impact research are transparent and disseminated accordingly.

It is therefore important to note that in 2017 the PRAC **established a strategy for measuring the impact of pharmacovigilance activities**,[6] exploring the most effective risk minimisation measures and the best ways to work with stakeholders such as patients and healthcare professionals. The ultimate aim of this initiative, which amongst other sources builds on the collaborative work carried out by the Member States and EMA as part of the SCOPE project,[7] (discussed under Simplification and Process Improvement, below) is to shift the focus of pharmacovigilance towards activities and regulatory tools that are most relevant to patients and make the biggest difference in daily healthcare. PRAC also established an interest group to provide expertise to support the strategy as it is taken forward and implemented.

Data sources which allow measuring health outcomes and on which the PRAC strategy lays particular focus are electronic health records, drug prescription, dispensing and utilisation data, and on patient registries. In this regard the implementation of the strategy has been supported by complementary initiatives including a survey amongst Member States in the context of the SCOPE project (Work Package 8) on available data sources for pharmacovigilance purposes other than spontaneous reporting databases, and inventories of registered data sources and databases by the European

[5] Goedecke T, Morales DR, Pacurariu A, Kurz X. Measuring the impact of medicines regulatory interventions - systematic review and methodological considerations. Br J Clin Pharmacol 2018; 84: 419-33. doi:10.1111/bcp.13469

[6] European Medicines Agency. PRAC strategy on measuring the impact of pharmacovigilance activities (Rev 1). Available at: https://www.ema.europa.eu/documents/other/prac-strategy-measuring-impact-pharmacovigilance-activities_en.pdf (accessed 08/10/18).

[7] Strengthening Collaboration for Operating Pharmacovigilance in Europe, an EU-funded joint action project involving regulators from 23 EU Member States plus Norway and Iceland. http://www.scopejointaction.eu/ (accessed 01/02/19).

Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP: http://www.encepp.eu/index.shtml).[8]

In addition, during the reporting period a number of academic studies, mainly within the framework of the above PRAC interest group or the ENCePP special interest group have **examined regulatory interventions** available under the legislation, that is to say the various options available to respond to safety concerns, and their impact and effectiveness.

Regulatory interventions such as withdrawals or restrictions of use of a medicine may trigger therapeutic switching to alternative medicines with sometimes unforeseen public health implications. One example is the unintended increased use of conventional antipsychotics in two European countries after the introduction of EU risk minimisation measures for the risk of stroke and all-cause mortality with atypical antipsychotic drug use.[9] Another unintended consequence may be that prescribers extrapolate warnings for one group of patients to other groups (so called spill-over effects), although these patient groups do not share the same risk factors. This was, for example, the case when in 2003 the FDA warned of an association between prescription of SSRI antidepressants and suicidality in patients under 18 years of age, and subsequently prescriptions of SSRIs in newly diagnosed adult patients declined but without any alternative medicines or treatment to compensate.[10]

The EU regulatory network has therefore conducted considerable collaborative research aimed at assessing the impact of measures introduced by EU regulators. For example, a study evaluated the impact of contraindications, warnings, and changes to the product information, including direct healthcare professional communication (DHPC) implemented in 2013 for diclofenac-containing medicines across the EU to reduce the risk of acute cardiovascular events. It showed for Denmark, the Netherlands, England and Scotland a reduction in diclofenac prescribing and significant changes in switching to alternative pain medications following diclofenac discontinuation, the extent of which varied by country and type of exposure.[11,12] For another example, see 'The system in action: measuring the impact of a referral on codeine use for pain in children', under *Public Health*, below.

Inevitably, sometimes studies have shown that risk minimisation measures have not had the desired impact, requiring further regulatory action (see 'The system in action: the story of valproate', under *Transparency and Stakeholder Engagement*), or are of uncertain benefit (see 'The system in action: measuring the impact of a referral on combined hormonal contraceptives' under *Public Health*).

The overall direction of travel is nonetheless positive. Another study by Lane *et al.* looked at the evidence base supporting withdrawals, revocations and suspensions of marketing authorisations since implementation of the pharmacovigilance legislation, and suggested progress was being made towards more rapid decisions based on more robust evidence.[13] Similarly, a review by Vora and others[14] of 19 post-authorisation studies on the effectiveness of risk minimisation measures in the EU PAS Register found that 21 of 29 determinable effectiveness metrics indicated success.

[8] A partnership involving 147 centres across Europe that brings together academic and clinical expertise and resources in pharmacoepidemiology and pharmacovigilance, particularly in the context of post-authorisation studies.
[9] Sultana J, Fontana A, Giorgianni F, Pasqua A, Cricelli C, Spina E, et al. The effect of safety warnings on antipsychotic drug prescribing in elderly persons with dementia in the United Kingdom and Italy: a population-based study. CNS Drugs. 2016 Nov; 30(11):1097–1109.
[10] Valuck RJ, Libby AM, Orton HD, Morrato EH, Allen R, Baldessarini RJ. Spillover effects on treatment of adult depression in primary care after FDA advisory on risk of pediatric suicidality with SSRIs. Am J Psychiatry. 2007 Aug; 164(8):1198–205.
[11] Morales DM *et al*. Impact of EU label changes for systematic diclofenac products: post-referral prescribing trends for systematic diclofenac products. 2019 (publication pending)
[12] Flynn R *et al*. Impact of EU label changes for systematic diclofenac products: post-referral prescribing trends in switching to alternative products following diclofenac discontinuation. 2019 (publication pending)
[13] Lane S, Lynn E, Shakir S. Investigation assessing the publicly available evidence supporting postmarketing withdrawals, revocations and suspensions of marketing authorisations in the EU since 2012. BMJ Open 2018;8:e019759.
[14] Vora P, Artime E, Soriano-Gabarró M, Qizilbash N *et al*. A review of studies evaluating the effectiveness of risk minimisation measures in Europe using the European Union electronic Register of Post-Authorization Studies. Pharmacoepidemiol Drug Safety 2018; 27: 695-706. doi: 10.1002/pds.4434.

Though these limited results should not be over-interpreted they nonetheless provide some general evidence that as the legislation embeds and regulators become more experienced with the range of tools it provides, this is leading to **improved outcomes**.

Public health

The primary aim of pharmacovigilance is to improve public health by ensuring that medicines are used as safely and effectively as possible. As indicated above, it is therefore essential when regulatory measures are taken in the context of pharmacovigilance that they too are effective and relevant. When PRAC makes recommendations for regulatory actions, impact studies are therefore frequently put in place to examine the working of any risk minimisation measures. These may be imposed on the marketing authorisation holders (MAHs) as part of a regulatory procedure, but EMA may commission independent academic studies or carry out its own analyses.

For example, one of the tools that the legislation provides to assess and act on a safety concern at the EU level is a referral to PRAC (see also *Referrals*, below). Ten separate academic **impact studies related to individual referrals** were initiated by EMA tender during the reporting period; 6 further studies were carried out by EMA using data from The Health Improvement Network (THIN) and various IMS Health databases to support referrals. These studies are tabulated in Annex 2 and some are further discussed in the case studies below. They represent a subset of the work funded by EMA or carried out in-house to provide real world evidence to support its scientific committees and ensure effective regulation.[15]

> *Avoiding risks is impossible, so managing those risks appropriately, on the basis of the best available scientific evidence, is the key to an EU pharmacovigilance system that can successfully protect public health. This means that measuring the impact of the measures we take, and being prepared to modify them promptly if the evidence requires it, is fundamental to the way we work.* **Dr Sabine Straus, Chair of PRAC**

Use of such real-world data reflective of the ways medicines are actually used in practice is an important contributor to successful pharmacovigilance and helps support the authorisation of innovative therapies such as the CAR-T cell therapies (see under Risk Management Plans), and cell- and gene-based therapies such as Zalmoxis to support blood stem cell transplantation (HSCT) or Strimvelis for the inherited immune deficiency ADA-SCID.[12]

Inevitably there is a timelag between the introduction of risk management measures and having a clear picture of their effect – this means that final outcomes are not available from many of the impact studies initiated during the reporting period. However, examples of the impact of enhanced risk management measures on public health can be found in the below case studies, discussing the impact of two important referrals that took place during the reporting period of the first 3-year pharmacovigilance report.

[15] Cave A, Kurz X, Arlett P. Real-world data for regulatory decision making: challenges and possible solutions for Europe. Clin Pharmacol Ther 2019; doi:10.1002/cpt.1426 (accessed 23/04/19).

The system in action: measuring the impact of a referral on combined hormonal contraceptives (CHCs)

Hormonal contraceptives – the risk of blood clots

In February 2013 the French medicines regulator, ANSM, had asked for a referral to PRAC under Article 31 to further review the risks of CHCs, which have long been known to be associated with an increased risk of the rare but serious formation of clots within blood vessels (thromboembolism). This risk varies depending on the progestogen component of the CHC as well as risk factors pertaining to the woman taking the medicine. The referral looked at the latest data on the risks with newer progestogens compared with the older alternatives levonorgestrel or norethisterone, and the information available to women and their health care professionals.

Identifying the risks and minimising them for patients

In October 2013 the PRAC confirmed that benefits with CHCs continue to outweigh their risks as the risk of thromboembolism in the veins (VTE) is small. It provided a table comparing the risks for the progestogens and recommended modifying the product information of CHCs to give up-to-date information to women and prescribers on the risks and how to minimise them, as well as communicating the outcome of the review through educational materials including a letter to healthcare professionals.

Measuring the impact of regulatory action

The PRAC's recommendations were supported by the CHMP and the European Commission adopted a legally binding decision in January 2014 modifying the product information of all CHCs throughout the EU.[16]

In order to measure the impact of the recommended measures impact studies were commissioned via an EMA tender. [17,18] These studies looked at

- changes in prescribing trends
- incidence of thromboembolism

before and after the Commission decision. They also examined the effectiveness of regulatory communications to stakeholders.

The outcomes

The studies found no clear trend in prescription patterns of different types of CHC nor in switching patterns between different types of CHC in the three participating countries (Denmark, the Netherlands and the UK) before and after the regulatory intervention. The high percentage of new users who started with a second generation CHC both before and after the review suggested that prescribing physicians were already aware of the lower risk of VTE associated with this preparation and were communicating this to women seeking contraception.[17]

With respect to communication, surveys and interviews with women found that they preferred to receive information on CHCs directly from healthcare professionals, who thus have a key role in supporting informed choice.[18] Over half the physicians surveyed were aware of the EMA recommendations. However, they relied mainly on national and local regulators to provide

[16] European Medicines Agency. Benefits of combined hormonal contraceptives (CHCs) continue to outweigh risks (published 31/01/2014). Available at: https://www.ema.europa.eu/medicines/human/referrals/combined-hormonal-contraceptives (accessed 01/02/18).
[17] Khialani D, van Hylckama Vlieg A. Study of utilisation of combined hormonal contraceptives in Europe. 2019 (pending publication).
[18] Stevenson, F. Study of regulatory communication and risk awareness following the Article 31 referral of Combined Hormonal Contraceptives in relation to thromboembolism: final report. EUPAS 21356.

prescribing guidance, showing the importance of the network in promulgating regulatory decisions taken at the EU level.

Another example providing clearer evidence of public health benefit from the referral process relates to the use of codeine in children. The example also shows the power of collaboration within the EU network.

The system in action: measuring the impact of a referral on codeine use for pain in children

Codeine, a derivative of opium, has been used for pain relief for well over a century. It is converted in the body into morphine, the main opium alkaloid. Like other opioid analgesics it is associated with risks, such as respiratory depression (shallow or inadequate breathing), particularly in excessive doses.

Reducing the risk of respiratory depression in children

In June 2013 the PRAC completed a review of the benefits and risks of the use of codeine to treat pain in children. This had been triggered by reports of respiratory depression, some fatal, in children in whom codeine had been used. The PRAC's recommendation was to restrict the use of the medicine to children over 12 years of age, for the shortest possible time, and only if other types of painkiller were ineffective. It also contraindicated use in children at high risk because of sleep apnoea or because they metabolised the medicine to morphine more rapidly.

Measuring the impact of regulatory action

A study was conducted to assess the impact of these measures on codeine prescribing in children.[19] It looked at how often codeine was prescribed in this age group, whether it was used after removal of tonsils or adenoids for sleep apnoea, and the doses and duration of treatment; the aim was to measure changes in prescribing over the period of the referral and the implementation of its recommendations. As medical practice varies across EU Member States, the study was conducted in 4 countries (France, Germany, Spain and the UK). The study was carried out by examining databases of electronic health records in these countries and was a joint collaboration between EMA and the Spanish and UK medicines agencies.

A positive public health outcome

The evidence indicated a decrease in codeine prescribing for pain in children less than 12 years of age during the study period. No child with a diagnosis of sleep apnoea received codeine within 30 days of removal of tonsils and adenoids after 2013. The results support the effectiveness of the measures recommended by PRAC, and show how the EU regulatory network can act to protect public health.

[19] Hedenmalm K *et al*.European Union drug utilisation study of codeine for pain to measure the impact of regulatory measures. 2019 (publication pending).

Simplification and process improvement

> *Just as we measure the impact of regulatory measures and modify them on the basis of the evidence if necessary, we constantly measure the effectiveness of our underlying processes so that we can deliver evidence-based improvements and enhance the positive impact of our work on those we serve.*
> **Dr Peter Arlett, Head of Pharmacovigilance and Epidemiology, EMA**

Safety monitoring through collection of *adverse effect reports*, the timely detection and assessment of *drug safety signals*, ongoing benefit-risk evaluation via *periodic safety update reports* (PSURs), and assessment and agreement of *risk management plans* and *post-authorisation studies* by the Pharmacovigilance Risk Assessment Committee (PRAC) are the cornerstones of EU pharmacovigilance as laid down in the legislation, optimising safe and effective use of medicines and supporting timely access to innovative medicines. However, the complexity of this task across a diverse population of over 500 million people, accessing varied healthcare systems, should not be underestimated.

During the reporting period important changes were made to some of the supporting systems and processes underpinning pharmacovigilance in the EU. These changes have simplified and improved certain important aspects of the overall system and thus impacted on their efficiency and effectiveness.

EudraVigilance

During the reporting period important enhancements and changes of reporting requirements were made to the EudraVigilance database,[20,21] (see also the section System improvements, below). EudraVigilance is the centralised database supporting safety monitoring and the safe and effective use of medicines in the EU. It is thus the network's link between the dedicated individuals – from PRAC and the national pharmacovigilance systems down to individual healthcare professionals and patients raising concerns – who are working to protect public health and the real world data that is needed to draw evidence-based conclusions on medicines safety. **The improvements made to EudraVigilance are therefore key to many of the other positive changes seen over the period of this report**.

As a result of these improvements there was an overall 19% increase in the number of reports received by the EudraVigilance database and available for signal detection and a 60% increase in EEA reporting in 2017 (1,471,596 reports related to ADRs, 543,548 of which originate from the EEA) compared to 2016. The major increase is due to the reporting of non-serious ICSRs after the go-live of the new system in November 2017. This effect continued into 2018 with a further 37% increase relative to 2017: there were 2,015,881 reports related to suspected ADRs, 1,028,386 of which originated from the EEA. The number of reports submitted directly by European patients and consumers through the NCAs and MAHs (90,358) also increased significantly in 2017 for the same reasons.

There has also continued to be a steady increase in EEA reporting for serious ICSRs over the entire reporting period, from 290,000 in 2015 to 424,000 in 2018. For further detail, see Adverse Reaction Reporting, under Overview of Key Activities by Area, below.

[20] European Medicines Agency. 2016 Annual Report on EudraVigilance for the European Parliament, the Council and the Commission. Available at: https://www.ema.europa.eu/documents/report/2016-annual-report-eudravigilance-european-parliament-council-commission_en.pdf (accessed 01/02/19).
[21] European Medicines Agency. 2017 Annual Report on EudraVigilance for the European Parliament, the Council and the Commission. Available at: https://www.ema.europa.eu/documents/report/2017-annual-report-eudravigilance-european-parliament-council-commission-reporting-period-1-january_en.pdf (accessed 01/02/19).

Article 57 database

Closely entwined with the EudraVigilance system is the eXtended EudraVigilance Medicinal Product Dictionary, the so-called 'Article 57 database' or xEVMPD, which contains structured, quality-assured information on more than 800,000 medicinal products authorised in the EEA by national and centralised procedures.

Since the last report, this system has been fully embedded in practice, supporting a wide range of pharmacovigilance processes. It allows the identification of medicines in suspected adverse event reports (ICSRs), supports the management of pharmacovigilance procedures (signals, PSURs, referrals) and facilitates the administration of pharmacovigilance fees. It also allows MAHs to update details of the qualified person responsible for pharmacovigilance (QPPV) and the pharmacovigilance system master file (PSMF) more easily without the need to apply for formal changes to the marketing authorisation (variations).

System improvements have increased network access to, and usability of, this invaluable resource over the reporting period. In addition, as envisaged by the legislation, a listing of authorised medicines from the database has been made **publicly available** via EMA's website. This provides dedicated contact details for pharmacovigilance enquiries to industry, and is also intended to help reduce the risk of proposing new medicine names that might be confused with those of existing medicines and lead to medication errors. It is also a valuable resource for medicines information centres and other secondary information providers helping clinicians and others to identify medicines.

Periodic safety update reports

Another important area of improvement during the past 4 years is found in the way in which periodic safety update reports for medicines (PSURs/PSUSAs) are handled.

These improvements to the process benefitted not only all EU single assessments but also purely national procedures. During the reporting period the PSUR process was improved and simplified through creation of a common repository with a single electronic point of access. This is used for both centrally and nationally approved medicines, with common templates and tools to support validation and workflow, including re-use of information on medicines already held in the system as part of the Article 57 database.

The creation of the single interface for PSURs has **simplified the entire process** and greatly reduced the resource burden of the system on the Member States as well as making it more straightforward for industry to comply with the reporting requirements imposed by the legislation. Its re-use of Article 57 data also illustrates the way in which different elements of the system support one another to improve outcomes.

Training

Ensuring that consistent and appropriate training is made available to keep scientific knowledge updated and support best practice in the EU network is essential. The establishment of the **EU Network Training Centre** (EU NTC) has provided a central platform for the supply of scientific and regulatory training practices between EMA and NCAs in the EEA to ensure the spread of good practices and improve the work done in the EU regulatory network. The EU NTC catalogue increased from 48 courses in 2015 to 100 courses in 2017. A digital training platform, the EU NTC Learning Management System (LMS), was implemented in January 2017. The online availability of extensive, high-quality training materials simplifies the provision of regulatory training across the breadth of a continent, increasing accessibility and compliance and reducing cost and is a key outcome of the collaborative work carried out by SCOPE (see also below).

The Operation of Pharmacovigilance in the EU Training Curriculum (EU PVOP TC) aims to provide an overview of the training areas related to the operation of pharmacovigilance. More specifically, the purpose is to drive training in key priority areas in a consistent way across the EU Network and to support objectives such as harmonisation and consistency of decision making in the EEA, as well as to facilitate collaboration for the entire EU network. Other key objectives are to increase capacity through effective training and induction of new staff, and to provide a platform for pharmacovigilance staff for knowledge sharing across the EU network. To meet the objectives, various training events/materials were developed and most of them are already available to the network through the EU NTC platform.

Amongst the key training objectives for pharmacovigilance is ensuring that regulators and other key players such as the pharmaceutical industry can use the EudraVigilance system appropriately. Over the period covered by this report, 4 or 5 introductory sessions have been held each year to explain the functioning of EudraVigilance and the analysis of EudraVigilance data, together with many annual training events on the correct submission of data (some 15 to 20 sessions annually, rising to 36 in 2017 to support the increased functionalities made available) and regular training sessions and ongoing e-learning on the xEVMPD.

Such training is also a part of EMA's ongoing work to ensure the quality of data in the EudraVigilance database, and it is perhaps notable that the number of ADR reports requiring recoding fell slightly from 54,535 in 2015 to 41,124 in 2017, despite a considerable expansion in their numbers.

Translating recommendations from signal assessments

Following its assessment of safety signals (see Signals, under Overview of key activities below) PRAC makes public recommendations when regulatory action, such as updates of product information, is required. Manufacturers are expected to take action accordingly, but since the working language of EMA is English, the initial recommendation is made in that language, which could lead to delays or concerns about the best way to translate the recommendation for product information in other EU languages. CMDh and industry associations requested support from EMA to mitigate such risks.

Since its January 2015 PRAC meeting, the Agency has therefore made translations of its recommendations for updates of product information available in all official EU languages, as well as Norwegian and Icelandic. The translations are reviewed by the national regulatory authorities in EU Member States and published on the EMA website. Marketing-authorisation holders can use these translations to update their product information, with less risk of any inconsistencies in the translations and with the expectation that this will support rapid implementation of changes to product information. Since 2015, 97% of all changes requested as a result of PRAC signal assessments have been implemented within the expected time period or with only slight delays.

SCOPE

The work of the Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Joint Action[22], which was begun in 2013, brought together national medicines regulators from the European Economic Area to evaluate their practices and develop tools to further improve the skills and capability in the pharmacovigilance network. Over the period of the present report it has delivered guidance, training in key aspects of pharmacovigilance, and tools and templates to support best practice.[23] The deliverables provide practical guidance to strengthen Member States national systems in the areas of reporting suspected adverse drug reactions, identifying and managing safety signals, communicating risk and assessing risk minimisation measures and may also prove useful for other stakeholders

[22] http://www.scopejointaction.eu/ (accessed 01/02/19).
[23] Radecka A, Loughlin L, Foy M, et al. Enhancing pharmacovigilance capabilities in the EU regulatory network: the SCOPE Joint Action. *Drug Safety* 2018; **41**:1285–1302.

involved in pharmacovigilance activities. The outputs are being maintained and delivered through the pharmacovigilance curriculum of the EU-Network Training Centre.

Transparency and stakeholder engagement

The EU regulatory network has been engaging with its multiple stakeholders, and issuing external communication since its inception. This two-way communication is critical to the network's regulatory function, and to the development of a culture of transparency, an area in which the EMA has consistently been at the forefront.

PRAC's **agendas and minutes**, for example, are routinely published, the former before the start of the plenary meeting to which they refer, and the latter after review and adoption at a subsequent PRAC plenary. In addition, EMA publishes communications on key safety-related outcomes on the day following the meeting's conclusion.

> *Publishing more and better information about how risks are going to be proactively managed and investigated helps empower patients and healthcare professionals and to bring them with us: greater transparency enables stakeholders to accept their respective responsibilities for safe and effective use of medicines, and this in turn supports innovation.* **Dr June Raine, PRAC Chair 2012-2018**.

Representatives of **patients, consumers and healthcare professionals** are members of EMA's management board, scientific committees such as PRAC, working parties, and of the expert groups convened to give scientific or protocol advice. This ensures that their input is considered at all levels not only of pharmacovigilance but of the overall medicines development process.

During the reporting period EMA also introduced a formal framework for interaction with another key stakeholder group, academics. **Academia** plays a significant role in generating the evidence on which regulators rely to make judgements about the benefits and risks of medicines, and it has also been one of the drivers of the transparency agenda. As part of the work to develop this framework, EMA held a workshop in June 2016,[24] and EMA's Management Board adopted the final framework in March 2017.[25] The Agency has also continued its close academic collaborations in the field of pharmacovigilance through the **ENCePP network**, which, as noted above, brings together nearly 150 academic and clinical research centres with expertise in pharmacoepidemiology and pharmacovigilance. ENCePP celebrated 10 years of existence in 2017, and has helped promote methodological standards, transparency and scientific independence in pharmacoepidemiological research over that period.[26]

Engagement and commitment to transparency has been prominent during the reporting period, and plays a major role in the network's ability to provide the high-quality pharmacovigilance needed for public health. Bringing together the participants for public hearings (see below) for example, has only been possible because of the ongoing programmes of **stakeholder engagement** carried out by EMA. Such stakeholder engagement is one of 4 pillars of the 2017 PRAC strategy for measuring the impact of pharmacovigilance.[5]

[24] https://www.ema.europa.eu/en/events/healthcare-professionals-organisations-working-party-hcpwp-workshop-academia
[25] https://www.ema.europa.eu/en/partners-networks/academia
[26] Kurz X, Perez-Gutthann S, and the ENCePP Steering Group. Strengthening standards, transparency, and collaboration tosupport medicine evaluation: Ten years of the EuropeanNetwork of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Pharmacoepidemiol Drug Saf 2018; 1-11. https://doi.org/10.1002/pds.4381.

Key elements of this have been the first **public hearings** on issues of medicines safety, for valproate-containing medicines in 2017, and quinolone and fluoroquinolone antibiotics in 2018.

Public hearings represent a valuable tool to improve assessment quality and foster trust in the system. They also improve transparency and public understanding of regulatory procedures. However, they do require considerable resources to organise and manage. Criteria have therefore been developed to help determine when a public hearing would be of high value.

Generally positive impressions have been received from participants in the public hearings to date – for further detail, see the case-study for valproate, below.

The system in action: the story of valproate

Valproate and related substances are medicines used in Europe for the treatment of epilepsy, bipolar disorders and, in some Member States, to prevent migraine attacks. For some patients with serious conditions, valproate may be the best or only treatment option. However, it has long been known that if taken during pregnancy it can damage the unborn baby and cause certain abnormalities.

History

Although valproate medicines are all authorised by national procedures, the EU pharmacovigilance system has regularly monitored and reviewed the safety of valproate as new data became available, and has recommended changes to the way these medicines are used and the information provided to patients and healthcare professionals.

In 2014 PRAC carried out an **Article 31 referral** to review new and concerning evidence about the effects of valproate exposure in the womb on the later development and brain function of exposed children. As a result the Agency recommended additional warnings to women and girls using valproate and restrictions to ensure that they used it only when appropriate.

As part of the procedure, PRAC required the companies marketing these medicines to carry out a **drug utilisation study to measure the impact** of the new measures and gain more data about how valproate was being prescribed. In addition, the pharmacovigilance systems of some Member States carried out additional studies at national level to provide further real-world evidence of impact.

By early 2017 the first data from these impact studies suggested that the measures introduced by the referral had not had the desired effect. Notably, valproate was still being widely used in women of childbearing potential and there was ongoing pregnancy exposure.

In March 2017 EMA was therefore asked to carry out a **further referral** to review the existing measures and consider whether further actions were needed to minimise the risks of valproate in women who were pregnant or of childbearing age. PRAC appointed experts from the Netherlands and Belgium as rapporteurs to lead the referral procedure and the analysis of the data.

Involving the stakeholders

The PRAC considered it was essential to take into account the views and experiences of patients, affected families and the wider EU public. It therefore decided to conduct its first **public hearing**, a new regulatory tool introduced by the 2012 pharmacovigilance legislation.

Participants were asked their views of the risks of valproate in pregnancy, the measures then in place to reduce those risks, and what other measures might be needed.

Some 89 requests for participation were received, resulting in 25 speakers grouped to provide 16 presentations. In the end there were 65 stakeholder attendees, including 28 patients and patient representatives, 19 healthcare professionals and academics, 11 from pharmaceutical industry and 7 from media. The hearing was also broadcast live on the EMA website.

EMA staff, using experience and skills developed through the EMA stakeholder interaction framework, helped support and guide participants through the unfamiliar hearing process.

What were the outcomes?

Following the public hearing and taking all the evidence into account, PRAC restricted the use of these medicines in any woman or girl able to have children unless the conditions of a new pregnancy prevention programme are met. The programme was designed to ensure that patients are made fully aware of the risks and the need to avoid becoming pregnant. It includes regular meetings of prescriber and patient, with a signed form to ensure the risks had been covered, and a requirement for visual warnings/patient alerts on the packaging (all strongly recommended by participants at the public hearing). Further studies were also recommended, including studies to address issues raised by participants in the public hearing and new impact studies to check that the outcomes meet regulator and stakeholder expectations.

What impact did the hearing have?

The public hearing was instrumental in recommending new measures to avoid exposure of babies to valproate in the womb:

- it placed **consultation** with patients and health professionals at the heart of the safety review,
- it helped to **identify the real problems** in clinical practice,
- the process supplied **insights and information** which otherwise would have not been gathered,
- stakeholder contributions **shaped** the subsequent parts of the PRAC assessment and **identified the questions** for the expert meeting (SAG),
- its input fed directly into the **final recommendations.**

Participants were surveyed to assess their satisfaction with the procedure: 88% felt the procedure would make a difference to the final outcomes, as did around 80% of PRAC members.

Conclusions

The recent regulatory history of valproate outlines the strengths and interactivity of the EU pharmacovigilance system, from the deployment of different regulatory tools as appropriate, impact assessments that feed back into the system, the sharing of knowledge and expert skills between the Member States and EMA, and above all the involvement of patients and healthcare professionals in the regulatory process.

Overview of key activities by area

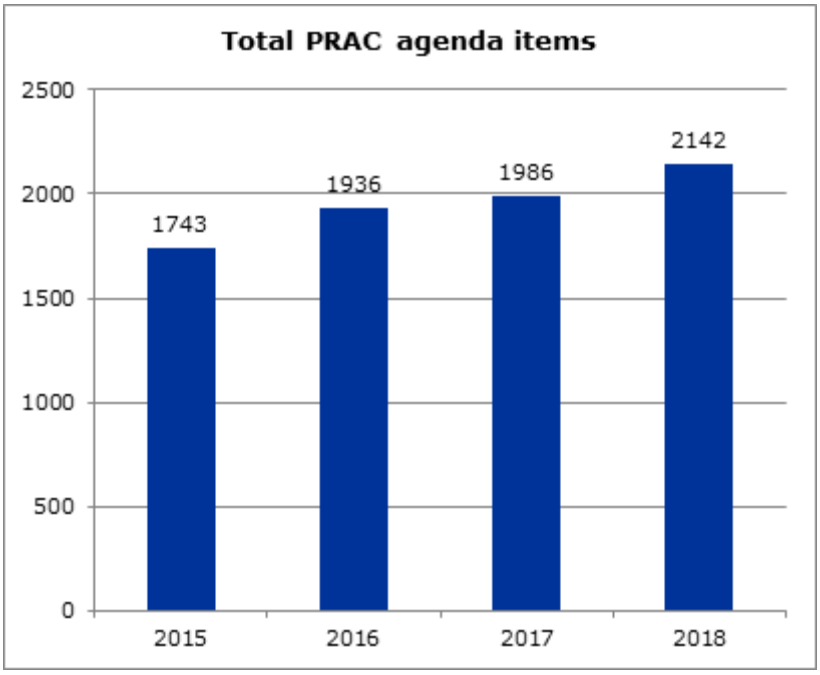
The reader is presented below with quantitative and qualitative data for various key aspects of the EU pharmacovigilance system between 2015 and 2018. Further quantitative data summarising the work of the EU pharmacovigilance network can be found in the Annexes at the end of the report.

PRAC activities – overview

In 2018, PRAC began its third mandate. Dr June Raine, who had successfully chaired PRAC from its inception and played a pivotal role in helping it master its new functions, completed her second and final period as Chair, and was succeeded by the experienced Dutch pharmacovigilance expert and long-time PRAC member, Dr Sabine Straus.

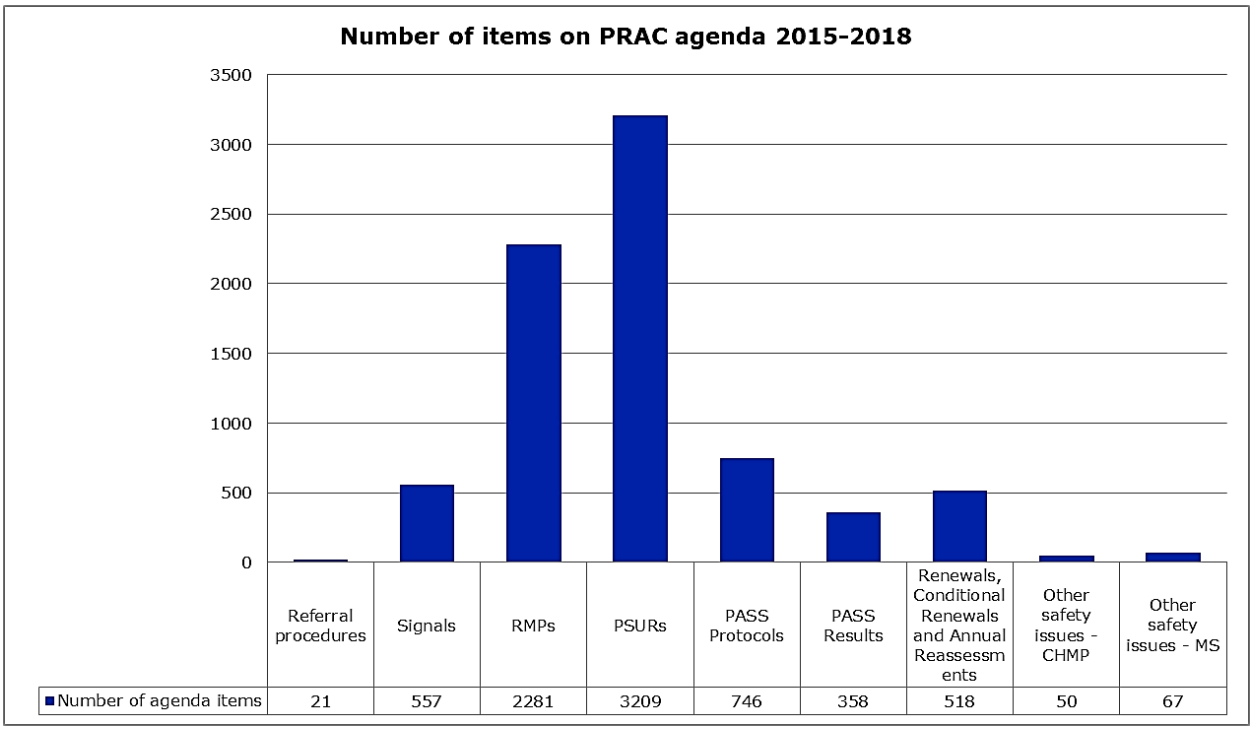
At the same time, the 6 Commission-appointed experts who play a vital role in augmenting the PRAC's knowledge in specific areas related to medicines safety also completed their mandate, and new experts were appointed. This provided an opportunity to further strengthen the available expertise in areas that had been identified as particularly important to the PRAC's continuing evolution, including pharmacoepidemiology and evidence-based medicine. New patient and healthcare professional representatives had previously been appointed in 2016 under the second mandate, bringing fresh input from those key stakeholder groups.

The number of items on PRAC's agenda continued to grow over the period 2015-18, continuing the trend seen in the previous report.



The bulk of the work related to ongoing safety monitoring (PSURs and signals) and the assessment of risk management plans (RMPs). Across the entire period covered by this report, PRAC assessed more

than 3,000 PSURs, and over 2,200 RMPs, in addition to more than 550 signals, around 750 protocols for post-authorisation safety studies (PASS) and results from more than 350 such studies, as well as making safety assessments for renewals of marketing authorisations and other safety issues, including requests for consideration of safety issues raised by the individual Member States.



Preparing for Brexit

On 29 March 2017, the United Kingdom notified the European Council of its intention to withdraw from the EU, a process known as 'Brexit'. This means that the UK is expected to become a 'third country', and its subsequent participation in the work of the European Medicines Agency and the EU pharmacovigilance network will depend on the nature of any future agreement.

The UK has made a substantial contribution to the work of both EMA and the network from their beginning, and the loss of UK expertise and input is greatly regretted. However, respecting the UK decision, considerable work has been carried out during the reporting period to mitigate the impacts of any loss,[27] and the associated relocation of EMA headquarters from London to Amsterdam in March 2019.

Preparations include:

- work with the national competent authorities of the remaining EU Member States and Norway and Iceland to redistribute the portfolio of centralised products for which the UK had responsibility. The redistribution was completed in April 2018;
- gradual withdrawal of the UK from rapporteurships/co-rapporteurships in pharmacovigilance processes at PRAC;
- redistribution of the active substances for whose signal monitoring UK was lead Member State;
- work to facilitate knowledge transfer to those states taking on the new responsibilities;

[27] https://www.ema.europa.eu/en/about-us/united-kingdoms-withdrawal-european-union-brexit (accessed 04/02/19)

- work through the EU-Network Training Centre to help build pharmacovigilance capacity in other Member States.

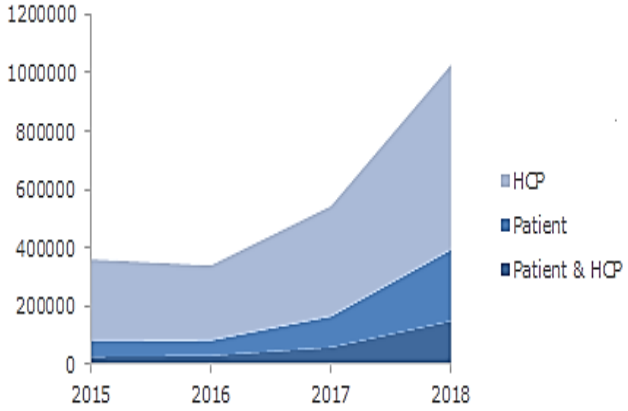
EMA has also developed a business continuity plan[28] to ensure that key activities necessary for public health can continue without interruption during the transition.

Adverse reaction reporting

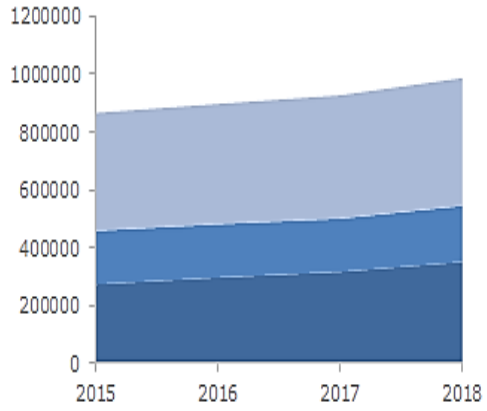
2017 saw a remarkable increase in reports of suspected adverse reactions: there was an overall 19% increase in reports received by EudraVigilance and a 60% jump in EEA reports (1,471,596 reports related to ADRs, 543,548 of which originate from the EEA) compared to 2016. This growth only continued in 2018, with a further 37% increase relative to 2017: there were 2,015,881 reports related to suspected ADRs, 1,028,386 of which originated from the EEA (an 89% increase compared to 2017).

The major increase is due to the reporting of non-serious ICSRs after the go-live of the new EudraVigilance system in November 2017. This was associated with a legal requirement to report all suspected adverse effects in the EEA, whereas previously this only applied to serious cases; similarly, more stringent reporting requirements were applied to non-EEA reports (all serious cases rather than just unexpected serious cases). Work was initiated in 2018 to look at the impact and utility of non-serious reports on detecting and evaluating safety issues.

Individual case safety reporting to EudraVigilance (EEA)



Individual case safety reporting to EudraVigilance (non-EEA)



The number of **serious** suspected adverse effects reported from the EEA has also continued to increase over the reporting period, from an annual total of around 290,000 ICSRs in 2014, at the end of the last reporting period, and a similar number in 2015, to around 424,000 in 2018 (a 46% increase). Looking at reports from outside the EEA, these increased from around 765,000 in 2014 to over 973,000 in 2018.

The majority of reports continue to be submitted by healthcare professionals. However, the campaigns by the network to facilitate and encourage **direct reporting by patients** have continued in many Member States, including regular EU-wide campaigns each November (supported, amongst other things, by multilingual materials developed through the SCOPE joint action), and continue to bear fruit.

[28] EMA. European Medicines Agency Brexit Preparedness Business Continuity Plan (13 October 2017). Available at: https://www.ema.europa.eu/en/documents/other/european-medicines-agency-brexit-preparedness-business-continuity-plan_en.pdf (accessed 28/06/19).

Patient reporting in the EEA increased from around 30,000 ICSRs for serious adverse effects in 2014 to over 50,000 in 2018; if non-serious reports are also included the increase, thanks largely to the changes in EudraVigilance reporting, is dramatic, from around 39,000 in 2014 to over 244,000 in 2018.

Patient reported ICSRs			
Year	Serious	Non-serious	Total
2014	29477	9770	39247
2015	34026	17100	51126
2016	37428	14450	51878
2017	60558	45456	106014
2018	51114	193048	244162

Additional monitoring

In 2013, the EU introduced a new system to label medicines that are being monitored particularly closely by regulatory authorities.[29] These medicines are described as being under additional monitoring. These medicines are marked by a black triangle in their product information and are monitored more intensively than other medicines. Reporting of suspected adverse reactions is particularly encouraged, and the interval between PSURs may be more frequent than for other medicines. This is generally because there is less information available, for example because a medicine contains a new active substance, is a biological product, or it has been approved in circumstances where there are limited data on its long-term use. Additional monitoring does not mean that any of the medicines affected are unsafe, and as more is understood about a new medicine it will eventually be removed from the list.

EMA maintains a list of medicines subject to additional monitoring, which is reviewed every month by PRAC and is published by EMA and the NCAs on their websites. The number of medicines on this cumulative list has increased from 193 centrally authorised and 8 nationally authorised medicines at the end of 2014 to 313 and 38 respectively by December 2018. In addition, 1,826 nationally authorised products were included in the Annexes to the list, which relate to individual active substances, present mainly as a result of referral procedures.

In 2018, EMA and the Member States evaluated experience with the scheme to date, including a survey of healthcare professional and patient perceptions. Although healthcare professionals were broadly aware of the scheme, the effects on reporting of side effects or validated signals appeared to be inconclusive, and further consideration of the concept and interaction with relevant stakeholders will be needed.

Signals

Signal detection and assessment is at the core of pharmacovigilance. It allows new or emerging concerns to be picked up quickly, and corrective regulatory action to be taken, thus minimising public exposure to harms. Inevitably, many potential signals prove not to be valid, and many validated signals do not require action when investigated, but in some cases the prompt action triggered by a signal has proved important in allowing swift action to be taken to protect public health. The continuing

[29] Defined by Article 23 of Regulation (EC) No 726/200 and Article 11 of Directive 2001/83/EU, as amended; the implementing regulation for the black triangle is (EU) No 198/2013.

improvement in EudraVigilance tools over the period of this report means that signal analysis has become ever more sophisticated and sensitive.

Over the reporting period, EMA's signal management team looked at nearly 9,000 potential signals, over 2,000 annually, the great majority of which had their source in EudraVigilance reports.

Member States evaluated a similar number of potential signals over the reporting period, that is, over 2,000 annually between them.

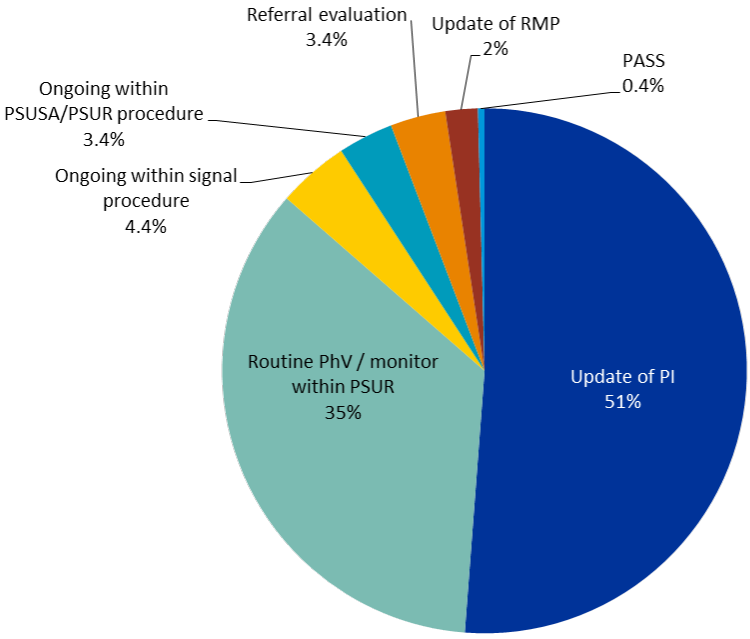
About 2% of the potential signals were confirmed by the PRAC rapporteurs or lead Member States and went on to be prioritised and assessed by PRAC.

Signals assessed by PRAC	2015	2016	2017	2018
Validated by EMA	61	48	43	74
Validated by Member States	41	46	39	40
Total	**102**	**94**	**82**	**114**

Following PRAC assessment, around half of these signals resulted directly in a recommendation to update the product information, the major source of guidance on the medicine for healthcare professionals and patients, thus contributing to safe and effective use of the medicine. As noted under the section on *Simplification and Process Improvement* above, the PRAC recommendations for update are now being translated into all official EU languages plus Norwegian and Icelandic, with review by Member States, in order to facilitate this process and ensure consistency.

In a very small proportion of cases more directed information, in the form of a Direct Healthcare Professional Communication (DHPC), was considered necessary, and in some cases a referral procedure, to examine the safety concern in more depth was deemed appropriate.

Signal outcomes (Sep 2012 to Dec 2018)



The signal system has proven to be a tool that can **respond very rapidly** to a potential problem. An example is the recent signal of developmental problems affecting the offspring of women with HIV treated with antiretroviral therapy including the integrase inhibitor dolutegravir.

The system in action: handling a signal of neural tube defects with dolutegravir

The concern

In May 2018, EMA was made aware of a signal deriving from the results of the Tsepamo study. The latter was an observational study carried out in Botswana that looked at birth outcomes in HIV-infected women. Preliminary data from the study suggested an increased risk of neural tube defects in the children of women who had received HIV treatment that included dolutegravir at the time of conception.

Dolutegravir (Tivicay), an integrase inhibitor, is available in more than 80 countries, including EU Member States. Given the potential severity of the harm, the regulatory system needed to move swiftly, and it was important that action was coordinated with regulators elsewhere in the world.

Prioritisation and interim action

The signal was confirmed, prioritised and assessed very rapidly. EMA was made aware of the study results on 8 May 2018, and by the time of the conclusion of the next PRAC plenary on 18 May, PRAC had agreed on the need for further swift evaluation of the findings and a plan of action to reduce any risks.[30]

As an interim measure the MAH was instructed to send out a DHPC to healthcare professionals advising them of the study results and to inform them of the PRAC's precautionary advice that dolutegravir not be used in women planning a pregnancy, that pregnancy be excluded before starting treatment and that women of child bearing potential who took dolutegravir should use effective contraception.

PRAC undertook to review the signal within 15 days, in the context of the available data. To this end it required the MAH to provide within 8 days, information on the safety of dolutegravir during pregnancy and pregnancy outcomes from all available data sources (including clinical trials, post-marketing experience and relevant literature). The MAH also had to provide proposals to update the product information for healthcare professionals and patients.

Global cooperation

Because dolutegravir is so widely used, it was crucial that healthcare professionals and patients across the world received coordinated and consistent information, to avoid causing confusion or artificially placing patients in some places at greater risk than others. EMA was in close contact with the FDA and WHO, and the three bodies cooperated to share data and ensure that advice in the different jurisdictions was not contradictory.

An FDA drug safety communication, WHO statement on the safety concern and the EMA's safety communication containing the PRAC's precautionary advice were released simultaneously on Friday 18 May 2018.

[30] EMA Pharmacovigilance Risk Assessment Committee. Minutes of PRAC meeting on 14-17 May 2018, item 4.1.2. Available at: https://www.ema.europa.eu/documents/minutes/minutes-prac-meeting-14-17-may-2018_en.pdf (accessed 29/01/19).

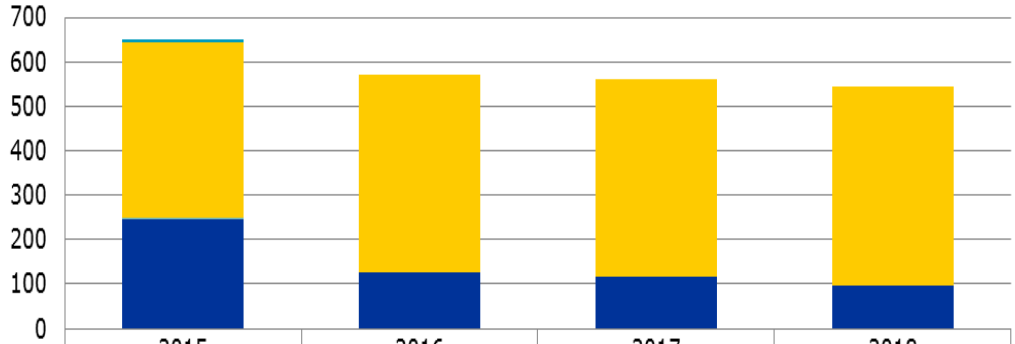
The final outcome

The PRAC's initial 15-day review confirmed the potential risks at the time of conception but the Committee considered that more information was needed on the effects of the medicine in later pregnancy, and the procedure was therefore extended. In October 2018 PRAC confirmed its precautionary advice that women should use contraception during dolutegravir treatment, that women should have pregnancy tests before starting treatment and that the medicine be avoided in the first trimester unless there is no alternative. Although there was no evidence of harm in the second or third trimester, warnings that it should only be used in later pregnancy if the expected benefit justified the potential risk were also added to the product information, and a plan set out for the collection of further information including monitoring of pregnancy outcomes in future PSURs.

Risk Management Plans

Every year PRAC assesses hundreds of risk management plans (RMPs) for medicines. The RMP is another of the key components of pharmacovigilance that together allow EU citizens safe and timely access to new and innovative treatments. Proactively identifying before marketing the areas in which safety concerns are most likely with a new medicine or indication, and proposing proportionate measures to manage and monitor these, helps medicines to be made available to patients without exposing them to unacceptable levels of risk, and thus allows regulators to authorise them in a timely manner.

PRAC evaluated 649 RMPs in 2015, 570 in 2016, 561 in 2017 and 543 in 2018. Many of these represent updates to the RMPs of existing medicines, but somewhere between a third and fifth are for new medicines.



	2015	2016	2017	2018
Post-auth Standalone	0	0	0	0
Post-auth with Renewal	4	0	0	0
Post-auth with Variation	396	444	446	446
Post-auth with PSUR	3	0	0	0
Pre-authorisation phase	246	126	115	97

A very large number of RMPs, particularly for generic medicines, are dealt with at national level. Over 36,000 RMPs were submitted to the national competent authorities of the Member States over the same period, and some 7,000 RMPs assessed.

Various measures are available to regulators to try to minimise the risks identified in the RMP, and some or all of these may be deployed as appropriate. A solid and well-thought out risk management strategy can be **key to allowing patients timely access to more innovative therapies**. For advanced therapy medicines (ATMPs) where conventional regulatory paradigms can be difficult to apply, a well-designed risk management plan, with appropriate use of available pharmacovigilance tools post-marketing to support and enhance the evidence initially available in the marketing application, may be essential to permit timely patient access. An example can be found in the EU approval of CAR-T cell therapies, innovative, personalised medicines that use the patients' own immune cells to treat blood cancers, following genetic modification to enhance their effectiveness.

The system in action: risk management in the approval of Kymriah and Yescarta

In 2018, the European Commission authorised the marketing of the first two CAR-T cell medicines in the EU, Kymriah (tisagenlecleucel) and Yescarta (axicabtagene ciloleucel). These treatments represent **a new generation of personalised cancer immunotherapies** that are based on collecting and modifying patients' own immune cells to treat their cancer. The medicines were approved for the treatment of certain advanced and aggressive forms of leukaemia and lymphoma[31] that had not responded to, or had come back after, other treatments. These patients have a poor prognosis with few alternative options and therefore a substantial unmet medical need.

By their very nature, such individualised treatments do not fit well with existing regulatory paradigms for assessing the efficacy and safety of medicines, which focus primarily on standardised medicines that do not vary from patient to patient and look at results in patient groups as a whole. In addition, because the conditions for which the medicines are licensed are orphan, a decision on their approval had to be made on the basis of relatively few patient data.

Building in risk management from the start

Although CAR-T cell therapies offer potential hope to patients with very serious conditions, it became obvious during development that they can have life-threatening side effects. The main safety concerns are cytokine release syndrome (CRS), which is a potentially fatal systemic response to the activation and proliferation of CAR-T cells causing high fever and flu-like symptoms, and neurological toxicities leading to events such as confusion, agitation and seizures. Only by **finding ways to better characterise and manage these risks** could such innovative treatments be made available to patients and this involved stringent planning to minimise the risks from the early stages of medicines development.

The medicines were entered into EMA's **PRIME scheme**, a voluntary scheme that provides early and enhanced scientific and regulatory support to medicines that have significant potential to address unmet medical needs. This allowed EMA's experts to provide guidance (scientific advice) on the sort of studies and evidence that the developer would need to provide in order to permit authorisation.

A stringent risk management plan

The RMP that was developed involved **detailed monitoring and mitigation strategies**, including use of a range of pharmacovigilance tools such as *post-authorisation safety and efficacy studies* to address unanswered questions on safety and efficacy, and a frequent *PSUR reporting regimen* (every 6 months for the first 2 years, then annually for a further 2 years). To address the safety

[31] Kymriah is indicated for the treatment of paediatric and young adult patients (up to 25 years of age) with B-cell acute lymphoblastic leukaemia that is refractory or in second or later relapse, and in adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy. Yescarta is indicated for the treatment of adult patients with relapsed or refractory DLBCL and primary mediastinal large B-cell lymphoma, after two or more lines of systemic therapy

concern related to CRS, the indications for another medicine, RoActemra (tocilizumab), were extended so that it could be used for the *treatment of CRS induced by CAR-T cell therapy*.

Measures were put in place to ensure that the medicines were supplied only to **qualified centres** that could guarantee strictly controlled conditions, including the availability of tocilizumab, by healthcare professionals who had undergone a special **educational programme** about the risks and how to manage them, and where it could be ensured that adequate monitoring and follow-up would be carried out. A patient educational programme and alert card was also put in place, to ensure patients were properly informed of the risks and the need to report symptoms to their treatment centre.

Working with registries

The use of **real-world data** to support the authorisation and post-marketing management of these medicines is key to their licensing. This includes collecting data for post-authorisation studies from major existing registries in which the patients are likely to be enrolled, such as the European Bone Marrow Transplant (EBMT) and the US-based Centre for International Blood and Marrow Transplant Research (CIBMTR) registries. As part of the work to support evaluation and ongoing monitoring of CAR-T cell therapy, EMA held a **workshop** with relevant stakeholders to agree the core data that should be collected, and explore ways for regulators to work with registry holders and medicine developers to ensure that this tool could be used effectively.

A long-term endeavour

Risk management for any medicine is a process that will continue as long as the medicine is marketed, with continuous monitoring of safety through PSURs and adverse event reports. For Kymriah and Yescarta, additional specific measures to build the evidence base will continue for many years, with a rolling programme of imposed studies over the coming years. This gradual increase in our knowledge not only serves to understand these specific medicines better, but will no doubt provide lessons in how the regulatory system can manage approval of other innovative medicines and develop ever more sophisticated ways to handle the associated risk and uncertainty, thus providing the means to address unmet medical needs while protecting patient health.

Flexible and proportionate risk management plans have supported the licensing of many other significant medicines over the reporting period. Some other examples are given below.

The system in action : selecting appropriate risk minimisation measures in the RMP

Hemlibra – more real world data from EMA's ongoing initiative with registries

In order to support the 2018 authorisation of Hemlibra (emicizumab),[32] a new type of medicine which provides benefit to patients for whom conventional haemophilia treatments are rendered ineffective by the development of antibodies (inhibitors), EMA again collaborated with relevant stakeholders and registry holders. This outreach included a workshop to ensure that postmarketing studies such as those envisaged in the risk management plan could incorporate effective collection of suitable data from registries.[33] Of course, the registry studies are only one, albeit crucial, part of a suite of options. Additional measures in the RMP include an educational programme, a patient alert card (including a warning that the medicine may interfere with the results of coagulation tests), and a survey of patients, carers and healthcare professionals to assess the impact of the risk

[32] See https://www.ema.europa.eu/en/medicines/human/EPAR/hemlibra (accessed 23/01/19)
[33] https://www.ema.europa.eu/documents/report/report-haemophilia-registries-workshop_en.pdf (accessed 23/01/19)

minimisation measures, particularly the avoidance of concomitant treatment with so-called 'bypassing agents'.

Darzalex – patient alert cards and an educational programme supporting a conditional approval

In 2016 conditional approval was granted to Darzalex, a new orphan treatment for relapsed or refractory multiple myeloma. Conditional authorisation allows marketing authorisation to be granted in the interest of public health where the benefit of a medicine's immediate availability to patients outweighs the risk inherent in the fact that additional data are still required. For Darzalex there was an important risk that the medicine can interfere with tests needed to ensure patients get appropriately matched blood transfusions, which was highly relevant in a population that may well need such treatment for severe anaemia. Among the measures proposed in the RMP to manage this, a patient alert card for patients to show to anyone performing blood tests, and educational materials for healthcare professionals and blood banks, were therefore key risk minimisation measures to support authorisation.

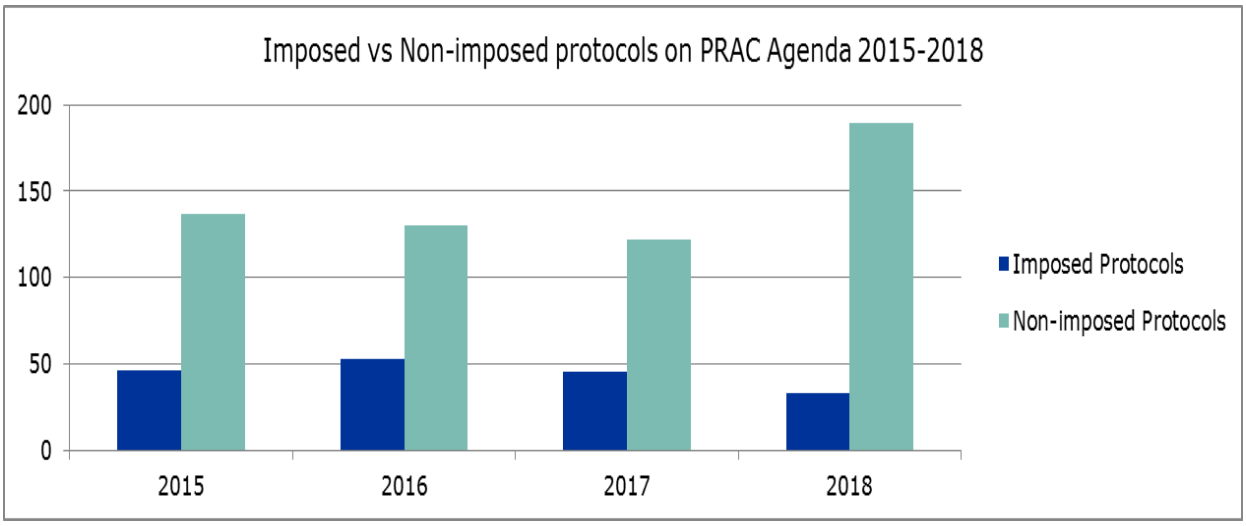
Maviret – the importance of prospective monitoring in managing liver risk

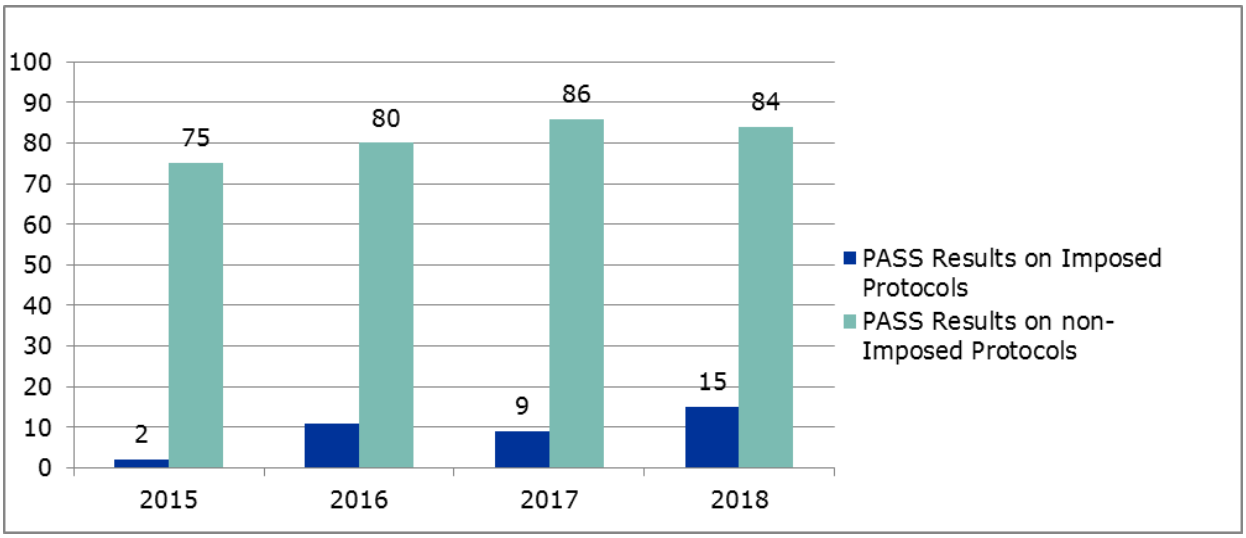
Another example is the 2017 approval of Maviret, one of the class of direct-acting antivirals that have revolutionised the treatment of hepatitis C. Maviret has the potential to be of value since it is active against all genotypes of the virus and may be useful in patients who have failed or cannot use other therapies. However, there have been concerns about the possibility of serious liver problems, including a possibly increased risk of hepatocellular cancer, with this class of medicines, so the risk management plan included a requirement for ongoing studies to monitor and this risk in the future and assess the size of it.

Post-authorisation studies

A post-authorisation safety study (PASS) can be carried out after a medicine has been authorised to obtain further information on its safety, or to gauge the effectiveness of risk-management measures. PRAC assesses the protocols and results of such studies when they have been imposed on marketing authorisation holders as part of their post-authorisation obligations, and also reviews many non-imposed PASS when assessing risk management plans.

Over the period of this report, PRAC reviewed 746 protocols for PASS, 177 of which were for studies imposed as part of the marketing authorisation. It also evaluated results for 77 studies in 2015, 91 in 2016, 95 in 2017 and 99 in 2018 (of these, 2, 10, 9 and 8 respectively were for imposed studies).





EMA's Committee for Medicinal Products for Human Use (CHMP) may also impose efficacy studies to be carried out after marketing (PAES) as part of a marketing authorisation. Over the period of the report CHMP imposed 23 PAES in 2015, 6 in 2016, 19 in 2017 and 4 in 2018.

Member states imposed 19 PASS over the reporting period (3 in 1015, 6 in 2016, 6 in 2017 and 4 in 2018), and 13 PAES (3, 4, 3 and 3 respectively).

Imposition of a PASS can be an important tool to evaluate the effect of regulatory measures taken post-marketing to address risk, for example as a result of a referral.

The system in action – using a PASS to measure the effect of risk minimisation measures
In 2013, EMA carried out a review of the medicine Diane 35, and similar products containing the active substances cyproterone acetate and ethinylestradiol. These nationally authorised medicines were used in some countries as contraceptives and in others for the treatment of acne in women. Like other hormonal products that can be used for contraception, they were known to carry some risk of causing venous and arterial thromboembolism (blood clots in the veins or arteries), and following ongoing reports of such problems the French medicines agency ANSM requested that PRAC review their safety at the European level (referral under Article 107i of Directive 2001/83/EC), as well as announcing its intention to suspend them from the French market.

Outcome of the referral

After reviewing the evidence, PRAC confirmed that the risk of venous thromboembolism with these medicines was 1.5 to 2 times higher than for combined oral contraceptives containing levonorgestrel and probably similar to the risk with contraceptives containing gestodene, desogestrel or drospirenone; the risk of arterial thromboembolism was somewhat lower. PRAC therefore recommended a number of measures to ensure the benefits of the medicine continued to outweigh their risks. It restricted its use to the treatment of moderate to severe acne related to androgen sensitivity or hirsutism (excessive unwanted growth of hair in women) in women of reproductive age, and only when alternative treatments, such as topical therapy and antibiotic treatment, had failed. Use at the same time as other oral contraceptives was contraindicated, since real world data had indicated that it was sometimes prescribed along with a contraceptive, burdening women with the thromboembolic risks of both.

To further minimise the risks, the Committee recommended a programme for the provision of information to prescribers and patients highlighting the risks of thromboembolism.

Measuring the effects of a risk minimisation measure

The information materials developed took the form of a Dear Healthcare Professional Communication, a patient information card and a prescriber checklist. As part of the package of measures imposed by the referral, a PASS was imposed on the marketing authorisation holders, requiring them to assess the effectiveness of these measures in alerting prescribers to the risks.

The study was an observational, cross-sectional survey of knowledge, understanding, and self-reported behaviour among a sample of physicians with recent experience with cyproterone/ethinylestradiol medicines in five European countries (Austria, the Czech Republic, France, the Netherlands, and Spain).[34] Eligible physicians were invited to complete a brief questionnaire regarding their knowledge of key safety messages as outlined in the information materials.

The study found that at least 80% of the physicians were aware of the thromboembolism risk, though only about half recalled receiving the information materials. Knowledge was more variable for topics that were more complex or less frequently encountered, where it might be expected that doctors would consult additional references such as product information or the prescriber checklist when prescribing. Awareness of the PRAC recommendation that the medicine should only be prescribed after failure of other acne treatments was approximately 48%.

A positive outcome but with room for improvement

Although around half of the physicians did not report receiving the educational materials, the high level of knowledge among treating physicians suggests that the key safety information is also available through other sources (e.g., product label, social media, seminars or symposia) to the treating physicians.

The results demonstrate a role for educational materials, but also illustrate that no single tool will be sufficient to fully minimise risks. The case also highlights the value of a PASS in assessing the effectiveness of particular measures.

[34] EUPAS 9312. Study to Evaluate Physician Knowledge of Safety and Safe Use Information for Diane-35 and Its Generics in Europe: An Observational Post-Authorisation Safety Study. http://www.encepp.eu/encepp/openAttachment/studyResult/16506

Equally, imposed PASS can also be an important part of **the regulatory package supporting marketing authorisations** for new medicines.

The system in action – how a PASS supports patient access to bronchodilator treatment

Antimuscarinic bronchodilators, which open the airways to improve breathing, play an important role in the management of chronic obstructive pulmonary disease (COPD). However, it is known that such medicines can also affect the function of the heart and circulation.

The case of Seebri Breezhaler

In the context of the marketing application in Europe of a new inhaled medicine containing glycopyrronium bromide (an antimuscarinic bronchodilator) for patients with COPD, marketed as Seebri Breezhaler and other names, the CHMP required a PASS to be carried out to assess the association between the use of the new product and cardiovascular events such as myocardial infarction or cerebrovascular events such as stroke.

The study and its outcome

The study was conducted in five European databases.[35] It observed no association between the product and all-cause mortality and cerebrovascular events in comparison with alternative treatments.

Like all medicines, the product continues to have its safety regularly monitored by the system, but the PASS results are reassuring in supporting the continued place of medicines of this type in therapy.

PASS are normally obligations imposed on marketing authorisation holders, but there can be circumstances in which the complexity of the situation – for example if it involves many active substances and MAHs – or the nature of the study required are such that it makes more sense to employ the specialised skills of EMA experts to commission or carry out post-authorisation studies. An example of this can be seen in a recent referral on the adverse effects of fluoroquinolones.

The system in action: how PASS results help shape a referral outcome

Quinolone and fluoroquinolone antibiotics are nationally authorised medicines that have been used for decades to treat a variety of infectious diseases, including some serious and life-threatening infections. However, these broad-spectrum antibiotics can have, in some cases, disabling and long-lasting or potentially permanent side effects, including on tendons, muscles, joints and the nervous system.

Addressing the risks of long-lasting effects

Fluoroquinolones had come to the attention of PRAC on a number of occasions, resulting in changes to the product information, but although the adverse reactions of these medicines were generally covered in their product information, the severity and the potential permanence of the effects were not fully addressed. In February 2017 the German medicines authorities therefore triggered an Article 31 referral asking EMA to assess the impact of these on the balance of benefits and risks of systemic or inhaled quinolone and fluoroquinolone antibiotics, and to recommend whether changes were needed to their marketing authorisations.

[35] EUPAS 5035. Multinational, multi-database cohort study to assess adverse cardiovascular and cerebrovascular outcomes and mortality in association with inhaled NVA237 in Europe. http://www.encepp.eu/encepp/openAttachment/studyResult/25563

Collecting all the evidence

The review involved gathering evidence affecting well over 2000 separate medicine presentations, marketed under varying indications in the 28 EU Member States plus Norway, Iceland and Liechtenstein.

As always, in order to ensure that its recommendations were scientifically rigorous and based on the best available evidence, PRAC sought to gather as much evidence as possible. This included a search of the literature for relevant non-clinical studies and guidelines, as well as assembling safety data including reports collected in EudraVigilance, postmarketing case reports and scientific literature data on disabling reactions with this class of medicines.

The referral also consulted experts in the treatment of infectious disease, and crucially, sought evidence from patients and the general public on the impacts of these side effects through the medium of EMA's second ever public hearing, which gave a voice to a highly motivated patient community and allowed PRAC to take direct account of the views of patients and carers.

The value of incorporating real world data

In order to assess the balance of benefits and risks, it is important to be able to determine the magnitude of the risk. However, spontaneous reports, whether in EudraVigilance or the medical literature, do not offer a suitable tool for this.

PRAC therefore requested EMA's in-house experts to conduct 2 real world data studies, using The Health Improvement Network (THIN) database, which contains electronic patient records covering some 4 million people in the UK, to assess the association between fluoroquinolone exposure and respectively tendon rupture or peripheral neuropathy.

Both these studies were able to show an increased risk of the relevant side effect. For example, in the study in tendon rupture,[36] the overall relative risk of tendon rupture with fluoroquinolones was about one-and-a-half times greater than without such treatment. The risk was greatest for ruptures of the Achilles tendon and was greatest in patients aged 60 years and over. Use of oral corticosteroids at the same time greatly increased the risk, particularly in males and older patients. The risk of peripheral neuropathy also seemed to be about one-and-a-half times greater than for similar patients taking an unrelated antibiotic (co-amoxiclav).[37]

Impact on the outcome

The final recommendations of the PRAC made use of the full spectrum of evidence available, including the representations made at the public hearing and the results of the PASS. The Committee concluded that in some cases serious adverse drug reactions associated with the use of quinolones and fluoroquinolones could be long-lasting, disabling and potentially irreversible and that these risks were a class effect. The medicines should not be used for mild or self-limiting infections, since the benefit did not outweigh the risk of these reactions, and they should only be used for serious infections susceptible to treatment, and where other therapeutic options were not available.

[36] Morales DR, Slattery J, Pacurariu A, Pinheiro L, McGettigan P, Kurz X. Relative and Absolute Risk of Tendon Rupture with Fluoroquinolone and Concomitant Fluoroquinolone/Corticosteroid Therapy: Population-Based Nested Case-Control Study. *Clin Drug Invest* 2018 Nov 21. doi: 10.1007/s40261-018-0729-y. Correction. *ibid.* 2019 Feb;39(2):215. doi: 10.1007/s40261-019-00755-y.

[37] Morales D, Pacurariu A, Slattery J, Pinheiro L, McGettigan P, Kurz X. Association between peripheral neuropathy and exposure to oral fluoroquinolone or amoxicillin-clavulanate therapy. *JAMA Neurol*. 2019 Apr 29. doi: 10.1001/jamaneurol.2019.0887.

Therefore, some of these antibiotics had their marketing authorisations suspended and PRAC recommended extensive changes to the product information of the remaining products.

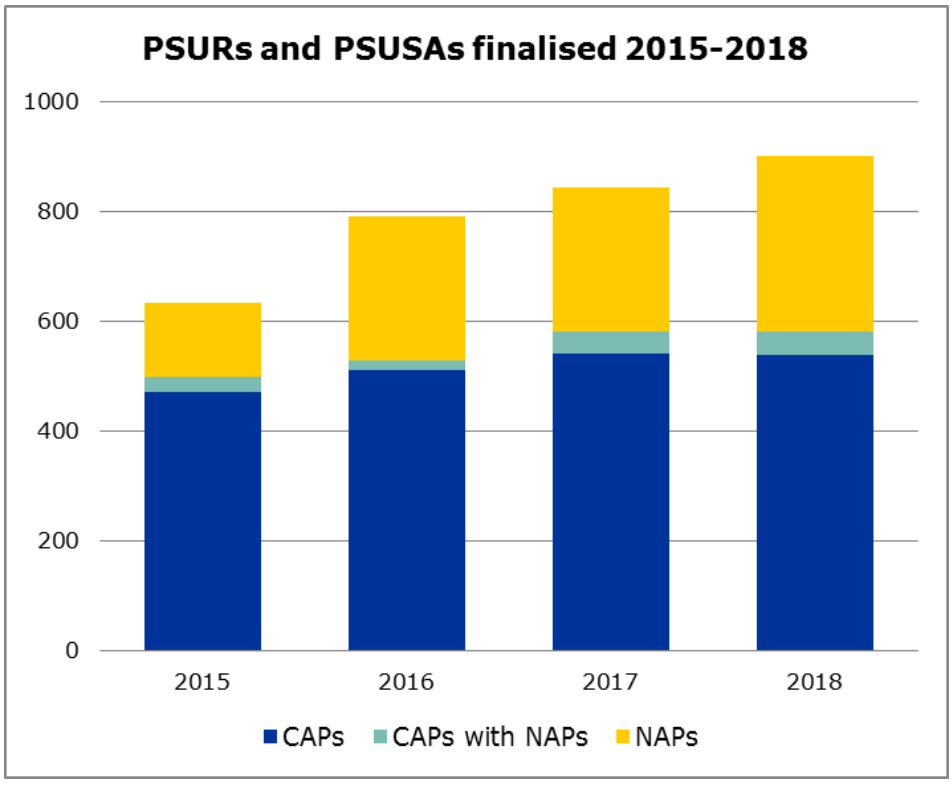
Supported by the findings of the two PASS studies, the recommended changes included a warning that these medicines should be used with special caution in elderly patients and that combined use with a corticosteroid should be avoided. In this way, the PASS findings fed directly into the measures taken to protect public health.

Periodic safety reporting

As noted under *Simplification and Process Improvement*, above, a radical reform of the system for periodic safety reporting was undertaken during the reporting period, with the introduction of a single electronic submission point and common interface for all types of PSURs, national and centralised (the 'PSUR repository'). Together with workflow support and design based on best practice, plus re-use of available data, this has resulted in a much improved system. Importantly, it means MAHs submit once to the system rather than separately to individual national competent authorities.

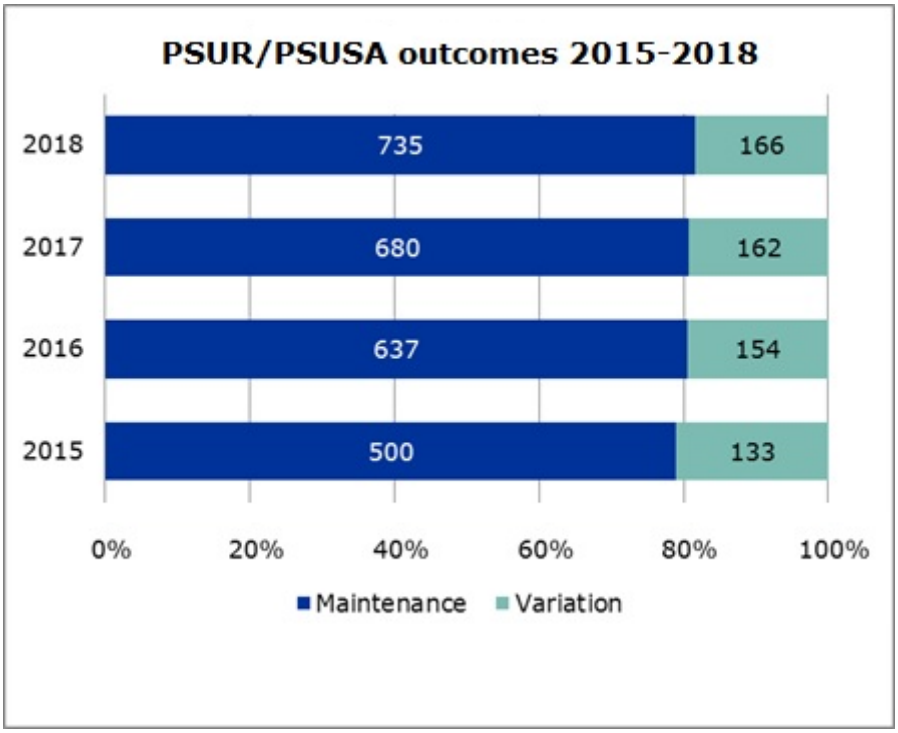
PRAC's work in reviewing PSURs/PSUSAs has increased considerably over the reporting period. In 2014, the last year of the previous reporting period, 471 were evaluated and finalised, whereas in 2015, 2016, 2017 and 2018 the numbers were 633, 791, 842, and 901 respectively. Of these, around half involved nationally authorised medicines alone or with centrally authorised products. About a third related to single assessments of active substances only contained in nationally authorised medicines, PRAC procedures for which only began in 2015.

Over 4,700 PSURs were also submitted to the national competent authorities of the 28 Member States between 2015 and 2018 for nationally authorised medicines.



Although the great majority of PSUR/PSUSA procedures result in maintenance of the product's marketing authorisation, PRAC's evaluation can lead to a variation to change the product information,

or to suspension or revocation of the medicine from the market.



The **continuous feedback loop** built into the pharmacovigilance system through the PSUR/PSUSA mechanism can also allow PRAC to align product information during a safety update following changes elsewhere in the system, to ensure consistent and helpful safety messages are provided to users as depicted in the case study below.

The system in action: use of the PSUSA tool to assist safe use of domperidone

In 2014, following a referral to the PRAC, CMDh agreed to restrict the uses of domperidone, a medicine used to treat nausea and vomiting. The reason for the referral was that domperidone, which was also originally used for some other minor stomach problems such as heartburn and bloating, can have serious effects on the heart's rhythm and electrical activity.

Among the PRAC recommendations put in place by CMDh, which restricted the doses and uses of domperidone, was a warning in the product information that domperidone should not be used with other medicines that affect the electrical activity of the heart since this had been shown to increase the risk of serious heart problems.

However, this evidence-based advice, finalised by a Commission decision in September 2014, led to an unforeseen consequence.

The problem of Parkinson's disease

Patients with Parkinson's disease (a progressive brain disease that affects movement) are sometimes treated with the medicine apomorphine. Apomorphine, originally derived from the poppy plant, can help control symptoms of Parkinson's disease, particularly when patients are experiencing fluctuations in their ability to move (known as 'on-off effect') with the standard treatment, levodopa.

However, apomorphine can make patients feel sick (nauseous) and vomit, and it can affect the electrical activity of the heart. Domperidone is often used to control the severe nausea – but because of the restriction of domperidone with medicines that affect the heart, this now went against the recommendations in the domperidone product information.

Using the PSUSA process to address the problem

During 2016 and 2017 periodic safety updates fell due for apomorphine-containing and domperidone-containing medicines respectively. PRAC was able to make use of these to clarify advice in the product information of these two medicines in order to ensure that they could be used together as safely as possible. As part of the process PRAC took into account advice from specialists in neurology, and the latest clinical guidelines.

Updated guidance for doctors and patients

The domperidone product information was modified to say that it was not to be used with other medicines that affect the electrical activity of the heart except apomorphine, and only when the benefits outweighed the risks. The product information for apomorphine had detailed advice added on when and how to start domperidone. Doctors were asked to carry out an individual risk assessment before starting patients on the combination, with advice on what factors to look for and on the need for subsequent checks.

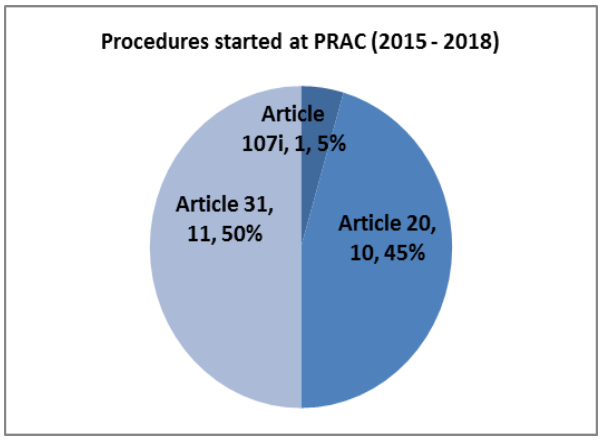
The end result is that the product information for both domperidone and apomorphine has much clearer and more detailed advice than ever before, aligned with scientific evidence, clinical practice and expert knowledge.

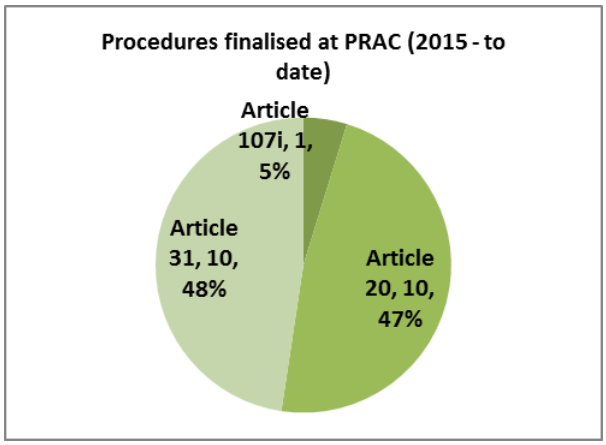
This should enable the two medicines to be used together for the benefit of patients with Parkinson's disease while preserving the intention of the original referral outcome to maximise patient safety when domperidone is used. It is also a good illustration of the way that various aspects of the pharmacovigilance system can interact in a complementary manner to respond to a developing situation.

Where a PSUR procedure results in a variation to a centrally authorised product, updated product information is made available in the Union Register of medicinal products and in the product's EPAR page on EMA's website, which includes its assessment history. For transparency, when PRAC recommendations following a PSUSA only result in changes to nationally authorised products, since 2015 information on the scientific conclusions leading to the change is also made available via the EMA website.

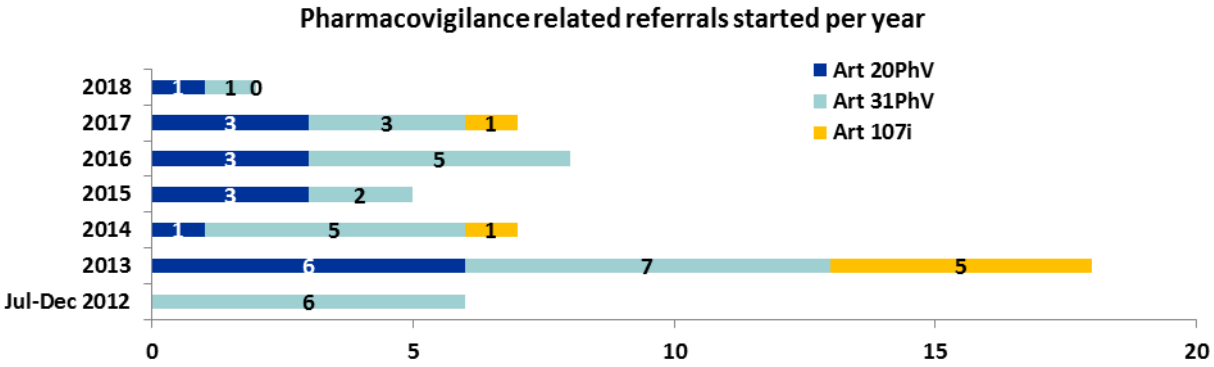
Referrals

During the reporting period 22 safety referrals started and 25 concluded (including 4 that started before 2015; 1 was ongoing at the data lock point.





This compares with the 31 referrals dealt with by PRAC over the previous (somewhat shorter) reporting period. There has been a gradual decline in the number of referrals being brought to PRAC. The reasons for this decline are likely to include improvements in other areas such as signal handling and PSURs that have increased the use of these alternative regulatory tools. Nonetheless, the PRAC workload during this period has included a number of large referrals with important implications for public health, including HPV vaccines, retinoids, gadolinium contrast agents, valproate, and quinolone and fluoroquinolone antibiotics. For a list of the referrals dealt with over the reporting period, see Annex 5.



The outcomes of the 25 referrals that concluded included variations of marketing authorisation in 16 cases, suspensions of marketing authorisation in 4 cases, and permanent revocations of marketing authorisation in 2 cases. (Where a referral refers to a group of medicines, combined outcomes, such as variations of certain marketing authorisations and suspension or revocation of others, are possible.)

For 4 medicines, PRAC made use of the option offered by the legislation to introduce temporary or provisional measures to protect public health while a referral was ongoing. A good example can be seen in the case of the multiple sclerosis medicine daclizumab (Zinbryta), in which use was first restricted and later suspended while referrals were in progress.

The system in action – managing the risks of Zinbryta
In June 2017, PRAC had been requested by the European Commission to review the risks of the multiple sclerosis medicine Zinbryta (daclizumab) in an Article 20 referral. The referral of the medicine, which had been approved for marketing the previous year, followed reports of serious

liver injury, including one death. Provisional measures were put in place to restrict use, in order to protect patients while the review was underway.

The final recommendation of the PRAC was to greatly **restrict the use** of the medicine to patients who had had an inadequate response to at least two disease modifying therapies (DMTs) and could not be treated with other DMTs, confirming and amplifying the provisional measures. The strengthened risk management measures recommended by PRAC were agreed by CHMP and the European Commission, which adopted a final legally binding decision in November 2017.

A second referral

However, even as the review and restrictions were being implemented, the pharmacovigilance system was continuing to collect data on the safety of Zinbryta. Spontaneous reports of effects on the brain and nervous system were received in February 2018, and within a few days the EU pharmacovigilance system responded and the European Commission launched a further referral to **re-examine the benefits and risks** of the medicine. In the light of the accumulating evidence of problems, the PRAC recommended suspending the marketing of the medicine and recalling it from the market while the evidence was examined, as a precaution to protect patients from any further exposure.

The marketing authorisation holder subsequently informed EMA that it would voluntarily **discontinue the marketing** of the product and the marketing authorisation was withdrawn at the end of March 2018.

Looking at the further data with which it had been provided, the PRAC concluded that **the benefits of the medicine did not outweigh the risk** of serious and unpredictable effects on the brain, liver and other organs.

Impact

The case demonstrates the way in which the pharmacovigilance system can act rapidly to protect patients once a problem is identified. Gathering and rigorously analysing the evidence for a referral necessarily takes some time, but proportionate use of provisional measures where there is a reasonable suspicion of a serious risk offers an invaluable tool to manage the risk in the interim.

Inspections

EMA, in cooperation with competent authorities in the Member States, maintains the risk-based programme for routine pharmacovigilance inspections of marketing authorisation holders of centrally authorised products and ensures its implementation. It also plays a key role in the coordination of pharmacovigilance inspections specifically triggered by the CHMP or CVMP and in inspection follow-up. The Committees requested 14 pharmacovigilance inspections in 2015, 8 in 2016, 15 in 2017 and 20 in 2018.

The majority of EU/EEA pharmacovigilance inspections (around 200 to 300 annually when both human and veterinary are included) are conducted under the national pharmacovigilance inspection programmes which relate to marketing authorisation holders with product authorisations of all types (including centrally authorised products). Over the reporting period, Member States issued penalties to marketing authorisation holders for non-compliance with pharmacovigilance obligations on 15 occasions.

Medication errors

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

In 2015 there were around 8,600 side effect reports received by EudraVigilance from the EEA associated with medication errors, (of which around 1,200 – 14% – were non-serious); by 2017 this increased to about 15,000, around 4000 (27%) of them non-serious, and by 2018 the total was nearly 38,000, of which some 24,000 (64%) were non-serious.

The continuing increase represents not only the 2017 improvements in EudraVigilance which have supported the systematic collection of non-serious adverse event reports, but also the fruit of efforts both at EU and national level to improve the reporting of medication errors so that appropriate action can be taken to minimise them and their associated harms.

A number of routine measures are put in place during the approval process for medicines, including ensuring that the proposed name and labelling of a medicine do not resemble those of an existing medicine, and that the instructions for use in the product information are clear. Where the risk of medication errors is high and routine measures are not considered sufficient, additional measures are taken to ensure that the medicine is used correctly, including educational programmes for healthcare professionals and patients. EMA systematically communicates on any additional measure decided upon at EU level to prevent medication errors.[38]

System improvements

As mentioned under *Simplification and Process Improvement* above, following various phases of system development and user testing and a successful audit, an improved **EudraVigilance** was launched on 22 November 2017. This allowed:

- Simplification of the reporting of adverse drug reactions (ADRs), in particular for marketing authorisation holders for whom EudraVigilance has become the sole reporting point in the EEA, with subsequent re-routing of reports to the Member States where the adverse reactions occurred;
- Direct and faster provision of EEA adverse reaction reports to the World Health Organization (WHO) Uppsala Monitoring Centre;
- Enhancements to safety signal detection and analysis tools for NCAs and EMA;
- Increasing EudraVigilance access for MAHs to allow them to fulfil their pharmacovigilance obligations and to validate safety signals via examination of ICSRs (individual case safety reports);
- Increased access to EudraVigilance data for healthcare professionals, the public and researchers;
- The use of internationally agreed formats, standards and terminologies (such as the ISO ICSR E2B(R3) format) resulting in improved data quality and better data analysis possibilities.

A second major system improvement was the creation of a single electronic point of access for **PSUR**s, which went live for MAH submissions on 13 June 2016. This has resulted in:

[38] EMA. Recommendations on medication errors. Available at: https://www.ema.europa.eu/en/find-medicine/human-medicines/recommendations-medication-errors (accessed 05/02/19).

- Creation of a single, secure electronic point of submission for all PSURs, thus streamlining access for Member States and assessors;
- A common interface and templates for communicating with stakeholders resulting in a simplification of the submission process for all types of PSURs and related documents;
- Enhancements to system capabilities including re-use of existing data from the Article 57 database which lists products on the EU market and validation and workflow support tools;
- Unified access to all documents in a common storage repository
- Best practice embedded in the design of the system;
- Efficiency savings in Member State resources (automation of previously manual processes, no need for reconciliation process for anomalies, etc.).

The EMA **literature monitoring service** was launched in June 2015. This monitors selected medical literature for reports of suspected side effects to certain active substances, covering 300 chemical substance groups and 100 herbal substance groups, and enters them into the EudraVigilance database as ICSRs, thus reducing the administrative burden on the marketing authorisation holders.

Year	Literature references reviewed	ADR reports added to EudraVigilance	Unique cases identified
2015	115,550	1,464	756
2016	275,954	8,495	5,595
2017	222,937	14,193	6,790
2018	n/a	13,275	n/a

Communication

EMA helps co-ordinate communications within the EU network, providing an Early Notification System (ENS) to the national competent authorities, the European Commission and other network partners, which provides early warning of expected **communications on safety issues** resulting from issues on the PRAC, CMDh or CHMP agendas. These include EMA's announcements of the start of referrals, communication of the recommendations issued by the PRAC, and a detailed communication on the final outcome (known as a public health communication and including elements tailored specifically to patients and healthcare professionals, which are produced with input from representatives of the relevant stakeholder groups). EMA also produces dedicated communications on medication errors and on other safety issues of public interest (typically when a safety related DHPC has been issued).

Number of communication items in PRAC and CHMP/CMDh ENS tables by year							
2015		2016*		2017		2018	
PRAC	*CHMP*	*PRAC*	*CHMP*	*PRAC*	*CHMP*	*PRAC*	*CHMP*
13	163	18	132	22	22	11	29

** in October 2016 the Agency altered its publication policy so that the CHMP ENS table only contained information on procedures that led to a stand-alone safety communication, and no longer provided information on other CHMP opinions on safety variations, PSURs and outcomes of PSUSAs, which are published separately. This markedly reduced the number of items included.*

The Agency shares information on the assessment of data, the decision-making process and the overall monitoring of medicine safety. In addition to any emerging safety information about medicines, EMA's website now regularly publishes: **information on safety signals**; information on the assessment of periodic safety update reports (**PSURs**); and **summaries of risk management plans**.

Publishing safety-related information as it becomes available keeps the public up to date with ongoing safety evaluations. As noted under *Transparency*, above, the agendas and minutes of PRAC and CHMP are also routinely published, providing additional information on the procedures. In addition, details of imposed PASS studies, including their outcomes, continue to be published in the ENCePP register: http://www.encepp.eu/encepp_studies/indexRegister.shtml.

EMA is also charged with co-ordinating media responses by preparing **lines-to-take** for press and communication officers in the Member States, detailing emerging product-related safety concerns which are known or thought likely to produce enquiries from the media or other stakeholders. These lines-to-take are produced with input from scientific experts within EMA and relevant national medicines regulators. Around 40 such lines-to-take are distributed each year within the network (on 42 occasions in 2015, 44 in 2016, 38 in 2017 and 37 in 2018).

Coordination and collaboration

The **EU regulatory network** requires close cooperation and coordination between over 30 national competent authorities, EMA and the Commission. An EU Medicines Agencies Network Strategy to 2020 was established to guide the network and emphasises the key role pharmacovigilance plays as an enabler for health protection and innovation.

As the various bodies involved have grown familiar with the roles and responsibilities envisaged in the 2012 legislation, and with the various system improvements implemented over the reporting period, this collaborative system has gone from strength to strength, resulting in the many successes noted in this report.

A streamlined EU network **governance structure** for pharmacovigilance implementation and operation was adopted by the Heads of Medicines Agencies in February 2016. This has reduced the resource commitments needed for governance by reinforcing the PRAC's role in operational issues and providing a unified Pharmacovigilance Business Team drawn from EMA and the Member States to focus on information systems and to support PRAC where needed. Oversight of the system is provided by an EU Network Pharmacovigilance Oversight Group (EU-POG) which reports to the Heads of Medicines Agencies and the EMA Management Board.

As mentioned under *Transparency and Stakeholder Engagement*, above, the Agency has also continued to work closely with EU expert centres in the field of pharmacovigilance through the ENCePP network, which celebrated 10 years of successful collaboration in 2017.

As well as the previously mentioned SCOPE, the period covered by this report has also seen delivery of a number of major, collaborative EU funded scientific projects such as PROTECT[39], WEDRADR[40] and the ADVANCE project on vaccine monitoring[41]. These are leading to the development of new tools and methodologies for use in the future; vaccine media monitoring conducted by EMA under the auspices

[39] A public-private partnership co-ordinated by EMA which looked at ways to strengthen safety surveillance and the monitoring of the benefit-risk of medicines in Europe, http://www.imi-protect.eu/
[40] An IMI-funded project to develop a mobile app to report suspected adverse drug reactions, and investigate the potential for publicly available social media data for identifying drug safety issues, http://web-radr.eu/.
[41] A regulatory science project to establish a blueprint for a sustainable system for vaccine benefit-risk monitoring in the EU, http://www.advance-vaccines.eu/

of the latter is expected to support the development of EMA's vaccine outreach strategy in the coming years.

International regulators and ICH

The EU pharmacovigilance system exists in the context of global safety monitoring and as part of a tradition of long-standing cooperation between regulators and harmonisation of guidelines and practices. EMA has continued to act as a central point of contact with other major regulators, with regular teleconferences and collaboration in particular with the US Food and Drug Administration (FDA), Health Canada and the Japanese regulatory authorities.

Additionally, EMA has helped share the network's best practice with external regulators via training courses and workshops, and participates in WHO committees as well as supporting collaboration on pharmacovigilance through the International Coalition of Drug Regulatory Authorities (**ICDRA**). International collaboration also included contributions to the work of the Council for International Organizations of Medical Sciences (**CIOMS**), in particular to reports on international pharmacovigilance, active vaccine surveillance and vaccine safety communication[42].

EMA has also continued to develop common standards with other regulators through the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (**ICH**). ICH brings together the regulatory authorities of a number of countries and regions including Europe, Japan and the United States, and experts from the pharmaceutical industry in these regions, with the aim of agreeing common approaches and requirements where possible for the authorisation of medicines.

[42] Bahri P, Rägo L; on behalf of the CIOMS Working Group on Vaccine Safety. CIOMS Guide to Vaccine Safety Communication: executive summary. Vaccine. 2019; 37: 401-8.

Conclusions and further steps

As reflected above, pharmacovigilance is perhaps the area of regulation that most depends on seeking feedback on the consequences of its own actions. Putting in place not only measures to try to mitigate risk, but concomitant monitoring of their impact, and being willing to modify those measures promptly if the accumulating evidence shows that they are not having the desired effect, is fundamental to its successful practice. As the EU pharmacovigilance system has matured in its operation of the 2012 legislation, and the roles of the various participants, it has increasingly turned its attention to understanding better the impacts of its actions, and fine-tuning the use of the available tools in order to achieve the best outcomes. Those outcomes are crucial in allowing patients timely but safe access to new and innovative medicines.

Ensuring that the European system has a positive impact for public health and for innovation is critical. During the period of this report the PRAC adopted a strategy and action plan on measuring the impact of pharmacovigilance. This strategy and plan represent the first time that a regulatory authority has implemented a systematic approach to measuring impact in pharmacovigilance and its contribution to promoting and protecting public health.

The early evidence, as documented in this report, is encouraging, showing the work of the various pharmacovigilance processes and how they have contributed to a robust and effective pharmacovigilance system in the EU. It indicates, for example, that roughly half of the drug safety signals detected and managed through PRAC lead directly to new and better warnings for patients in product labelling. Examples are provided of rapid action to withdraw products where the risks were considered to outweigh the benefits, to restrict the use of products to those most likely to benefit and least likely to suffer harm and the extensive work done to ensure patients and healthcare professionals receive up-to-date information about the safety profile of medicines.

The report also outlines some of the ways in which the European pharmacovigilance system is supporting innovation. Innovation in this context relates to ensuring that patients with unmet medical needs receive new products to fulfill those needs. Such a contribution includes advice on the design of post authorisation data collection and the design of risk minimisation measures. Examples of contributions made to support innovation include use of real-world data, epidemiology methods, patient registries, and use of new data sources.[43]

The period covered by this document includes important progress on delivery of improved IT systems and simplification of processes. The fruits of this include translations of signals into all EU languages to simplify update of product information, a single assessment process and single point of reporting for periodic safety update reports, the further development of the Article 57 database of medicinal products, and finally the rollout in 2017 of the new EudraVigilance system along with updated requirements for reporting. The latter has delivered simplified reporting for the pharmaceutical industry, better searchability so that drug safety issues could be detected more quickly, rapid and complete EU data provision to the World Health Organisation to support international collaboration in pharmacovigilance, marked increases in transparency with provision of data to the general public and the rollout of advanced analytics systems for safety monitoring. These vastly improved tools modernise the European pharmacovigilance system and make it simpler and easier to report and identify potential problems and so protect public health.

Important progress has also been made in the areas of transparency, communication and engagement with stakeholders. Though we continue to strive for further improvements, the transparency of the EU

[43] Cave A, Kurz X, Arlett P. Real-world data for regulatory decision making: challenges and possible solutions for Europe. Clin Pharmacol Ther 2019; doi:10.1002/cpt.1426 (accessed 23/04/19)

pharmacovigilance system is already very high. The agendas and minutes of all PRAC meetings are published on the web and all safety signals are published and recommendations for labelling are translated into all EU official languages to facilitate rapid implementation. As a measure of patient engagement, the reporting period shows increases in patient reporting of suspected adverse drug reaction including a doubling of patient reports included in the EudraVigilance database between 2017 and 2018 once non-serious reports began to be routinely included, as well as the introduction of public hearings for major drug safety and benefit risk reviews. This report contributes to the transparency and reporting on the European pharmacovigilance system and shows that the system is operating effectively and efficiently for the promotion and protection of public health and to support innovation in pharmaceuticals such as the authorisation of CAR-T cell therapies.

The period covered has not only shown major progress in terms of strengthening systems, improving business processes and availability of information systems tools, it has also seen significant progress in terms of scientific methods. This has included delivery of EU funded projects such as EU PROTECT, WEDRADR and the ADVANCE project on vaccine monitoring, and the enrichment of the network's best practice through the deliverables of the SCOPE Joint Action. Scientific progress is also been made in the use of patient registries to support collection of data, in understanding the place of big data in supporting decision-making by regulators and in methodological guidance particularly through the ENCePP network.

Looking to the future there are opportunities to build on the strength, effectiveness and efficiency of the current system. This will be through ever greater engagement with stakeholders, particularly patients and healthcare professionals, providing ever more support to their decision-making and enabling enhanced risk minimisation. Building on strengths will also entail further transparency, evidence-based process improvement, and better use of real-world data and its analysis to generate real-world evidence. Finally, through earlier engagement of pharmacovigilance and real-world data support to products in development we will be able to optimise surveillance and risk minimisation as soon as products enter the market. In this way we are sure that the current strong, effective and efficient EU pharmacovigilance system can go from strength to strength, delivering for public health and product innovation.

Annexes

Annex 1: Legal basis

The legal framework of pharmacovigilance for medicines marketed within the EU is provided for in Regulation (EC) No 726/2004[44] and in Directive 2001/83/EC,[45] as amended. These were updated by the new pharmacovigilance legislation contained in Regulation (EU) No 1235/2010[46] and Directive 2010/84/EU,[47] which entered into force from July 2012.

The performance of pharmacovigilance activities was further refined in 2012 by Commission Implementing Regulation (EU) No 520/2012[48] which stipulates roles and responsibilities regarding certain aspects of pharmacovigilance for marketing authorisation holders, national competent authorities and EMA.

Member States and EMA, in consultation with relevant stakeholders, have also produced, and regularly update, good pharmacovigilance practice guidelines (GVP)[49] which explain in detail how pharmacovigilance activities should be carried out.

This report is produced in response to the Commission obligation under Article 29 of Regulation (EC) No 726/2004[23] as amended by Regulation (EU) No 1235/2010,[25] regarding reporting on the activities of EMA as well as a similar obligation under Article 108b of Directive 2001/83/EC as amended by Directive 2010/84/EU regarding the performance of pharmacovigilance tasks by the Member States.

[44] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0001:0033:en:PDF
[45] http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf
[46] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0001:0016:EN:PDF
[47] http://ec.europa.eu/health/files/eudralex/vol-1/reg_2010_1235/reg_2010_1235_en.pdf
[48] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:159:0005:0025:EN:PDF
[49] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp

Annex 2. Impact studies related to EMA referrals

The table below shows studies that EMA has funded during the reporting period to provide evidence of the impact of referral procedures.

Study title	Lead author	Objective	Status
Study of regulatory communication and *risk awareness* following the Article 31 referral of **Combined Hormonal Contraceptives** in relation to thromboembolism (related to EMEA/H/A-31/1356)	Aarhus Consortium	• Patient and health professionals awareness in their knowledge, attitudes and practices of the risk of VTE in users of CHCs • How is advice from regulators concerning CHCs perceived • Improvement of communication	Finalised; final study report submitted Feb 2018.
Study to investigate the *utilisation* of **combined hormonal contraceptives (CHC)** in Europe before and after the 2013 regulatory review of CHCs and the risk of thromboembolism and the possible impact on clinical outcomes relating to venous thromboembolism morbidity (related to EMEA/H/A-31/1356)	Aarhus Consortium	• Trends in first ever user prescribing 2 years before the Commission Decision (01/12–01/14) and 2 years after (02/14-02/16) • Trends in switching between products among existing users including reasons • stratify changes in utilisation in terms of patient clinical and demographic risk factors for venous thromboembolism • Incidence of VTE and VTE-related morbidity between the two periods (association between incidence change and observed changes in CHC use)	Finalised
Study to characterise the prescription patterns of **antiepileptic medicines** in women of childbearing potential, in particular in relation to the indications for prescribing and to use during pregnancy. Evaluation of methods and data sources available for the assessment of potential long term effects (e.g. neurodevelopmental disorders, growth retardation, immune disorders, oncological disorders) of pregnancy exposure to medicinal products. (related to EMEA/H/A-31/1387)	EUROmediSAFE Consortium	• Drug utilisation/ prescription patterns of antiepileptic medicines in girls and in women of childbearing potential in first ever users • Time trends in prescribing over a period 8 years including 2015 and 2016 • Switching between antiepileptic drugs • Inventory of data sources for evaluating the long-term risks for children associated with drug exposure in utero • Feasibility study protocol to assess the association between exposure to antiepileptic medicines in utero and neurodevelop-mental disorders in the offspring	Finalised (1-4) Ongoing (5)
Impact of EU label changes for systemic **diclofenac** products: post-referral prescribing trends to evaluate the impact of the risk minimisation measures implemented in 2013 to manage cardiovascular risks (related to EMEA/H/A-31/1344)	University of Dundee	• Drug utilisation and prescription patterns of systemic diclofenac-containing medicinal products by indication, age, gender; • Discontinuation and changes in dose and duration; • Time trends in prescribing 3 years before intervention (i.e. CI, warnings, other PI changes) including data up to 2017	Ongoing; final study report due Q1 2019

Study title	Lead author	Objective	Status
		• Prescribers' compliance with SmPC 4.3 and 4.4 by indication (i.e. arthritic conditions and acute musculoskeletal disorders) • Drug utilisation and prescription patterns for alternative medicines	
Metformin initiation and renal impairment: a cohort study in Denmark and the UK (related to EMEA/H/A-31/1432)	Aarhus Consortium	• To estimate prevalence of renal impairment, rate of decline in kidney function and changes in metformin use after decline in kidney function, in metformin initiators. • Understand use of metformin in renal insufficiency to determine if current contraindications should be replaced to avoid risk of lactic acidosis in T2DM patients).	Completed; study published in BMJ Open 2015;5:e008531. doi:10.1136/bmjopen-2015-008531
Metformin use and risk of lactic acidosis in people with diabetes with and without renal impairment: a cohort study in Denmark and the UK (related to EMEA/H/A-31/1432)	Aarhus Consortium	To assess risk of lactic acidosis among metformin users compared with other glucose-lowering agent users, according to renal function. • Understand use of metformin in renal insufficiency to determine if current contraindications should be replaced to avoid risk of lactic acidosis in T2DM patients).	Completed; study published in Diabet Med. 2017 Apr; 34(4):485-489. doi: 10.1111/dme.13203.
Prescribing of **codeine** for the treatment of pain in children. Drug utilisation study using IMS electronic health records in Germany and France. (*Pilot study of the EU Regulatory Network Strategy for Best Evidence using electronic patient healthcare databases (BIFAP in Spain, CPRD in the UK and IMS in France and Germany)* (related to EMEA/H/A-31/1342)	EMA-ES-UK	• Assess the impact of PI changes on prescribing patterns for codeine for the treatment of pain in children in DE and FR.	Finalised
Tramadol (related to EMEA/H/A-31/1342)	EMA	• Provide estimates of the utilisation of codeine, and tramadol, dihydrocodeine and metamizole (DE) as possible alternatives to codeine for treatment of pain, and of dextromethorphan and ethylmorphine as possible alternatives to codeine for treatment of cough, in children by age group and gender. • Assess whether the codeine referral for pain and cough was associated with significant changes in prescribing of the above mentioned analgesic and	

Study title	Lead author	Objective	Status
		cough agents in children by age group and gender.	
Impact of withdrawal of **fusafungine** from the market on the prescribing of alternative treatments in Germany (related to EMEA/H/A-31/1420)	Karin Hedenmalm	• To analyse changes in alternative treatments for upper respiratory airways disease after market withdrawal of fusafungine. Source and population is IMS® Germany and the study period is from 29 May 2013 to 28 May 2017, including 3 years before and 1 year after the withdrawal of fusafungine. The study includes the most common prescribers of fusafungine for most common upper respiratory airways diseases (URAD).	
Evaluation of the impact of the risk minimisation measures implemented in 2015 to manage the potential risk of QT interval prolongation and cardiac arrhythmia of **hydroxyzine** containing medicinal products authorised in the European Union (EU) in clinical practice (related to (EMEA/H/A-31/1400)	University of Dundee	• Drug utilisation and prescription patterns of hydroxyzine containing medicinal products (ATC codes: N05BB01, N05BB51) and to investigate whether significant changes occurred following the 2015 referral. • Prescribers' compliance with recommendations included in sections 4.2, 4.3, and 4.4 of the SmPC for hydroxyzine containing medicinal products, by country, by indication (i.e. anxiety disorders, skin conditions, preoperative sedation, sleep disorders), by age and by gender; • Drug utilisation and prescription patterns over time for alternative medicines that have been prescribed to patients where hydroxyzine has previously been prescribed or discontinued, by country, by indication (i.e. anxiety disorders, skin conditions, preoperative sedation, sleep disorders), by age and by gender.	

In addition, EMA has carried out the following studies in-house, using data from the THIN and IMS regional databases.

EMA in-house studies performed			Databases used	
Referral Scope	**Active substance**	**Finalised**	**THIN**	**IMS**
Codeine for cough in paediatric population	codeine	Apr-15	√	√

EMA in-house studies performed			Databases used	
Hydroxyzine	hydroxyzine hydrochloride	Mar-15	√	
Hormone Replacement Therapy	All products	Sep-15	√	√
Fusafungine nasal and oral solution	fusafungine	Mar-16	√	√
Valproate	valproate	ongoing	√	√
Hydroxyethyl starch (HES)	hydroxyethyl starch	Jan-18	√	

Annex 3. Pharmacovigilance activities at Member State level

The following tables provide detailed quantitative information regarding pharmacovigilance activities undertaken at national level as reported by the national competent authorities of the EU Member States, Iceland and Norway.

In addition to their standard activities and ongoing communication work, 23 Member States (Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Romania, Slovenia, Slovakia and UK), as well as Iceland and Norway, reported having undertaken additional pharmacovigilance activities during the reporting period, including training and educational activities aimed at healthcare professionals or patients, programmes to stimulate ADR reporting, development of improved methods of reporting and communication of safety-critical information (including work to develop web services, social media channels and smartphone apps) and funding of studies and academic projects.

3a. RMPs submitted to Member State medicines authorities

	AT	BE	BG	CY	CZ	DE-Bfarm	DE-PEI	DK	EE	ES	FI	FR	GR	HR	HU	IE	IS	IT
2015	185	278	448	266	NA	605	37	143	312	1528	110	NA	613	57	400	88	10	550
2016	167	254	427	226	NA	668	17	149	290	1426	124	NA	428	127	440	70	25	519
2017	128	204	395	211	NA	607	33	103	239	1329	110	NA	259	100	550	56	14	480
2018	125	332	291	5	NA	668	81	144	203	1082	260	NA	161	200	410	69	4	195
Total RMPs submitted	*605*	*1068*	*1561*	*708*	*0*	*2548*	*168*	*539*	*1044*	*5365*	*604*	*0*	*1461*	*484*	*1800*	*283*	*53*	*1744*

	LT	LU	LV	MT	NL	NO	PL	PT	RO	SE	SI	SK	UK	EU total
2015	NA	NA	458	NA	472	143	1012	511	419	401	206	135	532	9919
2016	NA	NA	459	NA	501	140	903	362	371	370	251	150	533	9397
2017	NA	NA	452	NA	559	140	825	505	548	399	216	111	433	9006
2018	0	NA	490	39	481	149	794	441	269	379	65	95	425	7857
Total RMPs submitted	*0*	*0*	*1859*	*39*	*2013*	*572*	*3534*	*1819*	*1607*	*1549*	*738*	*491*	*1923*	***36179***

3b. RMPs assessed as reference Member State for mutual recognition or decentralised procedures

	AT	BE	BG	CY	CZ	DE-Bfarm	DE-PEI	DK	EE	ES	FI	FR	GR	HR	HU	IE	IS	IT
2015	183	91	1	0	89	282	33	121	46	46	26	NA	0	0	82	11	8	6
2016	194	62	1	0	127	229	10	149	33	61	27	NA	4	10	58	7	24	5
2017	151	34	2	0	114	233	26	96	36	44	24	NA	0	5	48	7	12	7
2018	259	88	2	0	106	263	15	112	14	93	16	NA	1	10	41	11	11	5
Total RMPs assessed	*787*	*275*	*6*	*0*	*436*	*1007*	*84*	*478*	*129*	*244*	*93*	*0*	*5*	*25*	*229*	*36*	*55*	*23*

	LT	LU	LV	MT	NL	NO	PL	PT	RO	SE	SI	SK	UK	Total EU
2015	3	0	12	29	228	1	44	70	0	96	4	3	313	1828
2016	2	0	6	26	196	6	36	70	4	80	5	14	299	1745
2017	1	0	11	22	255	12	50	85	0	117	8	21	215	1636
2018	1	0	12	36	230	14	49	164	3	72	7	7	140	1782
Total RMPs assessed	*7*	*0*	*41*	*113*	*909*	*33*	*179*	*389*	*7*	*365*	*24*	*45*	*967*	***6991***

3c. PASS imposed at national level (excluding those resulting from EU regulatory action)

	AT	BE	BG	CY	CZ	DE-Bfarm	DE-PEI	DK	EE	ES	FI	FR	GR	HR	HU	IE	IS	IT
2015	NA	0	0	0	0	0		0	0	0	0	NA	0	0	0	0	NA	0
2016	NA	0	0	0	0	0	1	0	0	0	0	NA	0	0	1	0	NA	1
2017	NA	0	0	0	0	0		0	0	1	0	NA	0	0	0	0	NA	1
2018	NA	0	0	0	0	2	0	0	0	0	0	NA	0	0	0	0	0	0
Total PASS imposed	*0*	*0*	*0*	*0*	*0*	*2*	*1*	*0*	*0*	*1*	*0*	*0*	*0*	*0*	*1*	*0*	*0*	*2*

	LT	LU	LV	MT	NL	NO	PL	PT	RO	SE	SI	SK	UK	Total EU
2015	0	0	0	0	2	0	0	0	0	0	0	0	1	3
2016	0	0	0	0	2	0	0	0	0	0	0	0	1	6
2017	0	0	1	0	1	0	0	0	0	0	0	0	2	6
2018	0	0	1	0	0	1	0	0	0	0	0	0	0	4
Total PASS imposed	*0*	*0*	*2*	*0*	*5*	*1*	*0*	*0*	*0*	*0*	*0*	*0*	*4*	***19***

3d. PAES imposed at national level (excluding those resulting from EU regulatory action)

	AT	BE	BG	CY	CZ	DE-Bfarm	DE-PEI	DK	EE	ES	FI	FR	GR	HR	HU	IE	IS	IT
2015	NA	0	0	NA	0	0		0	0	0	0	NA	0	0	0	0	NA	2
2016	NA	0	0	NA	0	0		0	0	0	0	NA	0	0	0	0	NA	4
2017	NA	0	0	0	0	0		0	0	0	0	NA	0	0	0	0	NA	2
2018	NA	0	0	0	0	2	0	0	0	0	0	NA	0	0	0	0	0	0
Total PAES imposed	*0*	*0*	*0*	*0*	*0*	*2*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*8*

	LT	LU	LV	MT	NL	NO	PL	PT	RO	SE	SI	SK	UK	Total EU
2015	0	0	0	0	1	0	0	0	0	0	0	0	0	3
2016	0	0	0	0	0	0	0	0	0	0	0	0	0	4
2017	0	0	1	0	0	0	0	0	0	0	0	0	0	3
2018	0	0	1	0	0	0	0	0	0	0	0	0	0	3
Total PAES imposed	*0*	*0*	*2*	*0*	*1*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	***13***

3e. PSURs submitted for purely nationally authorised products (active substances not in EURD list and not covered by worksharing)

	AT	BE	BG	CY	CZ	DE-Bfarm	DE-PEI	DK	EE	ES	FI	FR	GR	HR	HU	IE	IS	IT
2015	299	37	0	NA	0	126	36	13	0	2	8	NA	1	0	13	110	NA	78
2016	186	21	0	NA	6	86	12	5	2	18	7	NA	4	0	5	48	NA	26
2017	215	21	0	0	20	64	8	4	3	61	4	193	13	0	31	12	NA	341
2018	1067	13	2	0	12	46	7	1	1	34	4	203	6	1	21	7	0	66
Total PSURs submitted	*1767*	*92*	*2*	*0*	*38*	*322*	*63*	*23*	*6*	*115*	*23*	*396*	*24*	*1*	*70*	*177*	*0*	*511*

	LT	LU	LV	MT	NL	NO	PL	PT	RO	SE	SI	SK	UK	Total EU
2015	0	NA	81	NA	141	2	81	16	1	17	0	NA	94	1156
2016	0	NA	14	NA	46	1	123	28	12	8	0	NA	36	694
2017	0	NA	13	NA	32	7	106	33	39	12	1	0	28	1261
2018	1	NA	7	0	6	4	55	29	15	7	0	2	31	1648
Total PSURs submitted	*1*	*0*	*115*	*0*	*225*	*14*	*365*	*106*	*67*	*44*	*1*	*2*	*189*	***4759***

3f. Penalties issued to marketing authorisation holders regarding noncompliance with pharmacovigilance obligations

	AT	BE	BG	CY	CZ	DE-Bfarm	DE-PEI	DK	EE	ES	FI	FR	GR	HR	HU	IE	IS	IT
2015	0	0	0	NA	1	0		0	0	0	0	2	0	0	0	0	NA	0
2016	0	0	0	NA	0	0		0	0	0	0	3	0	0	0	0	NA	0
2017	0	0	0	NA	1	0		0	0	0	0	2	0	0	0	0	NA	0
2018	0	1	0	0	0	2	0	0	0	0	0	2	0	0	0	0	0	0
Total issued	*0*	*1*	*0*	*0*	*2*	*2*	*0*	*0*	*0*	*0*	*0*	*9*	*0*	*0*	*0*	*0*	*0*	*0*

	LT	LU	LV	MT	NL	NO	PL	PT	RO	SE	SI	SK	UK	Total EU
2015	0	0	0	0	0	0	0	0	0	0	0	0	0	3
2016	0	0	0	0	0	0	0	0	0	0	0	0	0	3
2017	0	0	0	0	0	0	0	0	0	0	0	0	0	3
2018	0	0	0	0	1	0	0	0	0	0	0	0	0	6
Total issued	*0*	*0*	*0*	*0*	*1*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	***15***

Annex 4. Pharmacovigilance activities at EU level

The following tables provide detailed quantitative information regarding pharmacovigilance activities undertaken at EU level, as collected and summarised by EMA.

4a. Summary of overall PRAC workload

Workload	2015	2016	2017	2018	Total
Referral procedures (started)	5	8	6	2	21
RMPs	607	570	561	543	2281
PSURs	650	796	847	916	3209
PASS Protocols	173	184	167	222	746
PASS Results	73	91	95	99	358
Renewals, Conditional Renewals and Annual Reassessments	53	129	168	168	518
Other safety issues - CHMP	17	15	12	6	50
Other safety issues - MS	22	13	10	22	67
Total items	*1600*	*1806*	*1866*	*1978*	*7250*

4b. Reporting of suspected adverse effects

Year	Number of ICSRs reported from EEA									
	Patients			Healthcare Professionals (HCPs)			Patients and HCPs			Total ICSRs
	Serious	Non-serious	All	Serious	Non-serious	All	Serious	Non-serious	All	
2015	34026	17100	51126	228570	54164	282734	26287	1275	27562	361422
2016	37428	14450	51878	226845	29973	256818	29618	1576	31194	339890
2017	60558	45456	106014	276900	101130	378030	48866	10638	59504	543548
2018	51114	193048	244162	301886	332755	634641	71079	78504	149583	1028386

Year	Number of ICSRs reported from non-EEA countries									
	Patients			Healthcare Professionals (HCPs)			Patients and HCPs			Total ICSRs
	Serious	Non-serious	All	Serious	Non-serious	All	Serious	Non-serious	All	
2015	183177	1830	185007	403387	4171	407558	271518	2719	274237	866802
2016	183344	1237	184581	410813	4936	415749	295286	2577	297863	898193
2017	182345	1413	183758	419598	6930	426528	314342	3418	317760	928046
2018	192066	1761	193827	433930	7729	441659	347071	4938	352009	987495

4c. RMPs on PRAC agenda

	2015	2016	2017	2018
Pre-authorisation phase	246	126	115	97
Post-authorisation with PSUR	3	0	0	0
Post-authorisation with Variation	396	444	446	446
Post-authorisation with Renewal	4	0	0	0
Post-authorisation standalone	0	0	0	0
Total RMPs	*649*	*570*	*561*	*543*

4d. PASS items on PRAC agenda

PASS Protocols & Results	2015	2016	2017	2018
Imposed Protocols	46	53	45	33
Non-imposed Protocols	137	130	122	189
Total Protocols	*183*	*184*	*167*	*222*
PASS Results on Imposed Protocols	2	11	9	15
PASS Results on non-Imposed Protocols	75	80	86	84
Total Results	*77*	*91*	*95*	*99*
Interim Results	117	108	146	181
Other PASS	12	28	48	61

Annex 5. List of safety related referrals 2015-2018

Procedure name	INN (for overview)	Legal basis (article)	Started	Finalised
Codeine for cough in paediatric population	codeine	31	Apr-14	Apr-15
Ambroxol/Bromhexine	ambroxol/bromhexine	31	Apr-14	Feb-15
Hydroxyzine	hydroxyzine hydrochloride	31	May-14	Mar-15
Ibuprofen and dexibuprofen	ibuprofen and dexibuprofen	31	Jun-14	May-15
Inhaled corticosteroid- containing medicinal products	beclomethasone, budesonide, flunisolide, fluticasone propionate, fluticasone furoate	31	May-15	Apr-16
Tysabri	natalizumab	20	May-15	Feb-16
SGLT2 inhibitors	canagliflozin, dapagliflozin, empagliflozin	20	Jun-15	Feb-16
HPV vaccines	human papillomavirus vaccine [types 6, 11, 16, 18], human papillomavirus vaccine rDNA, human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed)	20	Jul-15	Nov-15
Fusafungine nasal and oral solution	fusafungine	31	Sep-15	Mar-16
Gadolinium	gadolinium	31	Mar-16	Jul-17
DAAV	daclatasvir, dasabuvir, simeprevir, sofosbuvir, sofosbuvir/ledipasvir, ombitasvir/paritaprevir/ritonavir	20	Mar-16	Dec-16
Zydelig	idelalisib	20	Mar-16	Jul-16
SGLT2 inhibitors and lower limb amputation	canagliflozin	20	Apr-16	Feb-17
Retinoids	Isotretinoin, Tretinoin, Acitretin, Alitretinon, Adapalene	31	Jul-16	Mar-18

Procedure name	INN (for overview)	Legal basis (article)	Started	Finalised
Paracetamol modified release	paracetamol	31	Jul-16	Dec-17
Human and recombinant coagulation factor VIII	human coagulation factor VIII, efmoroctocog alfa, moroctocog alpha, octocog alpha, simoctocog alfa, susoctocog alpha, turoctocog alfa	31	Jul-16	Sep-17
Bovine lactose	methylprednisolone	31	Dec-16	Jul-17
Quinolone and fluoroquinolone antibiotics	nalidixic acid, pipemidic acid, cinoxacin, enoxacin, pefloxacin, lomefloxacin, ciprofloxacin, levofloxacin, ofloxacin, moxifloxacin, norfloxacin, prulifloxacin, rufloxacin, flumequin	31	Feb-17	Nov-18
Valproate	valproate	31	Mar-17	Mar-18
Zinbryta	daclizumab	20	Jun-17	Nov-17
Flupirtine	flupirtine	31	Oct-17	Mar-18
Hydroxyethyl starch (HES)	hydroxyethyl starch	107i	Oct-17	Jun-18
Xofigo	radium Ra223 dichloride	20	Dec-17	Jul-18
Esmya	ulipristal acetate	20	Dec-17	May-18
Zinbryta	daclizumab	20	Mar-18	May-18
Methotrexate oral formulations	methotrexate	31	Apr-18	ongoing

List of abbreviations and definitions

A list of abbreviations used in this document, together with high-level definitions of key terms for the benefit of non-specialist readers, is provided below.

ADR	adverse drug reaction (side effect)
ADVANCE	Accelerated Development of VAccine beNefit-risk Collaboration in Europe, a project to improve assessment of benefits and risks of vaccines
ANSM	Agence Nationale de Sécurité du Médicament et des Produits de Santé, the French medicines regulator
Article 107i	Article 107(i) of Directive 2001/83/EC. It applies when, on the basis of concerns resulting from the evaluation of data from pharmacovigilance activities, a Member State or the European Commission • considers suspending or revoking a marketing authorisation (MA); • considers prohibiting the supply of a medicinal product; • considers refusing the renewal of a MA; • is informed by the marketing authorisation holder that, on the basis of safety concerns, they have interrupted the placing on the market of a medicinal product or have taken action to have a MA withdrawn, or intend to take such action or have not applied for the renewal of a MA.
Article 20	Article 20 of Regulation (EC) 726/2004. It applies when a referral procedure is initiated as a result of the evaluation of data relating to pharmacovigilance of medicinal product(s) authorised via the centralised procedure only.
Article 31	Article 31 of Directive 2001/83/EC. It applies where the interests of the Union are involved. When a referral procedure is initiated as a result of the evaluation of data relating to pharmacovigilance of an authorised medicinal product(s) the issue is referred to the PRAC (see PRAC, below)
Article 57 database	*See* xEVMPD, below
ATC code	An identifier in the WHO's Anatomical Therapeutic Chemical classification system for medicines

BfARM	Bundesamt für Arzneimittel und Medizinprodukte, the Federal Institute for Medicines and Medical Devices, one of the two German federal medicines regulators
BIFAP	Base de datos para la investigación farmacoepidemiológica en atención primaria, a database compiling patient data from primary care practices in Spain
CAP	Centrally authorised product, a medicine for human use authorised by the European Commission based on an evaluation by EMA
CAR-T	Chimeric antigen receptor T-cell, a type of white blood cell that has been modified outside the body to enable it to attack cancer cells
CHC	Combined hormonal contraceptive
CHMP	Committee for Medicinal Products for Human Use, EMA's scientific committee responsible for the overall evaluation and opinion on marketing authorisation applications for centrally authorised products
CI, c/i	contraindication
CIOMS	Council for International Organizations of Medical Sciences, an international, non-governmental, non-profit organisation established jointly by WHO and UNESCO to advance public health through guidance on health research including ethics, medical product development and safety
CMDh	Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human, a medicines regulatory body representing the European Union (EU) Member States, Iceland, Liechtenstein and Norway.
COPD	Chronic obstructive pulmonary disease, lung diseases such as emphysema and chronic bronchitis
CPRD	Clinical Practice Research Datalink, a research resource compiling patient data from primary care practices in the UK
CVMP	Committee for Medicinal Products for Veterinary Use, EMA's scientific committee responsible for the overall evaluation and opinion on marketing authorisation applications for centrally authorised products for animals
DAAV	Direct acting antiviral, one of a class of medicines used to treat the viral liver disease hepatitis C

DHPC	Direct Healthcare Professional Communication, a letter sent to inform doctors about an issue relating to a medicine
EC	European Commission
EEA	European Economic Area
EMA	European Medicines Agency
ENCePP	European Network of Centres in Pharmacoepidemiology and Pharmacovigilance, a partnership involving 147 centres across Europe
ENS	Early notification system
EPAR	European Public Assessment Report, a dossier of public information relating to the approval of a medicine
EU	European Union
EudraVigilance	The EU database that collates worldwide reports of suspected side effects (adverse reactions) and supports their detection and analysis
EURD	List of European Union reference dates and frequency of submission of periodic safety update reports (a list of active substances for which PSURs must be submitted and the dates and frequencies at which this should occur).
FDA	Food and Drug Administration, the medicines regulator for the United States of America
GVP	Good Pharmacovigilance Practice, guidelines on how pharmacovigilance activities should be carried out
HCP	Healthcare professional
HES	Hydroxyethyl starch, a type of medicine used to support the circulation and prevent shock after blood loss
HPV	Human papillomavirus, a virus implicated in causing genital warts and certain cancers including cervical cancer
ICDRA	International Conference of Drug Regulatory Authorities, a forum for drug regulators under the auspices of WHO
ICH	International Coumcil on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, which brings together regulatory authorities from countries including the EU, Japan and United States
ICSR	Individual Case Safety Report, a standardised report of a suspected side effect
IMI	Innovative Medicines Initiative, a public-private initiative aiming to speed up the development of better and safer medicines for patients

IMS	Information Medical Statistics, (now called IQVIA), a commercial company providing prescribing data and statistics about healthcare
INN	International non-proprietary name
IT	Information technology
LMS	Lead Member State, a Member State who acts on behalf of the Network in assessing pharmacovigilance data for a particular active substance *or* Learning Management System
MAH	Marketing Authorisation Holder, the company marketing a medicine
MS	Member State, one of the constituent nations of the European Union
NAP	Nationally authorised product, a medicine evaluated and approved by national regulators
NCA	National competent authority, a national medicines regulator
NTC	Network Training Centre
PAES	Post-authorisation efficacy study, a post-marketing study focusing on the benefits of a medicine
PAS	Post-authorisation study, a study carried out after a medicine has been authorised and marketed; may be imposed or requested by regulators during the authorisation process
PASS	Post-authorisation safety study, a post-marketing study focusing on the safety of a medicine
PEI	Peter Ehrlich Institut, one of the two German federal medicines regulators
Pharmacovigilance	Planned monitoring of the safety of medicines so that anything that affects their safety profile can be swiftly detected, assessed, and understood and appropriate measures can be taken to manage the issue and assure public health
PhV	Pharmacovigilance
PI	Product information (in the EU consists of the SmPC for healthcare professionals and the package leaflet for patients)
PRAC	Pharmacovigilance Risk Assessment Committee, EMA's main committee for assessing issues of medicines safety
PROTECT	Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium, a public-private partnership to examine ways to strengthen safety surveillance and the

	monitoring of the benefit-risk of medicines in Europe. Completed in 2015
PSUR	Periodic safety update report, a report that each marketing authorisation holder must submit at defined intervals, providing an updated evaluation of the benefit-risk balance of a medicine. They include the results of studies carried out with the medicine, as well as any other new information on safety or benefits, and cover both authorised and unauthorised uses.
PSUSA	Periodic safety update – single assessment, a PSUR carried out for a group of medicines that contain the same active substance or combination of active substances and whose assessment period has been synchronised. This allows for more efficient use of resources and also ensures that these related medicines are evaluated in a consistent way.
Real world data	Data derived from a variety of sources relating to the use of medicines in patients in real-world settings, as opposed to the controlled conditions of a randomised controlled trial. They may include data from electronic health records, patient registries and health insurance claims
Real world evidence	Clinical evidence regarding the use and potential benefits or risks of a medical product derived from analysis of real world data
Referral	A legal procedure with a defined timetable that is used to resolve issues such as concerns over the safety or the benefit-risk balance of a medicine or a class of medicines. The matter is 'referred' to EMA, so that it can make a scientific assessment leading to a recommendation for a harmonised position across the European Union. May be triggered under various articles of the legislation, depending on the nature of the concern and the medicines involved (see also Article 107i, Article 20 and Article 31 above).
Risk Management Plan	Part of the dossier of information legally required from each company wishing to market a medicine in the EU. The plan identifies known and potential safety issues with the medicine, and includes binding commitments on how the medicine will be monitored for safety during its lifetime. It also identifies the actions that will be taken to minimise the risks and provide evidence where it is lacking, so as to ensure the most favourable balance of risks against the medicine's benefits.

RMP	Risk Management Plan
SAG	Scientific Advisory Group, a group of external experts convened to provide expert advice during an evaluation or review of a medicine
SAR	Serious Adverse Reaction
SCOPE	Strengthening Collaboration for Operating Pharmacovigilance in Europe, an EU-funded joint action project involving regulators from many EU Member States plus Norway and Iceland
SGLT2 inhibitor	Medicines used to treat diabetes by blocking the action of an enzyme that normally helps the kidneys to retain sugar (glucose) in the body
Signal	A safety signal is information on a new or known adverse event that is potentially caused by a medicine and that warrants further investigation. Signals may be generated from any information source but most come from ICSRs, clinical studies or the scientific literature. This information undergoes an initial examination to determine that it can be considered a possible signal (validation), before being confirmed as appropriate to be passed to the PRAC for evaluation and regulatory action as required.
SmPC	Summary of Product Characteristics, EU product information for healthcare professionals
T2DM	Type 2 diabetes mellitus
UNESCO	United Nations Educational, Scientific and Cultural Organization
Variation	A formal procedure to make a change in the marketing authorisation of an authorised medicine
VTE	Venous thromboembolism (a blood clot obstructing a vein)
WEB-RADR	An IMI-funded consortium developing a mobile app to report suspected adverse drug reactions, and investigating the potential for publicly available social media data for identifying drug safety issues. The first 3-year project (WEB-RADR1) ran from 2014-17. WEB-RADR2 launched in September 2018
WHO	World Health Organization
xEVMPD	eXtended EudraVigilance Medicinal Product Dictionary, also known as the Article 57 database, containing information on all authorised medicines in the EU