

What's new in Pharmacovigilance? QPPV UPDATE

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QPPV Update

This issue provides you with information on recent developments in EU Pharmacovigilance, relating to medicines for human use, and includes updates on the EU network activities, relevant projects and publications. We would welcome your feedback as well as any suggestions on topics you think would be of interest to colleagues. Your feedback should be sent via [ASK EMA online form](#).

EMA now operates from Amsterdam

The European Medicines Agency (EMA) physically relocated to the Netherlands in early March 2019. EMA now operates from the Spark building in Amsterdam Sloterdijk, until its final premises in Amsterdam Zuidas become available.

From 4 March 2019 the official address of EMA is that of the permanent building:

*European Medicines Agency,
Domenico Scarlattilaan 6, 1083 HS
Amsterdam, The Netherlands*

Meetings and visits take place at the Spark building:

*Orlyplein 24, 1043 DP Amsterdam,
The Netherlands*

For more information, see [How to find us](#) section on EMA's website.

Need more information?

Further information about the work of the European Medicines Agency is available on our [website](#)

For topics on Pharmacovigilance legislation – [see here](#)

Links to the National Competent Authorities can be found [here](#)



Pharmacovigilance IT Systems

EudraVigilance in 2018: annual update

In 2018, EudraVigilance (EV) continued to be a central pillar of European medicine safety surveillance. The significant enhancements implemented in the database in 2017 are now in routine operation and delivering improved functionalities for signal detection and monitoring of risks, performance of pharmacovigilance activities and identification of medicinal products for the EU network.

- Collecting and processing of adverse drug reaction reports (ADRs)

In 2018, 2,015,881 reports related to suspected adverse reactions occurring in the post-authorisation phase were collected and managed in EV (a 37% increase compared to 2017). This is explained in part by the launch of the new EudraVigilance system on 22 November 2017 which now also includes mandatory reporting of non-serious cases in addition to the existing serious case reporting from the EEA. An unprecedented number of these reports, 1,028,386, originated from the EEA (an 89% increase compared to 2017). The number of reports submitted directly by European patients and consumers through the National Competent Authorities (NCAs) and Marketing Authorisation holders (MAHs) (172,762) increased 91% in 2018.

With currently over 14.5 million ADR reports, EudraVigilance is now among the largest databases of its kind in the world and is used by EMA, EU NCAs and MAHs for safety surveillance.

- EudraVigilance data quality activities
- The Agency continued to operate procedures to ensure the quality and integrity of the information collected in EV in collaboration with the EU medicines regulatory network. In 2018 this included the identification of 177,811 duplicate reports, the coding of the 61,202 reported medicines and reported active substances, and the provision of feedback to 237 organisations on the quality of ADR reports.
- Maintaining and updating the database of information on all medicinal products authorised in the EU

The database (the so-called "Article 57 database") now contains information on 816,765 medicines (authorised, transferred and withdrawn).

- Provision of EU case reports to the World Health Organization (WHO) Uppsala Monitoring Centre directly from EudraVigilance

Direct provision of data to the WHO from EV in 2018 saw 1,010,544 individual case safety reports (ICSRs) forwarded to WHO from EudraVigilance, making it one of the largest contributors to the WHO database.

- Training and support activities

Many of the training and support activities organised by the EMA were open to all stakeholders, including two EudraVigilance and Signal Management information days (with combined attendance of 244 delegates), 2 training sessions on the EudraVigilance Data Analysis System (EVDAS), 27 training sessions on EudraVigilance ICSR submissions (469 users trained) and 5 training sessions on the XEVMPD (64 users trained), with an additional 153 users trained on the XEVMPD e-learning platform. Furthermore, 11 and 14 webinars were organised for NCAs and MAHs, respectively, to aid with the resolution of operational and technical questions and 5 additional signal management webinars were organised for MAHs.

For further information on the available EudraVigilance training courses please visit the dedicated [EudraVigilance training and support](#) webpage.

What you need to know?

As described in the [Eudravigilance operational plan \(2018-2020\)](#), on 26th July 2019 EMA delivered Substance Management Services (SMS) to support EU-wide regulatory activities. As part of SMS Phase 1 activities, EMA has extended the use of the [EMA Service Desk portal](#) for registration of substances to Clinical Trial Sponsors. This means that Sponsors, instead of creating development substances directly in the xEVMPD, now need to request a new substance in advance, if they want to submit a Clinical Trial Application or to submit an Investigational Medicinal Product in XEVMPD. These substances will be registered in xEVMPD as approved substances with any confidential information restricted from the public systems. EMA will process these requests in 4 working days.

Further information on SMS and Product Management Service (PMS) is available at the dedicated [Substance and product data management services](#) webpage.

Pharmacovigilance Processes

Screening for and review of potential signals for centrally authorised products (CAPs) as well as nationally authorised products (NAPs)

In 2018, the EMA's signal management team reviewed in detail 2,204 potential signals, i.e. drug-event pairs from screening of the EudraVigilance database (78.7%), medical literature (17.8%) or information received from Non-EU regulatory authorities or other sources. The Pharmacovigilance Risk Assessment Committee (PRAC) prioritised and assessed 114 confirmed signals (a 39% increase compared to 2017); 79% included data from EudraVigilance. Fifty of the assessed signals (44%) resulted directly in a recommendation for an update of the product information for patients and healthcare professionals, thus providing updated guidance on the safe and effective use of the medicines.

In six of these cases, the PRAC also recommended Direct Healthcare Professional Communications (DHPCs) to highlight new important safety information to prescribers. In 24 cases (21%) continuing with routine safety monitoring of the medicine was considered sufficient. The evaluation of 39 signals (34%) is ongoing in 2019, including 22 via a follow-up signal procedure and 17 in the upcoming PSUR/PSUSA.

Quicker product information updates

What's new?

Every month the Agency publishes PRAC recommendations on safety signals. Those that require labelling changes are translated into all official EU languages.

During the period May 2017 – April 2018 the PRAC adopted 19 recommendations for product information update of centrally authorised products. A high level of compliance was observed in the implementation of those recommendations via submission of variations, i.e. 97% of the variations were submitted by MAHs in compliance with the recommended timeframe (30, 60 or 90 days) or with a negligible delay.

What do you need to know and do?

MAHs should monitor [EMA website](#) to remain informed about the PRAC recommendations concerning their products.

Update of the signal management worksharing list

For medicinal products authorised through the national, mutual recognition or decentralised procedures in more than one Member State and for active substances contained in several medicinal products where at least one marketing authorisation was obtained through the above-mentioned procedures, the legislation foresees that a lead Member State may be appointed to monitor data in EudraVigilance, and to validate and confirm signals on behalf of the other Member States. The Agency provides the appointed Lead Member States with reaction monitoring reports from EudraVigilance for the substances allocated to them. For substances with no Lead Member State, all Member States have joint responsibility for monitoring those medicines they have authorised. The signal management worksharing list has been regularly updated since its first publication in October 2012.

What's new?

In the context of Brexit, the latest update includes the change of lead Member State for 108 active substances previously monitored by the UK, as well as the appointment of lead Member States for 219 previously unallocated substances. The signal management worksharing list and other information on signal management can be found on the EMA [signal management webpage](#).

EU PAS Register: 1,500 studies registered by April 2019

What's new?

The 1,500th study was registered in the EU PAS Register (study EUPAS29415) in April 2019. This study, titled 'Observational Patient Evidence for Regulatory Approval and uNderstanding Disease' (OPERAND), looks at the replicability of two RCTs with observational data and is conducted in the US by Harvard Pilgrim Health Care Institute, illustrating the increasing globalisation of the EU PAS Register. The register is key to supporting transparency in post-authorisation research: by April 2019, 46% of the registered studies were requested by regulators, 10% were imposed as a condition of marketing authorisations (i.e. EU RMP category 1 and 2 studies) and 84% of finalised imposed studies had their protocols and abstract of results posted in the EU PAS Register in compliance with Article 26 (1)(h) of Regulation (EC) No 726/2004. By facilitating the review of protocols and results, the EU PAS Register is also increasingly used for academic research.



Monitoring benefits and risks of vaccines in Europe: from ADVANCE to VAC4EU

From 2013 to 2018, EMA participated to the Innovative Medicines Initiative (IMI) funded ADVANCE project. Triggered by the lessons learnt from the H1N1 influenza pandemic, ADVANCE established a framework for vaccine benefit-risk monitoring in Europe, including a network of electronic health databases and methodological tools for their analysis. After the end of the project, the framework delivered by ADVANCE is now being developed as a non-for-profit international association named VAC4EU. Members of VAC4EU are research organisations and public health institutes that can generate evidence on vaccine coverage, safety and effectiveness using standardised procedures and methods. By 31 May 2019, the VAC4EU study network included 12 research organisations and 5 public health agencies and it is gradually expanded.

For more information, please visit <https://vac4eu.org/>.

Pharmacovigilance dialogue

Publications

The HMA/EMA Joint Big Data Task Force - summary report

On 15 February 2019, the HMA/EMA Joint Big Data Task Force published a summary report containing its recommendations for a path towards understanding the acceptability of evidence derived from big data in support of the evaluation and supervision of medicines. The recommendations and associated actions set out what needs to be addressed, but the mechanisms by which this may be achieved requires further focused work over the coming year.

The report can be found [here](#).

For more information, see [HMA/EMA Task Force on Big Data](#).

Barriers and Opportunities for use of Patient Registries in Medicines Regulation

The article on 'Barriers and Opportunities for use of Patient Registries in Medicines Regulation' was published in *Clinical Pharmacology & Therapeutics* in April and describes the extensive work done over the past 4 years and learnings developed through a series of multi-stakeholder workshops.

For more information on the patient registries initiative, stakeholder collaboration and workshop reports, please visit the [Patient registries](#) webpage.

Olmo CA, McGettigan P, Kurz X, [Barriers and opportunities for use of patient registries in medicines regulation](#), *Clin Pharmacol Ther.* 2019 Apr 10. doi: 10.1002/cpt.1414. [Epub ahead of print]

Real World Data for Regulatory Decision Making: Challenges and Possible solutions for Europe

The article introduces the OPTIMAL framework, which describes a number of OPERational, TechnIcal and MethodologicAl solutions to enhance the quality of the evidence generated from real-world data and support its acceptability for regulatory decision-making.

Cave A., Kurz X., Arlett P, [Real world data for regulatory decision making: challenges and possible solutions for Europe](#), *Clin Pharmacol Ther.* 2019 Apr 10. doi: 10.1002/cpt.1426. [Epub ahead of print]

First collaborative inter-agency regulatory study published

A paper entitled 'A European multi-centre drug utilisation study of the impact of regulatory measures on prescribing of codeine for pain in children' has been published in *Pharmacoepidemiology and Drug Safety*. The study involved EMA and two national competent authorities (Spain and United Kingdom) working directly through a common protocol to analyse electronic healthcare records stored in databases to which they have access. As such it is the first collaborative inter-agency study and the specific topic is an important public health issue relating to restrictions on the use of codeine in children and adolescents introduced by PRAC.

Hedenmalm K, Blake K, Donegan K, Macia MA, Gil M, Williams J, Montero D, Candore G, Morales D, Kurz X, Arlett P., [A European multi-centre drug utilisation study of the impact of regulatory measures on prescribing of codeine for pain in children](#), *Pharmacoepidemiol Drug Saf.* 2019;1-11

IMI WEB-RADR project proposes framework for the use of social media and the use of mobile applications in pharmacovigilance – articles published

The Innovative Medicines Initiative (IMI) WEB-RADR (Web-Recognising Adverse Drug Reactions) project looked at opportunities and challenges in using technology and social media in pharmacovigilance.

This recently published article proposes a regulatory framework on the use of social media in pharmacovigilance that aims to ensure a continuous monitoring of the safety of medicines without overburdening established pharmacovigilance systems and taking into account that analytical results of WEB-RADR indicated limited value of social media in detecting or confirming signals for a majority of the drugs studied.

Brosch, S., de Ferran, AM., Newbould, V. et al. [Establishing a framework for the use of social media in PhV](#) Drug Saf (2019) 42: 921. <https://doi.org/10.1007/s40264-019-00811-8>

As part of the WEB-RADR project three apps were developed and publicly launched within Europe and assessed to determine their value in Pharmacovigilance. The recommendations on the Use of Mobile Applications for the Collection and Communication of Pharmaceutical Product Safety Information: Lessons from IMI WEB-RADR can be accessed [here](#).

Pierce, C.E., de Vries, S.T., Bodin-Parssinen, S. et al. Drug Saf (2019) 42: 477. <https://doi.org/10.1007/s40264-019-00813-6>

These publications will be taken into consideration for any future amendments of GVP or other guidelines.

'The ENCePP Code of Conduct: A best practise for scientific independence and transparency in non-interventional post-authorisation studies'

For more than 10 years EMA has been at the forefront of scientific independence and transparency in real world data studies through ENCePP. A review article about Revision 4 of the ENCePP Code of Conduct has been published in Pharmacoepidemiology and Drug Safety where patients, academia, contract research organisations, regulators and manufacturers provide their perspectives on ten years of stakeholder experience with non-interventional post-authorisation studies for regulatory purposes. The fourth revision defines scientific independence and clarifies uncertainties on the applicability to post-authorisation safety studies requested by regulators. The paper also compares ENCePP recommendations with ISPE Good Pharmacoepidemiology Practices and the Code of Conduct published by the ADVANCE project on collaborative vaccine studies.

Gini R, Fournie X, Dolk H, et al. [The ENCePP Code of Conduct: A best practise for scientific independence and transparency in noninterventional postauthorisation studies](#). Pharmacoepidemiol Drug Saf. 2019;1–12

Engagement of patients and healthcare professionals in regulatory pharmacovigilance

In collaboration with the University of Amsterdam, EMA has published a paper entitled 'Engagement of patients and healthcare professionals in regulatory pharmacovigilance: establishing a conceptual and methodological framework'. This paper is an output of the Impact Strategy of the Pharmacovigilance Risk Assessment Committee. The article provides definitions for pharmacovigilance engagement, and describes pharmacoepidemiological and social-science methods to create synergies for measuring engagement processes and outcomes.

Brown P, Bahri P, [Engagement of patients and healthcare professionals in regulatory pharmacovigilance: establishing a conceptual and methodological framework](#), Eur J Clin Pharmacol (2019).

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