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What's new in Pharmacovigilance?

QPPV UPDATE

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QPPV Update

This last issue of 2018 provides you with information on recent developments in EU Pharmacovigilance, relating to medicines for human use, and includes updates on the EU network activities and relevant projects.

We wish you a Happy Christmas and New Year and look forward to continued collaboration in 2019.

Update on EMA's Brexit preparedness

On 1 October 2018 the European Medicines Agency's (EMA) Brexit preparedness business continuity plan (BCP) entered into its third phase.

In phase three EMA temporarily scaled back and suspended additional activities through to 2019. While all product related pharmacovigilance continues, this had an effect on: international collaboration, organisation of workshops and non-product related working groups and development and revision of guidance.

Temporary suspension and scaling back of activities is currently scheduled to last until 30 June 2019, but will be reviewed in April 2019, once the Agency has completed its move to its temporary building in Amsterdam.

Further details are available in the BCP phase 3 implementation plan.

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—one year of operation

The new EudraVigilance (EV) system was launched on 22 November 2017 and has now been operational for over a year. The enhanced system is one of the largest pharmacovigilance databases in the world and currently holds over 13 million Individual Case Safety Reports (ICSRs) referring to more than 8 million of individual cases.
During the first year of operation, the enhanced EV System processed 1,578,723 ICSRs related to suspected serious adverse reactions. In addition, 647,192 ICSRs of suspected non-serious adverse reactions have been submitted to EV in line with the new legal requirement to report all cases of EU origin.

EudraVigilance as a single reporting point in the EEA

MAHs in the EEA now use EV as the single point to report suspected adverse reactions for medicines with one set of agreed business rules applied for the validation of the format and content of reports. Through the new EudraVigilance rerouting functionalities, the electronic reporting of ICSRs has been significantly simplified. So far, a total of 390,527 ICSRs reported by MAHs and originating from the EEA have been re-routed to National Competent Authorities (NCAs) in accordance with their specified requirements. Furthermore, ICSRs originating from the EEA are routinely made available to WHO-UMC, with a total of 1,006,045 ICSRs made available so far.

1,668 MAHs have submitted download request to EudraVigilance, with 253,294 download requests successfully executed resulting in a total of 15,1 million ICSRs downloaded. To facilitate the processing of the downloaded ICSRs by MAHs, EMA published a note for clarification in July 2018.

EudraVigilance and the new ICH E2B(R3) ICSR format

The enhanced EudraVigilance system is based on the new ISO ICSR standard and delivers a mechanism to allow for stakeholders to continue to report in the previous ICH E2B (R2) format until their local pharmacovigilance systems have been upgraded to the new ICH E2B(R3) standard.

Since November 2017, 18,2% of ICSR submissions to EudraVigilance are in the new ICH E2B(R3) data format. These are submitted by:

- 79 MAHs with gateway profile (including affiliates) (30% of all MAHs with gateway profile)
- 9 NCAs with gateway profile (70% of all NCAs with gateway profile)
- 930 MAHs using EVWEB and the new ICH E2B(R3) data format
- 19 NCAs using EVWEB and the new ICH E2B(R3) data format
- 3 commercial and 1 non-commercial sponsor organisations with gateway profile (6% of all sponsors with gateway profile).

A survey, to define a date to make the use of the ISO ISCR standard mandatory in the EU was launched with the European industry associations in November 2018. The results of the survey will be considered by the EU regulatory network in 2019.

EudraVigilance Data Analysis and signal detection

The implementation of the new EudraVigilance system provides enhanced functionalities to NCAs and MAHs for effective analysis based on an extensive data set for the monitoring of adverse drug reaction data and the detection of risks related to the safety of medicines, thus contributing to the protection and promotion of public health.
EMA is one of the first medicines regulators to provide access to MAHs to advanced signal detection and management functionalities, in line with those which are used by medicines regulators. At present more than 2,000 MAHs with 6,000 users are registered with the EudraVigilance Data Analysis System (EVDAS) to fulfil their new signal management responsibilities.

Pharmacovigilance IT Systems

In December 2018, the relocation of the data centres was initiated by EMA, which resulted in downtimes of the EV transactional system and EVDAS. As a result, data in EVDAS could not be refreshed as of 3 December and the fixed monthly electronic Reaction Monitoring Report (eRMR) for MAHs could not be produced for November 2018. The technical team is currently working on resolving the issue to ensure that the data in EVDAS are brought up-to-date.

EudraVigilance organisation and user management and registration

The number of EV users has significantly increased. For marketing authorisation holders (MAHs), more than 5,000 companies with over 18,000 users are now authorised to access EudraVigilance.
With the aim of bringing greater efficiencies for both users and EMA, as well increased data security, EMA is standardising how people and organisations register for EMA services through the Agency's new Organisation Management System (OMS). The new process for registration was incorporated into EudraVigilance at the end of July 2018, replacing the previous EudraVigilance Registration system. Taking into account the large number of organisations and users including the hierarchical structure of managing headquarters and affiliates, the integration of EudraVigilance with the new identity and access management was a major undertaking. EMA is in a process of resolving some remaining technical and data migration issues which impact certain organisations and users as follows:

- Merging of duplicated user accounts to support the new principle of a single user profile. The merging is needed due to users having more than one e-mail address registered previously in EV for different organisations they represent;
- Correcting certain linkages between EV organisation identifiers and the OMS identifiers as part of the data migration activities;
- Reviewing EudraVigilance legacy user registration data, which may have led to the assignment of more than one responsible person for pharmacovigilance;

- Resetting the EudraVigilance transmission mode (Gateway/Webtrader) for some organisations;
- Addressing certain synchronisation issues between OMS and EV that may cause issues with users access;
- Reviewing the contributor role for virtual affiliates where this was not set automatically for all headquarter users.

EMA acknowledges the challenges that some users have faced with the new OMS. We are working hard to resolve those that remain.

What MAHs should know and do:

- MAHs wishing to register with, access or manage their account for the EudraVigilance (human) production environment should consult the Registration manual and Frequently Asked Questions document.
- For support on access and registration related questions, companies should refer to EudraVigilance support guide and use the EMA service desk.
- EMA will regularly communicate on potential EV system downtimes due to the relocation activities and the resolution of technical issues.

For further information please visit the dedicated EudraVigilance webpages.

Pharmacovigilance Processes

Prolongation of the pilot on signal detection by MAHs in EudraVigilance

The EU Pharmacovigilance legislation requires marketing authorisation holders to continuously monitor data in EudraVigilance and to inform EMA and NCAs of validated signals detected when monitoring the database. Regulatory guidance on the detection and reporting of signals from EudraVigilance is provided in the Good Vigilance Practice (GVP) Module IX on Signal Management. To streamline the involvement of MAHs in the monitoring of EudraVigilance data, a phased implementation was agreed with the European Commission. A pilot started on 22 February 2018 focusing on active substances included in 'List of active substances involved in the pilot on signal detection in EudraVigilance by marketing authorisation holders'.

What's new?

- With a view to gain more experience with the process, the pilot, initially planned for one year, has been prolonged beyond February 2019 in agreement with the European Commission. This means that until further notice, only those MAHs with an active substance or combination included on the 'pilot list' will have to continue performing signal detection in EudraVigilance for these substances.

What MAHs need to know and do:

- By the end of September 2019, the Agency will finalise a report outlining the first year of experience (February 2018 - February 2019). In that context, EMA intends to survey MAHs involved in the pilot on their experience, including signals reported within PSURs or safety variations in line with the process outlined in GVP IX. Therefore, MAHs are encouraged to prospectively record such information.
- By the end of December 2019, a decision on the next implementation phase, including the scope of products to be included and the date of coming into effect, will be communicated to stakeholders.

More information can be found on the EMA signal management and EudraVigilance training and support webpages.

European Electronic healthcare databases available to be used in medicines regulation

The number of European database that meet minimal regulatory requirements and are readily available to be used in a regulatory context has been reviewed. This review confirmed the fragmentation, heterogeneity and lack of transparency existing in many European electronic healthcare databases.
The full article could be accessed here.

Use of patient disease registries for regulatory purposes

What's new?

On 8 November 2018 the EMA cross-committee task force on registries published a discussion paper on methodological and operational considerations in the use of patient disease registries for regulatory purposes. The document is planned to be finalised in 2019.

Discussion paper: Use of patient disease registries for regulatory purposes – methodological and operational considerations

How is it relevant for you?

Interested parties can send their comments and suggestions using the Form for submission of comments or an annotated version of the document mentioning the individual's name, affiliation and contact details on the first page, to EMAregistries@ema.europa.eu by 30 June 2019.

Pharmacovigilance guidance

Revision 4 of the ENCePP Checklist for Study protocols

The Guidance for the format and content of the protocol of non-interventional post-authorisation safety studies requires that a copy of the ENCePP Checklist for Study protocols, completed and signed by the main author of the study protocol, should be included in Annex 2 of the PASS study protocols. ENCePP has completed Revision 4 of the Checklist which has been posted on the ENCePP website: ENCePP Checklist for Study Protocols (Revision 4).

Pharmacovigilance guidance

Good pharmacovigilance practices

Guideline on GVP Product- or Population-Specific Considerations IV: Paediatric population has been released as final, following the public consultation in 2017.

Pharmacovigilance dialogue

Reports from meetings and events

- A report from the Haemophilia registries workshop, held on 8 June 2018, has now been published. The report summarises observations made by the participants on the use of registry data to support regulatory benefit-risk evaluations and, in particular, post-authorisation follow-up. It makes recommendations for actions that aim to facilitate and improve registry data use including the systematic collection of a set of core commonly-defined data elements.
  Other workshop reports outlining the recommendations and actions to be implemented in each case are published on the webpage of the Patient Registries Initiative here.

- The twelfth pharmacovigilance stakeholder forum took place on 24 September 2018. A video recording is now available.

- The fourteenth industry stakeholder platform on operation of European Union pharmacovigilance took place on 28 September 2018. The meeting documents can be accessed here.

'A common data model for Europe' workshop report

On 11 and 12 December 2017, EMA hosted a multi-stakeholder workshop that sought to define the opportunities and challenges in standardising observational data from across Europe into a common data model, in order to deliver timely evidence that can support regulatory decision-making. In the context of this meeting, a common data model was defined as "a mechanism by which raw data are standardised to a common structure, format and terminology independently from any particular study in order to allow a combined analysis across several databases/datasets." The workshop report has been published on the Agency's corporate website, and suggests a number of fundamental guiding principles for the development of common data model in Europe including key criteria for validation in the context of regulatory decision-making.

'Data anonymisation - a key enabler for clinical data sharing' workshop report

On 30 November and 1 December 2017, EMA hosted a multi-stakeholder workshop jointly organised with the MRCT Center (Brigham and Women's Hospital and Harvard, USA). Proactive sharing of clinical trial data has long been a key strategic aim of EMA culminating in 2014 with the publication of Policy 0070 which led to the creation of a dedicated portal in 2016 that give access to over 6650 documents. This workshop explored how anonymisation of internationally sourced clinical trial data may be achieved while maintaining the scientific utility of the data in order to deliver benefits for the public good. The workshop report is available on the Agency's corporate website, and advocates for a global framework for anonymisation that is able to meet the varied international legislative requirements, that highlights the methodology employed, and assesses the current and future risk of re-identification. This is essential to build patient and public trust, build confidence, and deliver an accountability of the process.

European Medicines Agency
30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union