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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Pharmacovigilance Programme UPDATE

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IN THIS ISSUE

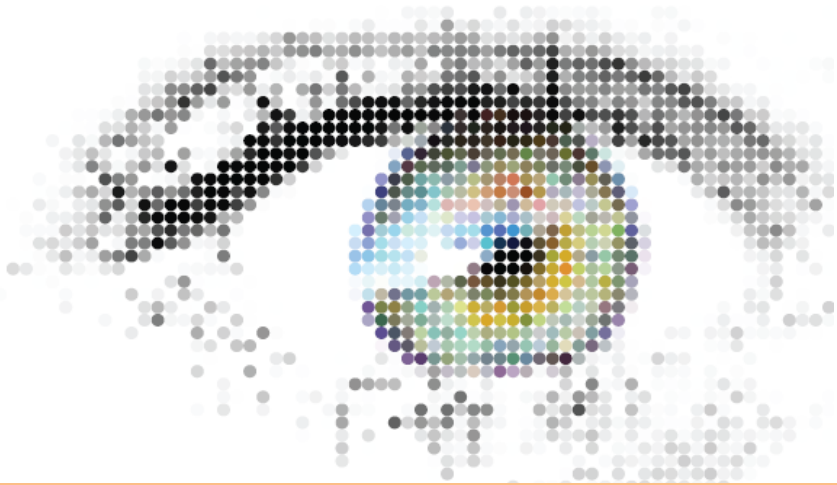
Preparing for business change

In July 2014 EMA started to issue quarterly Updates primarily aimed at providing marketing-authorisation holders (MAHs) with information on the development of new systems and services, to help MAHs prepare for business change.

Each issue has focussed on the most critical questions: what needs to be done by whom and by when.

This Update provides you with an overview on the highlights so far and the next steps for 2016.

We wish you a happy Christmas and New Year and look forward to continued collaboration in 2016.



Need more information?

For topics on implementation of the new Pharmacovigilance legislation – see here.

Further information about the work of the European Medicines Agency is available on our website.

Links to the National Competent Authorities can be found here.

Medical Literature Monitoring

Need more information?

Medical Literature Monitoring website

Scope:

- Legal requirement for EMA to monitor selected medical literature for reports of suspected adverse drug reactions containing certain active substances and to enter individual case safety reports into the EU adverse reaction database (EudraVigilance).

Highlights of 2015

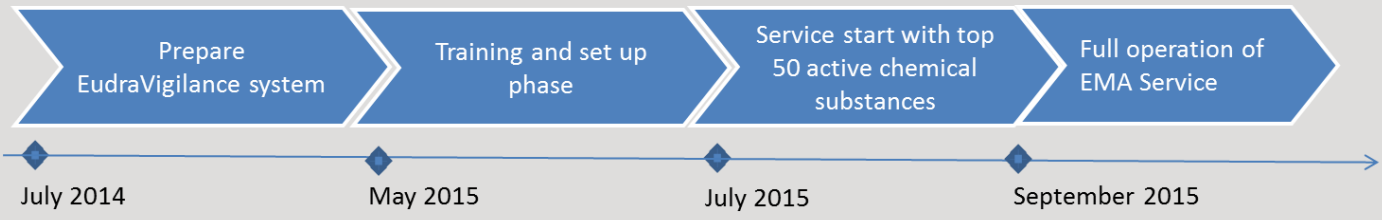
- On 12 May 2015 the dedicated Medical Literature Monitoring (MLM) website was launched with the key documents regarding the monitoring of medical literature;
- On 1st July 2015 the MLM service was launched, covering the 50 most common chemical active substance groups. The launch phase was completed on 31st August 2015;
- On 1st September 2015 the full operation of the MLM was launched. The service now covers 300 chemical active substance groups and 100 herbal active substance groups.

What's coming in 2016

- Since the service launch in July 2015 the support webinars for stakeholders have been organised and will continue throughout 2016 on a monthly basis;
- An independent audit of the service provider's internal quality management and control systems and of the output of the service will be conducted in early 2016 (and 2-yearly thereafter);
- Customer satisfaction surveys will be launched in 2016 and will be distributed to all NCAs and MAHs impacted by the service;
- A quarterly service update report will be made available on the dedicated MLM website, and other key documents will be updated as needed including: search strategies, the list of active substances, list of journals, and the user manual.

What MAHs need to do:

- The list of active substance groups and a reference to the journals covered by EMA's medical literature monitoring service are available on the Medical Literature Monitoring page. Companies are advised to consult the list to check whether their products are covered by the service;
- For products containing active substances covered by Agency's MLM service, marketing authorisation holders shall not be required to report to EudraVigilance the suspected adverse reactions from the medical literature monitored by EMA. It is important to note that marketing-authorisation holders need to continue to monitor all other medical literature not covered by the literature reference databases applied for the service by the Agency (e.g. monitor scientific and medical publications in local journals in countries where medicinal products have a marketing authorisation);
- Please send any enquiries to mlm@ema.europa.eu.



Database of Products (Article 57)

Need more information?

Data submission for authorised medicines

A new webpage dedicated to ISO IDMO standards implementation is now available

Scope:

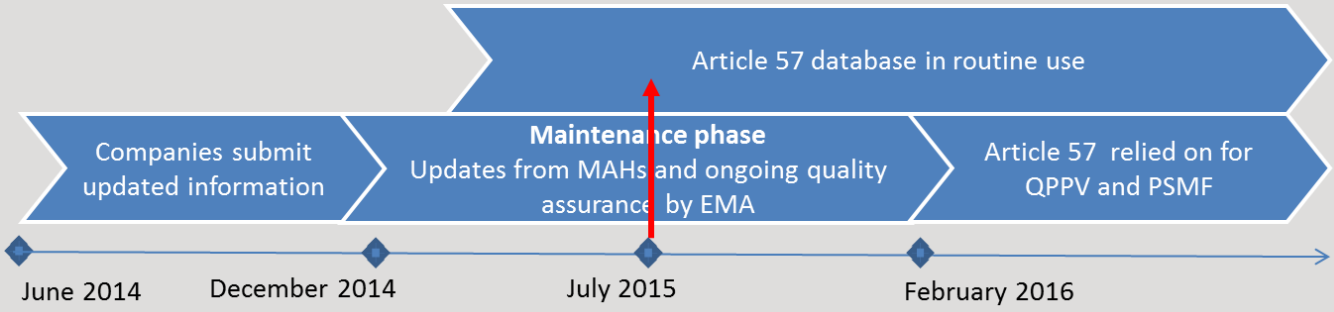
- To deliver structured and quality assured information on medicinal products authorised in the EU that can support EU terminologies of products, substances, and organisations used to power pharmacovigilance and regulatory systems.

Highlights of 2015

- The Article 57 database of medicinal products authorised in the EU was set up in 2012 and is now established and operational. The database contains approximately 500,000 medicinal products and is the most comprehensive database of medicinal products authorised in the EU;
- The EU regulatory network continues co-operation with Industry to ensure completeness and correctness of Article 57 data. In October 2015 the Agency published a document detailing the measures taken at the pre-submission, submission, and post-submission phases of data entry into the eXtended EudraVigilance Medicinal Product Dictionary (XEVMPD) to ensure data quality;
- On 19 October 2015 the Agency launched the Article 57 Publication Dashboard Report for the National Competent Authorities (NCAs). The dashboard is designed to make available key data as recorded in the Article 57 database including information on Pharmacovigilance System Master File (PSMF) location and Qualified Person for Pharmacovigilance (QPPV);
- To further support data quality, from 4th November 2015 the EMA started to communicate the outcome of the quality assurance process via an additional XEVPRM XML Acknowledgement message (the so called "3rd Acknowledgement") to the MAH sender's organisation ID;
- On 17 December 2015 the EMA Management Board decided that the Article 57 database is functional for the purpose of notifying changes in QPPV and location of the PSMF. Therefore, from 1 February 2016, Type 1A variations should no longer be submitted for changes to QPPV details and PSMF location.

What's coming in 2016

- The reliance on the Article 57 database of medicinal products for QPPV details and PSMF location delivers an important simplification for the pharmaceutical industry whereby Type 1A variations no longer need to be submitted for QPPV details and PSMF location.



Database of Products (Article 57)

What MAHs need to do:

- Using the electronic XEVPRM format, marketing-authorisation holders need to:
  - Notify the Agency of any new marketing authorisations in the EEA within 15 calendar days from the date of authorisation (i.e. 15 calendar days from the date of notification of the granting of the marketing authorisation by the competent authority);
  - Notify to the Agency changes to the terms of the existing marketing authorisations following variation, transfer, renewal, suspension, revocation or withdrawal of the marketing authorisation as soon as possible and no later than 30 calendar days from the date of which the changes have been authorised;
  - Ensure that all products entries in the Article 57 database have up-to date information on QPPV and PSMF location.

PSUR repository

Need more information?

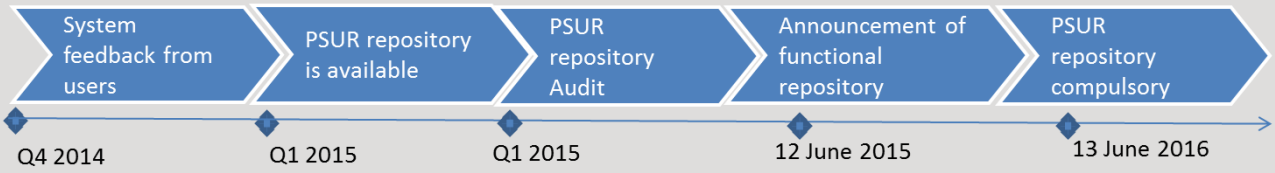
http://esubmission.ema.europa.eu/index.htm

Scope:

- Legal requirement for EMA to set up a repository for periodic safety update reports (PSURs) and their assessment reports;
- To allow centralised PSUR reporting and to enhance access to data and information, thereby supporting benefit risk assessments of medicines.

Highlights of 2015

- The Repository for PSURs and their assessment reports was launched by the European Medicines Agency on 26th January 2015;
- The initial pilot phase for centrally authorised products (CAPs) started in February and the extended pilot phase started in May to include nationally authorised products (NAP) in addition to CAPs;
- The independent audit of the repository was conducted from January to March 2015;
- Based on the positive recommendation of the Pharmacovigilance Risk Assessment Committee (PRAC), on 12 June 2015 the EMA Management Board announced that PSUR Repository has achieved its full functionality and the use of the repository in the European Union will become mandatory on 13 June 2016;
- From 1 September 2015, the use of the XML delivery file for all PSUR submissions to the EMA via the eSubmission Gateway and/or the Web Client has been mandatory;
- The new PSUR Repository version (v.1.04.00) was released in October 2015. This new release provides new functionalities including linking of the PSUSA procedure number with products which are in scope of the procedure allowing more direct searches and improved validation functionality.



PSUR repository

What's coming in 2016

- The release of the new PSUR Repository version (v.1.05.00) is scheduled for January 2016. The most important feature of this release will be the delivery of the post-audit functionalities in line with the plan approved by the EMA MB in June 2015. This consists of an Application Programming Interface (API) allowing an automated 2-way exchange between the NCAs' IT systems and the PSUR Repository;
- The release of the new PSUR Repository version (v.1.06.00) is scheduled in Q2 2016. This is an important release as it will be the last scheduled release prior to the mandatory use of the repository. The scope of this release is currently under finalisation in discussion wit the EU Network;
- The use of the PSUR repository in the European Union will become mandatory on 13 June 2016. From then onwards, industry stakeholders no longer need to submit PSURs to National Competent Authorities, the only requirement being the submission to the PSUR Repository.

What MAHs need to do:

- It is important for MAHs to consider the following points when planning a submission to the repository:
- Consider which business processes will have to be adapted to use the repository;
- Access the available updates and guidance on the use of the PSUR Repository and the eSubmissions Gateway/Web Client well in advance of any planned submission to the repository;
- Check that product data in the Article 57 database is correct prior to a planned submission;
- In addition to any submission to the PSUR Repository, MAHs for nationally authorised products (NAPs) are reminded that submissions to the relevant NCAs must continue until the use of the system becomes mandatory;
- Users should report any issues they may have with the system through the PSUR Repository mailbox: PSURrepository@ema.europa.eu

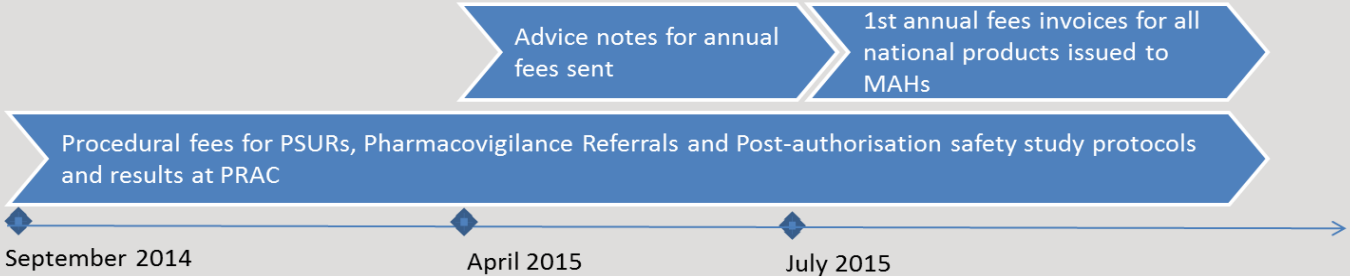
Pharmacovigilance Fees

Need more information?

Pharmacovigilance fees payable to the European Medicines Agency

Scope:

- The pharmacovigilance legislation foresees that pharmacovigilance activities conducted at EU level for medicinal products for human use should be financed by fees paid by MAHs. The pharmacovigilance fees regulation adopted in 2014 allows the EMA to collect these fees;
- The income will be used to remunerate national competent authorities (NCAs) of the EU for the scientific assessment carried out by the rapporteurs and to contribute to the pharmacovigilance-related costs of the Agency.
- Delivers functionality for online payment of fees and updating of account details.



Pharmacovigilance Fees

Highlights of 2015

- Procedural fees for pharmacovigilance were first invoiced in 2014;
- In March 2015, the EMA published an Explanatory Note on pharmacovigilance fees payable to the Agency and launched a dedicated Pharmacovigilance Fees webpage;
- Pharmacovigilance annual fee advice notes were sent to QPPVs on the 20th April 2015. This gave MAHs the opportunity to review their product information as recorded in the Article 57 database. The advice note contained the chargeable units line listing and provided further information on PhV fees;
- The EMA invoicing portal was launched in April 2015 (enabling MAHs to get instant access to their account, view and print invoices, raise invoice queries and make payments via SEPA direct debit) https://fees.ema.europa.eu/bd/public/zindex.jsp;
- The 1st pharmacovigilance annual fee invoices were issued in July 2015;
- On 21 July 2015 the Agency published a guidance document which outlines how 'chargeable units' for Pharmacovigilance fees are calculated.

What's coming in 2016

- Prior to issuing an invoice for procedure-based fees or the PhV annual fee, the Agency will provide MAHs with an opportunity to review their product information as recorded in the Article 57 database by supplying the qualified person for pharmacovigilance with an advice note. The advice note contains the chargeable units line listing and provides further information on PhV fees. For procedure-based fees, the advice note also contains regulatory background and electronic submission guidance. Please note that an advice note is supplied for the Annual Fee, PSURs and Referrals only – it is not applicable for PASS procedures (where the fee amount levied is not based on the number of 'chargeable units');
- The next pharmacovigilance annual fee invoices for the concerned MAHs will be issued in July 2016;
- In order to simplify the creation/change of Customer Accounts process for invoicing purposes, a new digital 'customer form' will soon be released.

What MAHs need to do:

- Please keep Article 57 up-to-date as 'chargeable units' will be derived based on medicinal product information held within the Article 57 database;
- If you have not yet registered for the EMA invoicing portal, please register by selecting "Register Now…" from the portal log-in page;
  NOTE: Your Customer Account Number and an Invoice Number will be required in order to register for the portal. Therefore, only existing customers of the EMA will be able to register at this stage.
  - If you are not an existing customer of EMA, please request a Customer Account Number by contacting the EMA via the following email address: accountsreceivable@ema.europa.eu;
- In order to benefit from a fee reduction or fee exemption, any marketing authorisation holder claiming to be a micro-, small- or medium-sized enterprise must complete the SME declaration form, found on the SME Office's "How to apply" page, and send it to sme@ema.europa.eu, at the latest, within 30 calendar days from the date of the invoice from the Agency. If a marketing authorisation holder already holds a valid SME status with the Agency, you are not required to re-submit this information;
- In case you need further information on receiving and paying invoices, please visit the Agency's How to Pay page;
- If you have a query related to an advice note, please visit the Pharmacovigilance fees: questions and answers page where a dedicated query form can be found.

Adverse Drug Reaction Reporting and Signal Management

Need more information?

EudraVigilance page (EMA public website)
Change management plan

Scope:

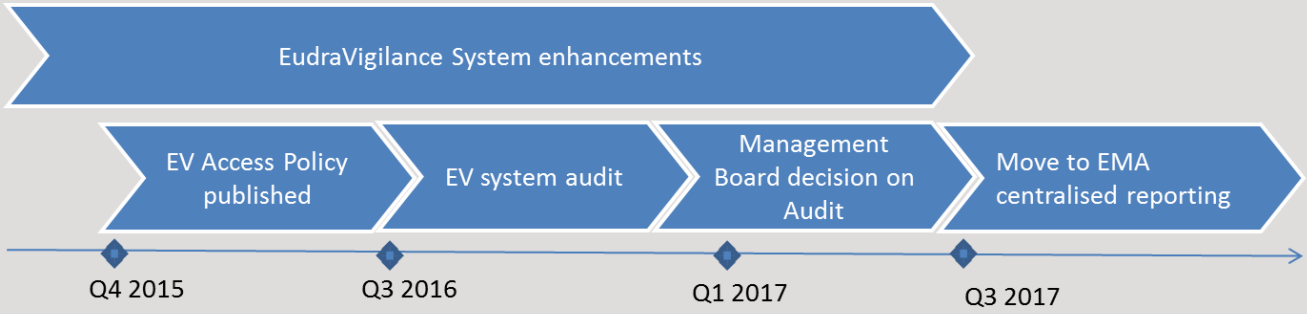
- Legal requirement for an enhanced adverse reaction collection and management system (EudraVigilance) that delivers better health protection through simplified reporting, better quality data and better searching, analysis and tracking functionalities. Enhanced detection of new or changing safety issues allows more rapid action to protect public health;
- Legal requirement for MAHs to monitor the EudraVigilance data to the extent to which they have access.

Highlights of 2015

- On 21st January 2015 the EMA published a guide to support the implementation of a new international standard, ICH E2B R3 for the electronic exchange of ICSRs within the EU Network to support the safety monitoring of medicines in the EU. The so-called ISO ICSR standard will improve the reporting of suspected side effects of medicines in Individual Case Safety Reports (ICSRs);
- On 27 October 2015, a dedicated EudraVigilance webpage was launched on the Agency's corporate website and included key documents for the operation of the future EV system, such as the EU Backwards Forwards Conversion Element Mapping spreadsheet, the draft EU Backwards Forwards Conversion Tool, the EU Reference Instance, the EU E2B(R3) Code Lists, the EU Example Instances, and the EudraVigilance Stakeholder Change Management Plan which outlines the IT & business changes to be made by users;
- Following public consultation the revised EudraVigilance Access Policy was adopted by the EMA Management Board on 17 December 2015. This foresees enhanced access for MAHs to adverse reactions reports from mid-2017. This also foresees the enhanced collaboration between EMA and the World Health Organization (WHO), as EMA will provide EU ICSRs to the WHO Uppsala Monitoring Centre directly from Eudravigilance. The revised access policy can be found here;
- Most of the IT development activities for the new EV system have now been completed.

What's coming in 2016

- In addition to the internal testing performed at the level of the EMA, external testing is planned for quarter two 2016 with some NCAs and MAHs. This pilot will be performed in advance of the Audit of the system. The organisations participating in the external pilot will be contacted several months in advance of the planned pilot period;
- Before the move to centralised reporting, the new EudraVigilance system has to undergo an independent audit. The EudraVigilance functionalities audit is scheduled to take place in 3rd quarter 2016;



Adverse Drug Reaction Reporting and Signal Management

What's coming in 2016 (continued)

- Once the Audit has been completed, all organisations with a registered Test EudraVigilance account will be able to start sending E2B(R3) Test files and will also be able to download E2B(R3) files based on test data. The go-live of the new external testing system (XCOMP) in mid-2016 will allow approximately one year for organisations to become familiar with the new system before it is implemented into production;
- The EudraVigilance project training and communication plans will be published in March 2016 and the list of the new EV system training dates, user manuals and training materials (mostly online) will be made available to support all users of the system in Q3-Q4 2016;
- To support the stakeholders in preparation for the new ISO standards and centralised reporting, by the end of 2016 the Agency will release the final version of several key technical documents. These will include the EU Backwards Forwards Conversion Element Mapping spreadsheet, final EU Backwards Forwards Conversion Tool, EU Reference Instance, EU E2B(R3) Code Lists, EU Example Instances;
- EMA Management Board will review the EudraVigilance system Audit outcome at its December meeting. If the functionalities agreed at the December 2014 audit have been delivered then the Management Board will announce the launch the new EV system and start of centralised reporting in 6 months, i.e. in mid 2017.

What MAHs need to do:

- It is suggested that all impacted organisations should prepare plans concerning the implementation of the new EudraVigilance system and the resulting changes that will occur to reporting, downloading and analysis of data;
- MAHs should consider participating in the public consultations on the revised Good Pharmacovigilance Practice (GVP) modules on adverse reaction reporting and signal management. These consultations are foreseen for quarter two 2016;
- Prepare for use of the new data format – ISO/ICH ICSR E2B(R3) – and simplified reporting to EV:
  - MAHs should plan to complete any testing of their existing systems at least 3 months prior to the new system going live in order to give time for any issues to be addressed.
- Engage with information and training events:
  - Training should be planned for MAH staff on the new business process and new IT systems 6 months prior to implementation in order to be ready once the new EudraVigilance system is implemented;
  - MAHs should consider developing a communication plan to ensure that the necessary information is circulated within their own organisation and with other organisations that they work with.

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