Clinical Safety & Pharmacovigilance
Regulatory Intelligence Review

Issue N°141 - January 2018

HIGHLIGHTS

- **EU ends infringement procedure against Roche**
  The European Commission has announced that it has closed the infringement procedure taken against Roche for failure to meet certain pharmacovigilance obligations after review of the remedial actions taken by the company.

- **EU suspends modified-release Paracetamol**
  The CMDh has endorsed a recommendation by the PRAC to suspend the marketing of modified- or prolonged-release products containing paracetamol due to the difficulty in managing overdose.

- **RSI in Clinical Trials: EU Guidance explained**
  This new Safety Observer blogpost takes a look at the issues raised by inspectors in the past and highlights the key messages brought by the new set of Q&As. It also presents the challenges brought by the EU requirements in the context of global Clinical Trials.

- **New PV guidance in Mexico**
  The Official Mexican Norm NOM-220-SSA1-2016 will come into effect on 15-Jan-2018 and several guidance documents have been published to support implementation.
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1. REGULATIONS, GUIDELINES AND OTHER STANDARDS

1.1 Newly Applicable Standards

1.1.1 EMA issues revised RMP, PSUR and PAM procedural advice (11-Dec-2017)

The EMA has published revisions to both the Pre- and Post-authorisation procedural advice for users of the centralised procedure in December. This includes a few new or revised Questions and Answers regarding PSURs and Post-authorisation measures. The most important changes concern the RMP section with updated information to support the implementation of the new RMP template for all RMP submissions from 31-Mar-2018, which impacts both the pre- and post-authorisation guidance.

- Link to EMA Procedural Advice (post-authorisation with track changes)
- Link to EMA Procedural Advice (pre-authorisation with track changes)

1.1.2 EMA issues revised ICH E2B(R3) implementation information (13-Dec-2017)

The new EudraVigilance System went live in November 2017, which brought the implementation of the ISO ICSR (E2B(R3)) format in Europe. The EMA has posted an updated version of the BFC conversion tool, which represents a component of the EU implementation guidance for ICH E2B(R3).

- Link to EudraVigilance Change Management Page

1.1.3 EMA issues ICH E17 guideline on Multi-Regional Clinical Trials (18-Dec-2017)

Further to its adoption at the ICH meeting in November 2017, the EMA has now published the ICH E17 guideline on the planning and design of multi-regional clinical trials (MRCTs), which is intended to facilitate the acceptability of MRCTs as part of global regulatory submissions. The guideline will come into effect in Europe on 14-Jun-2018 and includes some considerations for the safety reporting and the use of an independent data monitoring committee.

- Link to EMA Page

1.1.4 France updates guide on off-label prescriptions and use (22-Dec-2017)

The French Agency has issued a new version of its guide on the notification of off-label prescriptions and use by French MAHs/"Exploitants" to the ANSM. The main modifications concern the following:

- Addition of "off-label use" the guide title (it was already included in the core of the document)
- Specification that the off-label may refer to authorizations (such as marketing authorization, compassionate use), registrations or temporary recommendations of use (RTU)
- The company is required to specify whether the off-label use is a potential pharmacovigilance signal as a result of its risk analysis, which is included in the notification to the Agency
- Provision of a template for the cover page for the notification to the ANSM

- Link to the ANSM Guide (in French)

1.2 Developments to Watch

1.2.1 EMA Management Board discusses Brexit (15-Dec-2017)

The EMA has published the highlights of the December 2017 meeting of the EMA Management Board. This was the first meeting since the decision was made to relocate the Agency to Amsterdam by 30-Mar-2019. The EMA and the Dutch government have agreed a joint governance structure for the relocation project. The new EMA building will not be ready until November 2019 and the Dutch government will offer temporary premises to the Agency in the interim period.

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The Board was also informed that the Brexit preparedness business continuity plan will enter Phase 2 in January 2018 in order to free up further resources to prepare for the withdrawal of the UK from the EU. A methodology has also been defined for the redistribution of the work currently carried out by the MHRA and the EMA will communicate further detail shortly.

In the meantime, the information published on the Brexit Page of the EMA website has been reorganised with new subpages now available to present Industry Guidance and Information on the EMA relocation.

→ Link to EMA Press Release
→ Link to EMA Brexit Page

### 1.2.2 EMA starts integration of ISO IDMP information into application process (15-Dec-2017)

The EMA has issued updated information related to the implementation of the ISO IDMP standards, which are due to replace the current eXtended EudraVigilance Medicinal Product Dictionary (XEVMPD).

The updates are linked to the launch of the Referentials management service (RMS) and Organisations management service (OMS), which represent two of the four domains of Substance, Product, Organisation and Referential (SPOR) master data in pharmaceutical regulatory processes.

The OMS supplies master data on Marketing Authorisation Holders and Applicants to the eAF (electronic Application Form) since 15-Dec-2017. This integration of the OMS with the eAF enables applicants to select their organisation details rather than entering this information manually. A new guidance document on “Using referential and organisation data in the electronic application form (eAF)” is available.

→ Link to EMA Page on RMS & OMS

### 1.2.3 EMA issues minutes of last ISO IDMP Task Force meeting (20-Dec-2017)

The EMA has now published the minutes and the presentations from the last Task Force meeting on the implementation of the ISO IDMP standard, which is due to replace the current eXtended EudraVigilance Medicinal Product Dictionary (XEVMPD). The meeting took place on 20-Oct-2017 to discuss aspects of planning, development, implementation and maintenance of the ISO IDMP standards in the EU and to present the current status of the project. The topics covered at this meeting include the OMS integration with eAF and the OMS & RMS Industry on-boarding, amongst others.

→ Link to EMA Page on IDMP
→ Direct link to EMA Meeting Page

### 1.3 Beyond the Scope of Safety Observer

This section includes announcements collected through our secondary sources, which originate from authorities that we do not monitor systematically. For more information, please check our Q&As.

#### 1.3.1 Mexico issues new Pharmacovigilance Guidance documents (28-Nov-2017)

As reported at the time, the Official Mexican Norm NOM-220-SSA1-2016 was published in the Official Journal on 19-Jul-2017. This document specifies the requirements for Pharmacovigilance in Mexico in replacement of the previous version from 2013. Although significant differences still exist (e.g. ICSR reporting timelines), this new version brings Mexican requirements closer to international standards.

The new requirements will come into effect on 15-Jan-2018 and several guidance documents have now been published to support their implementation. All documents are available on the same page of the Cofepris Website, in Spanish only. Separate guidance documents cover the aspects related to the PSUR, the RMP, the notification of relevant reports, and Pharmacovigilance in Clinical Trials.

→ Link to NOM-220-SSA1-2016 (in Spanish)
→ Link to Cofepris PV Page (in Spanish)
1.3.2 Australia issues new Pharmacovigilance guidance for Biologicals (13-Dec-2017)

Following the consultation initiated in October 2016, the Australian TGA has now issued its final guidance document on biovigilance responsibilities of sponsors of biologicals. As a reminder, “Sponsor” refers to the holder of the registration of a medicine for marketing in Australia.

The TGA RMP guidance has also been revised concomitantly to include content relevant for biologicals.

→ Link to TGA Biovigilance Guidance Page
→ Link to TGA RMP Guidance Page

1.3.3 Canada issues consultation results on mandatory ADR reporting (22-Dec-2017)

The Protecting Canadians from Unsafe Drugs Act (Vanessa’s Law) makes several amendments to applicable regulations and includes a new requirement for certain health care institutions to provide Health Canada with information on serious Adverse Drug Reactions and Medical Device Incidents.

As we reported at the time, Health Canada launched a consultation in June 2017 on various aspects of this mandatory reporting. This would apply to all hospitals that provide acute care services, who would be required to provide Health Canada with information on Serious Unexpected ADRs within 30 days.

A summary of the feedback received on the Consultation Paper has now been published by Health Canada, which will inform the development of draft regulations and relevant guidance documents.

→ Link to Health Canada Consultation Page
→ Link to Consultation results

1.4 The Safety Observer Tracker

This section includes a cumulative list of the future implementation and consultation deadlines. For your convenience, a link is provided and we also specify the issue where the corresponding article can be found.

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<th>When?</th>
<th>What?</th>
<th>Issue</th>
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<td>Deadline of CMDh consultation on PSUSA Follow-Up Procedure (Link)</td>
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<td>Revised EU Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials comes into effect (Link)</td>
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<td>Legal requirement to monitor EudraVigilance data starts for MAHs with active substances included in the list of medicines under additional monitoring (Link)</td>
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<td>28-Feb-2018</td>
<td>Deadline for stakeholders to send contributions to EMA regarding initiatives on electronic/digital formats for Medicines Product Information (Link)</td>
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2. PRODUCT SAFETY ANNOUNCEMENTS

2.1 Paracetamol (a.k.a. acetaminophen)

Modified-release products to be suspended from EU market (15-Dec-2017)

The CMDh has now endorsed a recommendation by the PRAC to suspend the marketing of modified- or prolonged-release products containing paracetamol, alone or combined with the opioid medicine tramadol, due to the difficulty in managing overdose.

The PRAC concluded that practical measures to reduce the risk to patients had not been identified and it was not possible to agree a feasible and standardised way to adapt the management of overdose across the EU to cover both immediate- and modified-release paracetamol products.

The products will remain suspended unless MAHs can provide evidence of appropriate and practical measures to help prevent overdose with these products and adequately reduce its risks. Because the CMDh decision was agreed by majority vote, it will now be sent to the European Commission for a final legally binding decision.

→ Link to EMA Press Release

2.2 Mycophenolate

EMA updates recommendations for contraception in men and women (15-Dec-2017)

The PRAC has now completed the review of mycophenolate medicines as part of the PSUR assessment for this immunosuppressant, which is approved for use in the prevention of transplanted organ rejection. The PRAC concluded that current evidence does not indicate a risk of malformations or miscarriages following exposure of the father even though the risk of genotoxicity cannot be completely ruled out.

Mycophenolate medicines are known to increase the risk of malformations and miscarriages during pregnancy if the fetus is exposed and the existing recommendations for female patients remain unchanged. On the other hand, the previous recommendation that male patients should use condoms in addition to their female partners using a highly effective method of contraception has now been removed.

The updated recommendations have been adopted by the CHMP and a corresponding letter will be sent out to healthcare professionals in the EU.

→ Link to EMA Press Release

2.3 Gadolinium-based contrast agents (GBCAs)

FDA requires multiple safety measures concerning gadolinium retention (19-Dec-2017)

As we reported in our previous issues, the Medical Imaging Drugs Advisory Committee met on 08-Sep-2017 to discuss the potential risk of gadolinium retention in the brain and other organs in patients receiving gadolinium-based contrast agents for magnetic resonance clinical imaging procedures.

This issue led the EMA to recommend the suspension of the Marketing Authorisations for 3 linear gadolinium products in July 2017. Until now the FDA considered that no restrictions were necessary in absence of a direct link between Gadolinium retention and safety risk in patients with normal kidney function.

After additional review and consultation with the Advisory Committee, the FDA is now requiring several actions to alert health care professionals and patients about gadolinium retention. These include a new class warning and a new patient Medication Guide. Manufacturers are also required to conduct additional studies to further assess the safety of these contrast agents.

→ Link to FDA MedWatch alert
→ Link to Medical Imaging Drugs Advisory Committee Page
2.4 Long-Acting Beta Agonists (LABAs) and Inhaled Corticosteroids (ICS)

FDA removes Boxed Warning about Asthma-related Death (20-Dec-2017)

The FDA has issued a Drug Safety Communication to announce that the Boxed Warning about asthma-related death has been removed from the drug labels of medicines that contain both an ICS and LABA. This follows the review of four large clinical safety trials showing that treating asthma with LABAs in combination with ICS does not result in significantly more serious asthma-related side effects than treatment with ICS alone. The labels of the concerned products have been updated to reflect this new information, along with additional efficacy information resulting from the same trials.

→ Link to FDA MedWatch alert

3. DEAR DOCTOR LETTERS AND SAFETY NEWSLETTERS

3.1 ANSM Dear Doctor Letters

Dear Doctor Letters sent in December 2017 are now available on the French Agency’s website (all in French). Letters associated to safety concerns include the following:

- Haldol and Haldol Decanoas: update of product information
- Radium 223 dichloride (Xofigo): increase of death and fracture risks in a randomized clinical trial
- Injectable Suxamethonium: restriction of indication
- Mexiletine AP-HP 200 mg: update of contraindications

→ Link to ANSM Page (in French)

3.2 MHRA Dear Doctor Letters

The letters sent by the MHRA are presented in the subsequent issue of the “Drug Safety Update” bulletin and concomitantly posted on the Agency’s website. The letters issued in November 2017 include the following:

- Eluxadoline (Truberzi▼): risk of pancreatitis and sphincter of Oddi spasm
- Fingolimod (Gilenya▼): contraindications in patients with cardiac conditions
- Bleo-Kyowa (bleomycin sulphate): use 5-micron filter during IV infusion or pre-injection

→ Link to MHRA Page

3.3 New issue of MHRA “Drug Safety Update”

The December issue of Drug Safety Update was published on 14-Dec-2017. It includes the following topics:

- Gadolinium-containing contrast agents: removal of Omniscan and iv Magnevist, restrictions to the use of other linear agents
- Cladribine (Litak, Leustat) for leukaemia: reports of progressive multifocal encephalopathy (PML)
- Radium-223 dichloride (Xofigo▼): do not use in combination with abiraterone and prednisone/prednisolone, following clinical trial signal of increased risk of death and fractures
- Eluxadoline (Truberzi▼): risk of pancreatitis; do not use in patients who have undergone cholecystectomy or in those with biliary disorders
- Fingolimod (Gilenya▼): new contraindications in relation to cardiac risk
- Fingolimod (Gilenya▼): updated advice about risk of cancers and serious infections

→ Link to Drug Safety Update (December 2017)
3.4 **New issue of Canadian “Health Product InfoWatch”**

The new issue of “Health Product InfoWatch” has been published, which provides an overview of safety labelling updates and safety reviews from the previous month.

The December issue was published by Health Canada on 20-Dec-2017. The monthly recap of safety reviews covers several products including Fluconazole 150 mg. The newsletter also describes Product Information changes for Mifegymiso (mifepristone/misoprostol), Eprex (epoetin alfa) and Gilenya (fingolimod).

→ Link to Newsletter

3.5 **New issue of WHO Pharmaceuticals Newsletter**

The latest edition of the WHO Pharmaceuticals Newsletter (N°6, 2017) is now available. Prepared in collaboration with the Uppsala Monitoring Center, it includes a section on Regulatory Matters and Safety of Medicines. This issue also includes a brief report on the 40th Annual Meeting of Representatives of the National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring.

As usual, the newsletter presents signals identified in the WHO VigiBase and the corresponding responses from MAHs, where available:

- Natalizumab and rapidly evolving central nervous system lymphoma

→ Link to WHO Pharmaceuticals Newsletter (N°6, 2017)

3.6 **New FDA Drug Safety Podcasts**

The FDA Drug Safety Podcasts provide emerging safety information about drugs in conjunction with the release of Public Health Advisories and other drug safety issues. Both Podcasts and Transcripts are posted on the FDA website and the following communications have been recently added:

- FDA warns that gadolinium-based contrast agents are retained in the body; requires new class warnings
- FDA review finds no significant increase in risk of serious asthma outcomes with long-acting beta agonists (LABAs) used in combination with inhaled corticosteroids (ICS)

→ Link to FDA Page

4. **OTHER PUBLICATIONS BY REGULATORY AGENCIES**

4.1 **US Food and Drug Administration (FDA)**

4.1.1 **FDA provides REMS Integration Initiative Overview**

The FDA has published the material used at a recent webinar held on 04-Dec-2017. This includes the slides supporting the webinar and a video recording of the event where the REMS Integration Initiative was presented, including the new REMS document template.

→ Link to FDA REMS Integration Initiative Page
→ Direct link to Webinar Slides
→ Direct link to Webinar Video Recording
4.1.2 FDA issues new CDER OSE Presentation Material

The FDA has published the presentation material used at the FDA/CMS Summit on 05-Dec-2017. This includes an update on 2017 activities and achievements at the CDER Office of Surveillance and Epidemiology. The presentation includes metrics on ADR reporting and highlights the introduction of the new FAERS Public Dashboard at the end of September 2017. The topics covered also include the Sentinel initiative and the Risk Evaluation and Mitigation Strategies (REMS).

→ Link to FDA Presentation Material

4.1.3 FDA announces Workshop on “Safety Assessment for IND Safety Reporting”

The FDA has announced a new public workshop entitled “Safety Assessment for IND Safety Reporting”, which refers to the draft guidance of the same name issued in December 2015. In response to comments received, the purpose of this meeting is to discuss the draft guidance and its implications in order to finalize it.

This draft guidance is a follow-on to the guidance entitled “Safety Reporting Requirements for INDs and BA/BE Studies” issued in December 2012. The draft document provides further guidance on the composition and role of the Safety Assessment Committee, aggregate analyses for comparison of adverse event rates across treatment groups, planned unblinding of safety data, reporting thresholds for IND safety reporting, and the development of a safety surveillance plan.

This event was previously announced and a correction was issued to reflect that the date of the meeting has changed. This public workshop is now scheduled to take place on 08-Mar-2018 in Washington, DC.

→ Link to Federal Register Notice (Original Notice dated 27-Nov-2017)
→ Link to Federal Register Notice (Correction dated 14-Dec-2017)

4.1.4 FDA announces 10th Annual Sentinel Initiative Public Workshop

As reported previously, the FDA has announced that the Tenth Annual Sentinel Initiative Public Workshop will be split in two separate events taking place on 07 and 08-Feb-2018, in different venues and with independent registration systems.

Day 1 will include an update on the Sentinel Initiative, key safety surveillance activities and emerging uses of the Sentinel System. In addition, panellists will discuss opportunities to modernize the system and expand its analytic capabilities.

Day 2 will actually be a training session, in continuity with the prior public training conducted by the FDA in July 2017 to address more advanced topics, including Sentinel’s inferential analytic capabilities and methods of identifying unexpected safety concerns.

A New CDER Conversation has also been published where the Deputy Director of the Office of Surveillance and Epidemiology at CDER describes the Sentinel System and how it can be used.

→ Link to FDA Sentinel Event Page
→ Link to CDER Conversation: The FDA’s Sentinel Initiative

4.2 European Medicines Agency (EMA)

4.2.1 EMA issues new QPPV Update

A new issue of “QPPV Update” has been published, which provides a broad review of the EU Pharmacovigilance arrangements on a periodic basis. This issue looks back at the achievements in relation to the implementation of the new and improved version of EudraVigilance, which was launched on 22-Nov-2017.

It also reviews other relevant activities including the EMA’s first public hearing in the context of the safety review of Valproate, the PSUR roadmap and the Patient Registries Initiative.

→ Link to EMA QPPV Update (issue 3 - 2017)
4.2.2 PRAC recommendations on Safety Signals

The EMA routinely issues the PRAC recommendations resulting from the assessment of safety signals. MAHs are legally obliged to monitor this information to keep informed about the PRAC recommendations concerning their products, which may require the submission of a Safety Variation.

The list of signals discussed at the PRAC meeting of 27 to 30-Nov-2017 was published on 04-Jan-2018. It includes a recommendation to update the product information for the following signals:

- Insulin (pre-filled pens and cartridges) – Potential increased risk of medication error associated with withdrawing insulin from pre-filled pens and cartridges, leading to dysglycaemia
- Tofacitinib – Angioedema

In complement, the EMA has published the corresponding document entitled: “New product information wording – Extracts from PRAC recommendations on signals”, which is available in all EU languages.

The list of all safety signals discussed at the PRAC since September 2012 has been updated accordingly. It includes links to the corresponding PRAC minutes and specifies whether a variation was recommended.

→ Link to EMA Page

4.2.3 EMA issues “Meeting Highlights” of last CHMP Meeting

The highlights of the December meeting of the CHMP have been published. As communicated separately (see Section 2), the Committee concluded that current evidence does not indicate a risk of malformations or miscarriages during pregnancy when the father has taken mycophenolate medicines. The recommendations for contraception have been updated accordingly.

→ Link to CHMP Meeting Highlights (11 to 14-Dec-2017)

4.2.4 EMA stakeholder platform on the operation of EU Pharmacovigilance

The EMA held the Twelfth platform meeting on 24-Nov-2017. The Meeting Agenda included the launch of the New EudraVigilance system and a presentation of the Signal Management GVP IX pilot. The discussions also covered the PSUR Roadmap, PASS studies and Brexit. The minutes and the presentations used during this meeting are now available on the EMA website.

→ Link to EMA Meeting Page (12th industry stakeholder platform)

4.2.5 EMA issues updated EURD list

The EMA has published an updated EURD list, which was last revised on 19-Dec-2017. It provides the EU Reference Dates, frequencies for submission of PSURs and data lock points for a list of active substances and combinations including those contained exclusively in nationally authorised medicines.

The changes to the EURD list are highlighted and the list should be filtered by cell colour to identify all revisions. Please note that as specified in the cover note, the “Publication Date” is not revised for all types of amendments and this date cannot be used to filter all amended substances in Excel.

→ Link to EMA PSUR Page

4.2.6 CMDh updates Cover Note to the list of safety concerns described in approved RMPs

The European CMDh (Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human) has published an updated Cover Note to the list that presents safety concerns of approved Risk Management Plans (RMPs) per product/active substance, which is intended to promote the harmonisation of RMPs for the same active substances.

The Cover Note has been revised to clarify that MAHs may provide the list of safety concerns of approved RMPs that are not included in the published list, even when this is not actively requested by authorities.

→ Link to CMDh Page
→ Direct link to Cover Note (track version)
4.2.7 EMA issues new information on outcome of PSUR Assessment for NAPs

Following the implementation of the PSURs Single Assessments (PSUSAs) for active substances contained only in Nationally Authorised Products (NAPs), the results of these procedures may require a safety variation. In such case, the information published by the EMA includes the scientific conclusions, a timetable for implementation, and the wording of the product information.

Pharmaceutical companies are advised to regularly monitor this information to check for outcomes relevant to their products in order to submit the corresponding variations.

The outcomes of PSUSAs have been published or updated since our previous issue and a variation is required for the following active substances:

- Chlormadinone
- Ipratropium/salbutamol
- Promestriene (cream and vaginal capsules)
- Ibuprofen, ibuprofen lysine (not indicated in ductus arteriosus)
- Mefloquine
- Fluticasone propionate
- Sodium iodide (131I)

→ Link to PSUSAs Search Page

4.2.8 CMDh issues new PSUR Assessment Reports for NAPs

In line with the Best Practice Guide to facilitate European Work Sharing of PSURs for Nationally Authorised Products (NAPs) during the transition period, the conclusions of the Assessment Report are published on the CMDh website. Following the implementation of the Single Assessment Procedure for NAPs, this will be gradually replaced by the publication on the EMA website started in July 2015.

The MAHs of products for which there are no routine PSUR submission requirements have to take account of final assessment conclusions and submit a variation within 90 days, as necessary.

The summary of the PSUR Assessment Reports for landiolol, eprosartan mesylate and eprosartan+hydrochlorothiazide were published in December 2017.

→ Link to Summaries of Assessment Reports

4.2.9 EMA provides updated guidance on submission of medicines information

The EMA has issued updated material related to the electronic submission of information on authorised medicines, as required under Article 57(2) of the 2010 pharmacovigilance legislation. New versions of the Controlled Vocabulary have been released for Substances and Organisations.

→ Link to Data Submission Guidance Page

4.2.10 Pharmacovigilance Fees expected to raise in January 2018

The EMA has issued a News Release to announce that Pharmacovigilance fees are expected to increase by 1.4% from January 2018. Additional detail will be published shortly when the amended regulation is made effective to reflect the 2015 and 2016 inflation rates.

→ Link to EMA News Release

4.2.11 EMA issues updated EudraVigilance Release Notes

Further to the launch of the new and improved version of EudraVigilance on 22-Nov-2017, the EMA has published revised versions of the release notes for the EudraVigilance web application (EVWEB), and for the European database of suspected adverse drug reaction reports' website (www.adrreports.eu).

Both these documents are available in the “User guidance and release notes” section of the EudraVigilance Training and Support Page of the EMA website.

→ Link to EudraVigilance Training and Support Page
4.3 UK Agency (MHRA)

4.3.1 MHRA enters partnership for safety monitoring in low and middle-income countries

The MHRA has announced a new partnership with the Bill & Melinda Gates Foundation and the World Health Organisation to improve the safety monitoring of medicines in low and middle-income countries (LMIC). WHO and the Gates Foundation have launched “Project Smart Safety Surveillance” (a.k.a. Project 3-S) to help LMICs identify, assess, and adequately manage the risks associated with new products. MHRA will be joining this initiative to bring regulatory expertise over a 3-year period.

→ Link to MHRA Press Release

4.4 French Agency (ANSM)

4.4.1 Commissions/Committees in relation with Pharmacovigilance

The Pharmacovigilance Committee has issued the minutes of several meetings. At the meeting of 04-Jul-2017, the following topics were discussed:

- Entyvio (vedolizumab): national monitoring to be continued (limited to serious adverse reactions)
- Coxibs: national monitoring to be continued for etoricoxib 30 and 60 mg (cardiovascular risks) and to be started for etoricoxib 90 and 120 mg
- Orencia (abatacept): end of national monitoring
- Docetaxel et Paclitaxel: impact analysis of the measures and recommendations to be performed

At the meeting of 12-Sep-2017, the following topics were discussed:

- Jakavi (ruxolitinib): end of national monitoring
- IV Amoxicillin and risk of crystalluria and renal impairment: harmonisation of SmPCs, implementation of a DHPC and end of national monitoring with impact study on the measures taken

→ Link to ANSM PV Committee minutes – 04-Jul-2017 (in French)
→ Link to ANSM PV Committee minutes – 12-Sep-2017 (in French)

The consultative Commission in charge of the surveillance of the risk/benefit profile of medicinal products has issued the minutes of its 11-Apr-2017 meeting where the national assessment of the risk/benefit balance of the following products was discussed:

- Théralène
- Ginkor fort
- Suxamethonium-containing products and update of Product Information

The following pharmacovigilance-related topics were also discussed for advice:

- Oral vasoconstrictor: serious cardiovascular and neurological adverse reactions
- Mycophenolate: off-label use and teratogenic risk

→ Link to ANSM R/B Commission Minutes – 11-Apr-2017 (in French)

4.4.2 ANSM issues results of study on the impact of its Ifosfamide Decision

In June 2016, the French Agency decided to reduce the shelf-life of Ifosfamide EG 40 mg/ml due to an increase in the reporting of pediatric encephalopathies after 7 months of preservation. The study on the impact of the measure shows a decrease in the sales of the product and the analysis of the encephalopathy cases is inconclusive due to their small number. Another study after 2 years is recommended to assess the impact of the measure on the incidence of pediatric encephalopathies.

→ Link to ANSM report (in French)
4.4.3 ANSM provides update on PRAC/CHMP/CMDh meetings

Following the PRAC meeting of October 2017, the ANSM has issued a summary of the PRAC decision regarding hydroxyethyl-starch containing products. The document does not include any ANSM recommendation.

→ Link to ANSM release – October 2017 PRAC (in French)

5. QUALITY ASSURANCE, INSPECTIONS AND AUDITS

5.1 European Commission closes infringement procedure against Roche

The European Commission has announced that it has closed the infringement procedure taken against Roche for failure to meet certain pharmacovigilance obligations. This decision follows the review of available evidence regarding the effectiveness of remedial actions taken by the company.

This is the end of a long process that started with an initial inquiry in October 2012 after a pharmacovigilance inspection performed by the MHRA. The results of this inspection suggested that 80,000 case reports, including more than 15,000 deaths had been collected through Patient Support Programmes in the USA but had not been evaluated to check if they qualified for reporting to EU authorities. This information was subsequently processed and submitted by Roche but its evaluation by the EMA did not identify any new safety concern.

This is the first and only case initiated until now under the Penalty Regulation, whereby the European Commission may impose financial penalties on Marketing Authorisation Holders, which can reach up to 5 % of the company’s annual EU turnover under applicable rules.

→ Link to EMA News Release
→ Direct link to European Commission News Release

5.2 Swissmedic implements new arrangements for foreign inspections

Further to the revision of the underlying legislation, the Swiss Agency has published a new Information Sheet describing the procedure for foreign governmental inspections in Switzerland. These arrangements came into force on 01-Jan-2018 and apply to all types of inspections, including GCP and Pharmacovigilance.

Foreign inspections are no longer subject to authorisation by Swissmedic but need to be notified at least 30 days before the date of the inspection agreed with the company to be inspected, which rules out the possibility to perform unannounced inspections. The foreign inspectorate must also agree to provide a copy of the inspection report.

→ Link to Swissmedic Cross-border inspections Page
→ Direct link to Information sheet

6. DRUG SAFETY AND LIABILITY RISK

6.1 Sanofi and Depakine

Sanofi convicted on appeal to compensate a victim

The pharmaceutical group was sentenced to pay 3 million Euros to the family and CPAM (social security). The Orleans Court of Appeal confirmed for the first time the responsibility of Sanofi in the malformation of a child whose mother took the antiepileptic Depakine. Sanofi announced its intention to appeal this decision.

→ Link to Liberation article (in French)
→ Link to Doctissimo article (in French)
7. OTHER NEWS AND RESOURCES

7.1 RSI in Clinical Trials: The New EU Guidance explained
As presented in our December 2017 issue, the EU Heads of Medicines Agencies (HMA) have published a new version of their guidance document entitled “Questions and Answers – Reference Safety Information (RSI)”. The revised document brings updated guidance to describe the expectations for the RSI. This topic has been at the top of the EU Inspectorate’s agenda for some time and this has led to a number of Inspection Findings. In this new Safety Observer blogpost, we take a step back to explain the issues raised by inspectors in the past and to highlight the key messages brought by the new set of Q&As. We also discuss the challenges brought by the EU requirements in the context of global Clinical Trials.

The Safety Observer blog is available publicly and you are welcome to share this post with your contacts and colleagues. It is also possible to post comments if you would like to bring your views to the discussion.

→ Link to the Safety Observer blogpost

7.2 New ENCePP Plenary Meeting
ENCePP has published the material from its last Plenary Meeting, which took place on 21-Nov-2017. The list of topics included Models for multi-database studies, Benefit-Risk Assessment, the EMA Patient registries initiative and Brexit. The information available includes the Meeting Report and the Presentations.

→ Link to ENCePP Page

7.3 Health Canada provides updated Adverse Reaction Online Database

→ Link to Health Canada Page

7.4 New issue of CIOMS Newsletter
Amongst other topics, the December 2017 Newsletter (Issue 20) provides an update about various on-going activities, including the CIOMS Working Group on Drug Induced Liver Injury and the WHO Global Vaccine Safety Initiative (GVSI).

→ Link to CIOMS Newsletter

7.5 New issue of Uppsala Reports
Uppsala Reports 77 – December 2017 is now available, which contains a wide range of news from around the world of pharmacovigilance. It includes a series of articles on various topics including a presentation of the new VigiFlow database and the new UMC distance learning platform. It also includes articles on duplicate detection and the use of Pharmacogenomics in Pharmacovigilance, amongst others.

→ Link to Uppsala Reports
8. CONFERENCES AND TRAINING EVENTS

EMA/DIA Events
→ The NEW EudraVigilance System and electronic reporting in the ISO/ICH E2B(R3) format
   3 day-training course (see agenda for venues and dates)
→ Extended EudraVigilance Medicinal Product Dictionary (XEVMPD) Training Course
   2 day-training course (see agenda for venues and dates)

DIA Events
→ Pharmacovigilance and Risk Management Strategies
   January 22 – 24 in Washington DC, USA
→ MHRA/DIA Excellence in Pharmacovigilance
   February 05 – 09 in London, UK
→ EU-RMP Creation
   February 26 – 27 in Prague, Czech Republic
→ How to Prepare for Pharmacovigilance Audits and Inspections
   March 12 – 13 in Berlin, Germany
→ Advanced Workshop: QPPV Tool Box – Your Key to Success
   March 12 – 13 in Berlin, Germany
→ Signal Management in Pharmacovigilance
   March 14 – 15 in Berlin, Germany

DSRU Events
→ GVP Module V Training Day (Risk Management Systems)
   January 18 in London, UK
→ Monitoring Safety in Clinical Trials and Drug Development
   February 07 – 08 in London, UK
→ Back to Basics in Pharmacovigilance
   February 21 – 22 in Fareham, UK
→ EU Regulations and Guidelines for Pharmacovigilance
   March 21 – 22 in London, UK

Other Events
→ Medicines for Europe (previously EGA) – 11th Pharmacovigilance Conference
   January 24 in London, UK
→ IFIS – PV roles and responsibilities of the Chief Pharmaceutical Officer (event in French)
   January 25 in Paris, France
→ Virtue Insight – 15th Pharmacovigilance 2018
   February 21 – 22 in London, UK
→ IQPC – Pharmacovigilance Summit 2018
   February 26 – 28 in Boston MA, USA
→ IFIS – Pharmacovigilance of clinical trials (event in French)
   March 13 in Paris, France
→ IFIS – Pharmacovigilance: Role, missions and responsibilities (event in French)
   March 15 – 16 and April 06 (3 days) in Paris, France
→ IFIS – Pharmacovigilance of Clinical Trials (event in French)
   March 22 in Paris, France
→ RQA – Practical Pharmacovigilance Auditing
   March 13 – 15 in Cambridge, UK