HIGHLIGHTS

- **EMA sets launch date for New EudraVigilance**
  The EMA has officially announced that the new EudraVigilance System will go live on 22-Nov-2017, which will support the central ICSR reporting and the use of the E2B(R3) format. MAHs will be granted access to the EudraVigilance Data Analysis System (EVDAS) for Signal Detection purposes and the registration process has now been initiated. A number of training events have been announced by the EMA to support all users through these important changes.

- **EU Authorities clarify Brexit implications**
  Following the notice to MAHs published in early May to remind MAHs of their legal obligations, a new Questions-and-Answers document has been published that provides further detail regarding the impact of Brexit in multiple areas, including the location of the EU QPPV and PSMF.

- **Regulatory Action over PV System failures**
  The French Agency decided to suspend clinical trials sponsored by AB Science until an independent audit demonstrates that the company has addressed issues identified during multiple inspections. The FDA has also issued a Warning Letters to Vertical Pharmaceuticals over Safety Reporting deficiencies.

- **FDA requests removal of Opana ER**
  The US FDA has requested Endo Pharmaceuticals to remove the product from the market. This is the first time the FDA takes steps to remove an opioid pain medication due to the public health consequences of abuse.
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1. REGULATIONS, GUIDELINES AND OTHER STANDARDS

1.1 Newly Applicable Standards

1.1.1 France issues updated Standard for Certification of Sales Representatives (13-Apr-2017)

The French Health Authority HAS (Haute Autorité de Santé) has issued a new version of the Certification Standard linked to the Charter for Promotional Information, which is intended to support the quality of information delivered to Healthcare Professionals and promote the safe use of medicines.

From now on the certification procedure includes 2 parts: one for the "Exploitant" (first published in 2016) and one for contractors.

→ Link to the Certification Standard on the HAS website (in French)
→ Link to the decision 2017.0044/DC/DEMESP – French Official Journal (in French)

1.1.2 France issue new Decree on harmonisation of vigilances (09-May-2017)

The Decree 2017-885 was published on 09-May-2017 and the article 5 modifies several articles of the Public Health Code with regards to the national organisation of pharmacovigilance. It however does not impact the pharmacovigilance responsibilities of marketing authorisation holders.

→ Link to Decree 2017-885 (in French)

1.1.3 EMA issues revised procedural advice (16-May-2017)

The EMA has published a revised version of the "Post-authorisation procedural advice for users of the centralised procedure", which includes updates in relation to Post-Authorisation Safety Studies (PASS) and more specifically the use of Scientific Advice for PASS (see section 13.9).

→ Direct link to EMA Procedural Advice (post-authorisation with track changes)

1.1.4 France updates requirements for Clinical Trial Safety Reporting (18-May-2017)

The ANSM has issued a revised version of the document "immediate safety reporting". This revision clarifies the requirements applicable to clinical trials on healthy volunteers: the reporting to ANSM of SUSARs with a seriousness criteria other than death and life-threatening is immediate (the 15-day deadline no longer applies to clinical trials on healthy volunteers).

→ Link to ANSM synthesis "immediate safety reporting" (in French)

1.2 Developments to Watch

1.2.1 EMA issues report on pilot to engage patients in benefit-risk assessment (08-May-2017)

The EMA has published the final report on the experience gained during its pilot project to involve patients in the assessment of the benefits and risks of medicines in the CHMP, which concludes that patients should continue to be invited when their input could be valuable to the assessment.

The pilot ran from September 2014 to December 2016 and patients participated in discussions to bring their perspective in the assessment for a number of medicines. Following the positive outcome of the pilot, it was agreed to use additional methods for regular involvement including teleconference or written consultations.

→ Link to EMA News Release
→ Direct link to EMA Outcome Report
1.2.2 EMA initiates registration process for EudraVigilance Data Analysis System (17-May-2017)

The EMA has published guidance on how to request access to the EudraVigilance Data Analysis System (EVDAS), which will become available to MAHs from November 2017. The EMA expects a large volume of registrations and MAHs should register from 01-Jun-2017 at allocated time slots.

The EU QPPV can appoint up to five EVDAS users at headquarter level. A trusted deputy of the QPPV can also register these users on their behalf. The EMA will communicate the exact date it will activate MAH User Accounts in Q3 2017, which will allow users to access EVDAS and related reports including the electronic Reaction Monitoring Reports (e-RMRs).

In addition, new versions of the other guidance documents for EudraVigilance registration have been published, including EudraVigilance registration documents, delegating the registration process, and Change of QPPV/Responsible Person for EudraVigilance.

→ Link to EudraVigilance Registration Page

1.2.3 EMA sets launch date for the New EudraVigilance System (22-May-2017)

The EMA has now officially announced that the new EudraVigilance System will go live on 22-Nov-2017. Following an independent audit and a favourable recommendation from the PRAC, the EMA’s Management Board confirmed that the database has achieved full functionality.

As a reminder, the new system will support the simplified centralised ICSR reporting and the mandatory reporting of non-serious cases from the EEA. It will also support the use of the ISO ICSR (E2B(R3)) format and MAHs will be granted access to the database for Signal Detection purposes through the EudraVigilance Data Analysis System (EVDAS).

All users of the system, including MAHs and Sponsors of Clinical Trials, have to make final preparations to ensure that their processes and systems are ready. The EMA will provide support through targeted e-learning and face-to-face trainings, webinars and information days, and users will be able to access a test environment as of 26-Jun-2017.

→ Link to EMA News Release

1.2.4 EMA updates information on Training to new EudraVigilance System (22-May-2017)

Following the confirmation of the go-live date for the new EudraVigilance System, the EMA has updated the EudraVigilance Training Page with the details of the upcoming Face-to-Face training courses on the new EudraVigilance system, Support Webinars and Information Days until the end of 2017.

The Training Page also includes all e-learning modules available to prepare for the new EudraVigilance system, including the implementation of ISO ICSR/ICH E2B(R3) (PhV-M2) and EVDAS training (EV-M5).

→ Link to EudraVigilance Training Page

1.2.5 EMA issues Draft Guideline on Serious Breaches in Clinical Trials (23-May-2017)

The EMA has released for consultation a draft guideline for the notification of serious breaches of Regulation (EU) No 536/2014 or the clinical trial protocol, which outlines the practical arrangements for the notification of serious breaches in clinical trials in Europe. It provides advice and examples on what should and what should not be classified as a serious breach, including in the area of SAE Reporting.

Comments on this document are expected by 22-Aug-2017.

→ Link to EMA Draft Guideline
1.2.6 EU Authorities provide further information on Brexit implications (31-May-2017)

As reported in our previous issue, both the EMA and the CMDh have issued a notice to MAHs to remind them of their legal obligations in preparation for Brexit. This includes the requirement that some activities be performed in the EU or EEA. MAHs may be required to make changes and they are invited to prepare sufficiently in advance to avoid any impact on the supply of medicines within the EU.

A new Questions-and-Answers (Q&A) document has been published that provides further detail regarding key aspects, including the location of establishment of the MAH, batch release, as well as the location of the EU QPPV and PSMF. Here again both the EMA and the CMDh have issued a Q&A document that follows the same structure but covers the specifics for European and Nationally Authorised Products, respectively.

→ Link to EMA Brexit Page (includes Notice to MAHs and new Q&As)
→ Link to CMDh Brexit Page (includes Notice to MAHs and new Q&As)

1.2.7 EMA issues updated information on ICH E2B(R3) implementation (08-Jun-2017)

The new EudraVigilance System will go live in November 2017 and will support the use of the ISO ICSR (E2B(R3)). The EMA has posted an updated set of “EU example instances” to be used for testing E2B(R3) transmissions with the enhanced EudraVigilance system. This represents one of the components of the EU implementation guidance for ICH E2B(R3).

→ Link to EudraVigilance Change Management Page
→ Direct link to “EU example instances”

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 India issues new Draft Guidance on Pharmacovigilance for MAHs (May-2017)

A new Draft Guideline was published by the National Coordination Centre-Pharmacovigilance Programme of India (NCC-PvPI), which provides guidance to MAHs in the Post-Marketing setting. The document includes six modules to cover various requirements, including ICSR, PSUR and Risk Management Plans. It also covers Quality Management, Audits and Inspections, and the Pharmacovigilance System Master File (PvMF), which refers to the Pharmacovigilance Officer-In-Charge (PvOI).

No information is available regarding the possibility to comment or the associated timelines.

→ Link to Draft PV Guideline

1.3.2 Singapore issues revised guidance on Clinical Trial Safety Reporting (02-May-2017)

The Health Sciences Authority (HSA) has published a revision of its Clinical Trial Guidance on Expedited Safety Reporting requirements, which describes the rules for the reporting of USADRs (Unexpected Serious Adverse Drug Reactions) to the Clinical Trials Branch depending on the regulatory status of the product.

→ Link to HSA Guidance Document

1.3.3 Europe issues new Medical Device Regulations (05-May-2017)

As already reported in our previous issue, an important step was reached in the revision of Medical Device legislation in Europe with the adoption of two new Regulations covering Medical Devices and In-Vitro Diagnostic Medical Devices. Both Regulations have now been published in the EU Official Journal. These new rules will apply after a transitional period, which will be of 3 years for the Regulation on Medical Devices and thus coming into force in May 2020. The new Regulations contain a series of important improvements to bring more consistency and modernise the current system, including strengthened post-marketing surveillance requirements for manufacturers.

→ Link to EU Commission Medical Device Page (includes links to Regulations)
1.3.4 Ireland issues updated Guidance on DHPCs (11-May-2017)

The Irish HPRA Agency has issued a revised version of its guide for MAHs on Direct Healthcare Professional Communications (DHPCs), which refers to the provisions of GVP Module XV on Safety Communications. Amongst other changes, the new version includes a new section on Joint DHPCs (section 6).

→ Link to HPRA Guide

1.3.5 China FDA to impose penalties for Clinical Trial Data Integrity Violations (24-May-2017)

This update from the Sidley Austin Law Firm provides an overview of the China FDA Circular No. 63 regarding penalties for clinical trial data integrity violations. It provides examples of intentional data falsification, which include concealing serious adverse events or serious adverse drug reactions. The type of penalties that may be applied is also described, which include bans on registration applications.

→ Link to Sidley Update

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.

By When? | What? | Issue
---|---|---
22-Nov-2017 | Implementation of the new EudraVigilance system in Europe (includes centralised reporting, E2B(R3), MAH obligation to monitor EudraVigilance for safety signals) (Link) | 135
01-Oct-2017 | EU RMP Template (Rev.2) becomes mandatory for RMPs submitted with the initial Marketing Authorisation Application (Link) | 133
Q3/Q4-2018 | Implementation of the ISO IDMP standards in Europe (Link) | 129
Oct-2018 | Planned date for implementation of Clinical Trials Regulation (EU) No 536/2014 (Link) | 119

2. PRODUCT SAFETY ANNOUNCEMENTS

2.1 Mirena (intrauterine device)

ANSM informs on the increase in adverse reactions reporting (12-May-2017)

The French Agency has recently noticed an increase in reports of suspicions of adverse reactions associated to Mirena (intrauterine device with levonorgestrel). Most of the reported reactions are already included in the patient information leaflet. However, some events including anxiety, dizziness, irritability, etc. are not currently mentioned in the product information, which is being evaluated at the European level with results expected in June 2017. The ANSM is also conducting national investigations on all ADR reports linked to Mirena but to date, the increased frequency and the nature of the events do not impact benefit/risk balance of Mirena, which remains positive in its current indications.

→ Link to ANSM Point of Information (in French)
2.2 **Canagliflozin (Invokana, Invokamet)**

*FDA warns about increased risk of leg and foot amputations (16-May-2017)*

The FDA has completed the review of the data from two large clinical trials and concluded that the type 2 diabetes medicine canagliflozin causes an increased risk of leg and foot amputations. The Agency is therefore requiring a new Boxed Warning in the labels to describe this risk.

This information is an update to the May 2016 MedWatch alert when the interim study results became available. In Europe, the EMA took similar action in February 2017 for the whole class of SGLT2 inhibitors.

→ Link to FDA MedWatch alert

2.3 **Vancomycin antibiotics**

*EMA recommends changes to prescribing information to ensure appropriate use (19-May-2017)*

The EMA has recommended changes to the prescribing information for the antibiotic vancomycin to ensure appropriate use in the treatment of serious infections caused by Gram-positive bacteria.

Vancomycin has been used since the 1950s and remains an important option for the treatment of serious infections. The EMA reviewed the available data as part of its strategy to update the product information of old antibacterial agents in the context of the fight against antimicrobial resistance. The Agency concluded that Vancomycin should no longer be used in some indications such as staphylococcal enterocolitis and the prescribing information will also be revised to include new dosing recommendations.

→ Link to EMA Press Release

2.4 **Gadolinium contrast agents**

*FDA finds no harmful effects caused by brain retention (22-May-2017)*

The FDA has announced that their review has not identified adverse health effects caused by the retention of gadolinium in the brain following the use of gadolinium-based contrast agents (GBCAs) for magnetic resonance imaging (MRI). All GBCAs may be associated with some gadolinium retention in the brain and other body tissues but in absence of evidence of harm, the FDA considered that restrictions are not warranted at this time. Further research is on-going and the Agency will continue to monitor this potential issue, which was first raised by the FDA in July 2015 and will be discussed at a public meeting in the future.

As a reminder, the EMA has recommended the suspension of Marketing Authorizations over the same issue in March 2017. The decision is however being re-examined at the request of concerned MAHs.

→ Link to FDA MedWatch alert

2.5 **Potassium chloride for injection**

*ANSM reminds the rules of safe use (30-May-2017)*

Following several reports of medication error linked to the direct intravenous administration of potassium chloride without dilution, including fatal cases, the French Agency reminds that KCl in hypertonic solution should be administered by slow intravenous infusion, and only after dilution. Those medication errors still occur despite the implementation of risk minimisation measures. The ANSM has designed a poster intended for healthcare facilities summarising the main recommendations.

→ Link to ANSM Point of Information (in French)
2.6 Oxymorphone hydrochloride (Opana ER)
FDA requests removal from the market due to the risks of abuse (06-Jun-2017)
The FDA requested that Endo Pharmaceuticals voluntarily remove its opioid pain medication from the market, as the Agency is concerned that the benefits of the drug may no longer outweigh its risks. In case the company chooses not to remove the product, the FDA intends to withdraw approval. This is the first time the FDA takes steps to remove an opioid pain medication due to the public health consequences of abuse.
→ Link to FDA News Release

2.7 Docetaxel
EMA concludes Docetaxel can continue to be used in line with Product Information (09-Jun-2017)
The PRAC has concluded that there is no evidence of a change in the known risk of neutropenic enterocolitis after treatment with the cancer medicine docetaxel.
The Committee concluded that the recent rise in reporting of the condition observed in France could be due to an increased awareness among healthcare professionals as the reporting rates in the EU as a whole do not show an increase in the incidence of neutropenic enterocolitis.
→ Link to EMA Press Release

3. DEAR DOCTOR LETTERS AND SAFETY NEWSLETTERS

3.1 ANSM Dear Doctor Letters
Dear Doctor Letters sent in May 2017 are now available on the French Agency’s website (all in French). Letters associated to safety concerns include the following:
• Levetiracetam oral solution (Keppra and generics): risk of medication errors associated with overdose
• Mitomycin C: pulmonary arterial hypertension and pulmonary veno-occlusive disease cases
• Amphotericin B injectable: risk of medication errors due to the different forms
• Haldol oral solution (haloperidol): risk of medication errors due to the new dosing syringe
→ Link to ANSM Page (in French)

3.2 MHRA Dear Doctor Letters
The letters sent to Healthcare Professionals are routinely posted on the Agency’s website. The letters sent by the MHRA are presented in the subsequent issue of the MHRA “Drug Safety Update” bulletin. The letters issued in April 2017 include the following:
• Cotellic▼ (cobimetinib): important additional warnings for haemorrhage and rhabdomyolysis, including dose modification recommendations
• Levetiracetam-containing products 100 mg/mL oral solution presentations: risk of medication errors associated with overdose
• ERWINASE: notice of special handling instructions
→ Link to MHRA Page

3.3 New issue of the French Bulletin "Vigilances"
The new French "Vigilances" Bulletin, number 73, has now been issued. It includes a summary of recent pharmacovigilance news and presents statistics on ADR notifications received in 2016.
→ Link to ANSM Bulletin "Vigilances" (in French)
3.4 New issue of MHRA “Drug Safety Update”
The May issue of Drug Safety Update was published on 24-May-2017. It includes the following topics:
- Finasteride: rare reports of depression and suicidal thoughts
- New CPD e-learning module on reporting suspected adverse drug reactions
  → Link to Drug Safety Update

3.5 New issue of Australian “Medicine Safety Update”
The Australian Therapeutic Goods Administration (TGA) has issued the new edition of Medicines Safety Update (Volume 8, Number 2, April-May 2017). The contents include:
- Viekira PAK and Viekira PAK-RBV – interaction with ethinyloestradiol
- Ingenol mebutate – severe allergic reaction, herpes zoster and eye injury
- Testosterone and arterial thromboembolism/venous thromboembolism
  → Link to Medicines Safety Update

3.6 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 May issue was published by Health Canada on 25-May-2017 and includes a monthly recap of Safety Reviews, which covers several products including Avastin (bevacizumab), Dipeptidylpeptidase-4 (DPP-4) inhibitors, Direct-acting antivirals and EpiPen amongst others. This issue also includes the Vaccine safety quarterly summary for Q3 2016.
  → Link to Newsletter

3.7 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 confirms increased risk of leg and foot amputations with the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR)
- FDA identifies no harmful effects to date with brain retention of gadolinium-based contrast agents for MRIs; review to continue
  → Link to FDA Page

4. OTHER PUBLICATIONS BY REGULATORY AGENCIES

4.1 US Food and Drug Administration (FDA)
4.1.1 FDA schedules Sentinel Training
As reported in our previous issue, the FDA has announced a public workshop entitled “Sentinel Training at FDA”, which will take place in Silver Spring MD, USA on 10-Jul-2017. The purpose is to provide training to better understand the capabilities of the Sentinel System.
  → Link to Federal Register Notice
4.1.2 Pediatric Advisory Committee: New material available

The Pediatric Advisory Committee met on 14-Sep-2016 to discuss pediatric-focused safety reviews for a group of products, which included several Vaccines, efavirenz, topiramate and omalizumab amongst others. In addition, the FDA provided an update of the ongoing analysis of a possible safety signal regarding the use of Exjade (deferasirox) in children with fever and dehydration. In addition to the material released earlier, the transcript of the meeting is now available on the FDA website.

→ Link to FDA Page

4.1.3 FDA consults on revisions to Blueprint for prescriber education on Opioids

The FDA has announced the availability of draft revisions to the “FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics”, which is a component of the approved Risk Evaluation and Mitigation Strategy (ER/LA Opioid Analgesics REMS).

The REMS was adopted in April 2011 in order to protect patients from serious harm due to addiction, misuse, abuse, and overdose. The plan is primarily focussed on educational activities and the associated Blueprint includes the core messages to be conveyed to prescribers in a two to three hour educational module, which is posted on the FDA website for use by continuing education providers.

The FDA is now calling for comments on the draft revisions to the Blueprint, which should be submitted to the Agency by 10-Jul-2017.

→ Link to FDA Page
→ Link to Docket Folder

4.1.4 Drug Safety and Risk Management Advisory Committee: New material available

The Drug Safety and Risk Management Advisory Committee met on 13 and 14-Mar-2017 in a Joint Meeting with the Anesthetic and Analgesic Drug Products Advisory Committee to discuss safety issues for Opana (oxymorphone hydrochloride) extended-release Tablets, by Endo Pharmaceuticals. A majority of committee members voted that the benefits of Opana no longer outweigh its risks, stating that the data showed a shift in abuse pattern from intranasal to injection following the release of reformulated tablets in 2011. In addition to the slides and webcasts released earlier, the minutes and transcript of this meeting are now available.

The same Advisory Committees met again on 05-Apr-2017 to discuss the NDA for RoxyBond, a new Oxycodone Hydrochloride Immediate-Release Oral Tablet. The participants voted to recommend approval of this new product, which could become the first abuse-deterrent immediate release opioid. The material available on the FDA website includes briefing information, slides and minutes of the meeting.

In a separate meeting on 04-Apr-2017, the Drug Safety and Risk Management Advisory Committee met with the Nonprescription Drugs Advisory Committee to discuss safety issues associated with OTC Analgesic Combination Products used for upset stomach and hangover indications. A majority of members voted that analgesic-antacid products were not a sensible combination in these indications. The material available on the FDA website includes briefing information, slides and transcript of the meeting.

→ Link to FDA Page

4.1.5 FDA to hold symposium on the safe use of drugs in the outpatient setting

As reported in our previous issue, the FDA has announced it will hold a public workshop entitled “Safe Use Symposium: A Focus on Reducing Preventable Harm From Drugs in the Outpatient Setting”, which will take place on 15-Jun-2017 in Silver Spring MD, USA. The purpose of this symposium is to discuss sources of preventable harm from drugs in the outpatient setting and how it can be reduced.

→ Link to Federal Register Notice
4.1.6 FDA invites workshop to discuss risks associated with Hypoglycemia

As reported previously, the FDA has announced it will hold a public workshop entitled “Reducing the Risk of Preventable Adverse Drug Events Associated with Hypoglycemia in the Older Population”, which will take place in Silver Spring MD, USA on 12-Sep-2017. The purpose of this workshop is to discuss the importance of individualized glycemic control targets for older patients with diabetes and other measures to reduce the risk of serious hypoglycaemia.

→ Link to Federal Register Notice

4.2 European Medicines Agency (EMA)

4.2.1 EMA issues new Pharmacovigilance Risk Assessment Committee (PRAC) material

The EMA routinely makes available the agendas, minutes and highlights of the Pharmacovigilance Risk Assessment Committee (PRAC).

→ Link to EMA PRAC Page

The minutes of the April 2017 PRAC meeting were published on 02-Jun-2017. The PRAC concluded that the data examined do not suggest an increase in mortality with Uptravi and the medicine can continue to be used according to the current prescribing information. In addition, the following Safety Signals were considered:

- Gefitinib – Recall phenomenon
- Meningococcal group B vaccine – Arthritis and synovitis
- Methotrexate – Pulmonary alveolar haemorrhage
- Pramipexole – Dystonia
- Azithromycin; tobramycin – Possible interaction between tobramycin and azithromycin leading to lower effectiveness of tobramycin
- Flucloxacinil – High anion gap metabolic acidosis (HAGMA)
- Mesalazine – Risk of photosensitivity reactions

→ Direct link to PRAC Meeting Minutes (03 to 06-Apr-2017)

The agenda and highlights of the June PRAC meeting were published on 09-Jun-2017. As communicated separately (see Section 2), the PRAC concluded that there is no evidence of a change in the known risk of neutropenic enterocolitis cases with docetaxel. The PRAC also started a new referral for the multiple sclerosis treatment Zinbryta (daclizumab) following the death of a patient from fulminant liver failure, as well as four cases of serious liver injury. The PRAC decided it will hold its very first public hearing on 26-Sep-2017 in the context of the safety review of valproate-containing medicines in the treatment of women and girls who are pregnant or of childbearing age. According to the agenda, the following new Safety Signals have been identified and considered:

- Amitriptyline – Risk of drug induced liver injury (DILI) and hepatocellular injury
- Ledipasvir/sofosbuvir – Blood cholesterol, low density lipoprotein increased
- mTOR4 inhibitors: everolimus, sirolimus, temsirolimus – Optic neuropathy and papilloedema
- Telmisartan and combinations – Risk of psoriasis or exacerbation of psoriasis
- Dasatinib and warfarin - Serious ADRs including bleeding events following potential drug interaction
- Phenprocoumon – Risk of birth defects and foetal loss following first trimester exposure as a function of the time of withdrawal
- Prednisolone – Induced scleroderma renal crisis

→ Link to PRAC Meeting Highlights (06 to 09-Jun-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 02 to 05-May-2017 was published on 29-May-2017 and includes recommendations to update the product information for the following signals:

- Brentuximab vedotin – Cytomegalovirus (CMV) reactivation
- Insulin (pre-filled pens and cartridges) – Potential increased risk of medication error associated with pre-filled pens and cartridges presentations, leading to inadequate diabetes control

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 May meeting of the CHMP have been published. No safety review was initiated or concluded at this meeting. As communicated separately (see Section 2), the Committee recommended changes to the prescribing information for the antibiotic vancomycin to better support appropriate use.

→ Link to CHMP Meeting Highlights (15 to 18-May-2017)

4.2.4 EMA stakeholder platform on the operation of EU Pharmacovigilance

As mentioned earlier, the EMA hosted the Tenth industry stakeholder platform on the operation of European Union pharmacovigilance legislation on 03-Feb-2017. The Agenda included presentations on the GVPs, PSURs and registries, amongst other topics. In addition to the presentations made available earlier, the minutes of this event have now been published on the EMA website.

The Eleventh platform meeting took place on 02-Jun-2017. Only the Meeting Agenda is available at this time and discussions included an update on EudraVigilance and the GVPs, Signal Management and other arising matters such as preparation for the Brexit.

→ Link to EMA Meeting Page (10th industry stakeholder platform)
→ Link to EMA Meeting Page (11th industry stakeholder platform)

4.2.5 EMA sets up Task Force to promote Patient Registry Initiative

As reported previously, the EMA held a Patient Registries Workshop on 28-Oct-2016. Through the Patient Registry Initiative launched in September 2015, the EMA aims to facilitate interactions between registry co-ordinators and potential users of registry data.

The EMA has now published the document describing the Strategy and Mandate of the Cross-Committee Task Force established to promote the Patient Registry Initiative. Additional Working Groups may also be created as necessary to take over specific tasks.

→ Link to EMA Task Force document
4.2.6 EMA issues 2016 Annual Report

The EMA has published its 2016 annual report, which describes the Agency’s key activities and achievements last year. Regarding safety monitoring, more than 1.2 million ADR reports were reported to EudraVigilance, a figure similar to the previous year while the proportion of reports from patients has decreased slightly. More than 2,000 potential signals were reviewed by the EMA, with more than 80% identified on the basis of the EudraVigilance database.

The activity related to the assessment of PSURs by the PRAC has increased by 25% in 2016, which is due to the increasing number of PSUSAs for Nationally Authorised Products started in 2015. It is highlighted that almost one in five of these assessments led to changes in the product information.

Other developments showcased in the report include new data sources such as big data, patient registries and real world data. The report also contains interviews with stakeholders and EMA representatives on topics of major interest, including vaccine hesitancy and the surveillance of antimicrobial consumption.

→ Link to EMA News Release
→ Direct link to EMA 2016 Annual Report

4.2.7 EMA interactions with Patients’ and Healthcare Professionals’ Organisations

The EMA has published a new report describing the achievements of the topic groups initiated in 2015. These groups were established in agreement with the Patients’ and Consumers’ Working Party (PCWP) and the Healthcare Professionals’ Working Party (HCPWP) to brainstorm on topics of mutual interest with the EMA.

The report provides an overview of the key milestones/activities and outcomes covering the period since June 2015 and includes all recommendations adopted. In relation to Pharmacovigilance, the selection of topics includes the use of Social Media and Risk Minimisation Measures and the assessment of their effectiveness, amongst others.

→ Link to EMA Report

4.2.8 EMA issues updated EURD list

The EMA has published an updated EURD list, which was revised on 23-May-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

4.2.9 EMA updates the list of Black Triangle Products

As described in GVP Module X, the EMA is publishing the list of medicines under additional monitoring, which must be identified by a Black Triangle (▼) throughout Europe. The list specifies the reason for a product to be subject to additional monitoring and 6 products were added to the list in May 2017, whereas 3 products were removed, as identified in the Summary of Changes presented on the EMA webpage.

Additionally, the lists of medicinal products containing cyproterone-acetate/ethinylestradiol, trimetazidine and flupirtine containing products have all been updated (Annex I, II and VI).

→ Link to EMA Page: Pharmacovigilance / List of Black Triangle Products
4.2.10 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 new PSUSAs have been published or updated since our previous issue and a variation is required for Finasteride.

→ Link to PSUSAs Search Page

4.2.11 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 Report for Levocetirizine was published on 08-Jun-2017.

→ Link to Summaries of Assessment Reports

4.2.12 EMA issues updated XEVMPD 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, routes of administration and pharmaceutical dose forms.

→ Link to Data Submission Guidance Page

4.3 UK Agency (MHRA)

No relevant announcement was identified in the period covered by this issue.

4.4 French Agency (ANSM)

4.4.1 ANSM provides update on PRAC/CHMP/CMDh meetings

Following the PRAC meeting of May 2017, the ANSM has issued a summary of the PRAC decisions on medicines containing factor VIII.

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

Following the CHMP meeting of April and May 2017, the ANSM issued a summary of the CHMP decisions. The documents do not include any ANSM recommendation.

→ Link to ANSM release – April 2017 CHMP (in French)
→ Link to ANSM release – May 2017 CHMP (in French)
4.4.2 Commissions/Committees in relation with Pharmacovigilance

The Pharmacovigilance Committee has issued the minutes of the meeting of 21-Feb-2017 where the following topics were discussed:

- Cyclophosphamide: harmonisation of product information and chemotherapy protocols
- Pylera: update of product information and termination of the national monitoring
- Diane 35 and generics: drug utilisation study and PASS results presentation
- MEOPA: national monitoring to be continued
- Selincro: national monitoring to be continued

→ Link to ANSM PV Committee minutes – 21-Feb-2017 (in French)

The Pharmacovigilance Committee has also issued the minutes of the meeting of 28-Mar-2017 where the following topics were discussed:

- Docetaxel: presentation of the national enquiry
- Vitamin D: harmonisation of dose regimen, development of national recommendations, information of parents and healthcare professionals

→ Link to ANSM PV Committee minutes – 28-Mar-2017 (in French)

4.4.3 ANSM issues report on the safe use of methylphenidate

This report is a follow-up to a report published in July 2013 on methylphenidate, a psychostimulant indicated in Attention Deficit Hyperactivity Disorder (ADHD) in children. No new risk has been identified based on the new data that were collected. However, off-label use situations are still observed, especially for treatment initiation in adults with ADHD. The ANSM reminds that off-label use situations may increase the occurrence of serious adverse reactions, including cardiovascular and cerebrovascular adverse effects. The report also reveals that about 30% of treatment initiations are prescribed by private practitioners, although the initial prescription must be performed by a hospital specialist.

Methylphenidate is monitored nationally including for addiction through regular analysis of use data, specific prescribing and dispensing conditions and a Risk Management Plan. An information brochure for patients and their entourage is available, which is intended to highlight the risks associated with the use of methylphenidate, the procedures for monitoring treatment and the rules for proper use.

→ Link to ANSM Point of Information (in French)

5. QUALITY ASSURANCE, INSPECTIONS AND AUDITS

5.1 New FDA Warning Letter published

The FDA has published a new Warning Letter for deviations to the Postmarketing Adverse Drug Experience Reporting Requirements identified during the inspection conducted at Vertical Pharmaceuticals and its affiliate Osmotica Pharmaceuticals in October and November 2016.

The Warning Letter refers to failures in relation to procedures supporting the performance of Pharmacovigilance activities. In the absence of clear procedures for the intake of ADE reports from various sources and for their evaluation, the inspectors identified 15-day Alert reports that were not submitted to FDA. In addition, the Warning Letter also refers to failures in the submission of Periodic Adverse Drug Experience Reports (PADERs) and non-15-day Alert reports to the FDA.

→ Link to FDA Warning Letter (Vertical)
5.2 ANSM takes action against AB Science

On 11-May-2017, the French Agency published a Decision on the temporary suspension of clinical trials on masitinib sponsored by AB Science. This decision is the results of several inspections conducted between 2006 and 2016 which showed serious and recurrent violations of the applicable GCP requirements, including a lack of reliability of the safety data collection during the clinical trials:

- Failure in the management of safety data received by the Sponsor with inconsistent coding rules, lack of quality control, etc. impacting continuous safety monitoring
- Failure in the reporting of safety data by the Sponsor with deficiencies in expedited and periodic reporting to Competent Authorities and Ethics Committees and the transmission of information to Investigators
- Critical Deficiencies of the Safety Database with absence of documentation regarding data changes, insufficient security and back-up arrangements.

The clinical trials are suspended until the compliance of the systems is proven by an independent audit.

→ Link to ANSM Decision (in French)
→ Link to GlobeNewswire release

5.3 EMA issues Work Plan for Pharmacovigilance Inspectors

The EMA has published the Work Plan 2017 for the Pharmacovigilance Inspectors Working Group (PhV IWG). The document includes a list of guidelines and training activities that the group is preparing to support Pharmacovigilance Inspections for both Human and Animal medicinal products. In the area of International Cooperation, it refers to the performance of joint inspections in the frame of the existing links with PIC/S. It also mentions the implementation of the Managing Meeting Documents system (MMD) to facilitate sharing of pharmacovigilance inspections information between Member States.

→ Link to EMA PhV IWG Work Plan 2017

5.4 EMA issues new GCP Inspections Procedure

The EMA has published a revised version of its SOP for the reporting of GCP inspections requested by the CHMP. In addition, new versions of the corresponding templates have been published, to be used for the reporting of inspections at the Sponsor and Investigator sites (Appendix 1 and 2 to INS-GCP-4).

→ Link to EMA GCP Inspection Procedure Page

6. DRUG SAFETY AND LIABILITY RISK

6.1 Depakine and derivatives

A Decree was published to give a legal framework for the compensation of victims. Decree 2017-810 of 05-May-2017 specifies the modalities for the compensation procedure linked to sodium valproate or derivatives. A panel of experts will be established to investigate the claims and a compensation committee created to review the circumstances, causes, nature and extend of the damages.

→ Link to Decree 2017-810 (in French)
6.2 Servier and Mediator

Servier and ANSM face new trial in the Mediator case

Six years after the legal process started, the Paris prosecutor’s office requested the referral to the correctional court of Laboratoires Servier and the ANSM in the Mediator case, the diabetes treatment blamed for an estimated number of deaths comprised between 500 and 2100.

→ Link to Le Monde press release (in French)

7. OTHER NEWS AND RESOURCES

7.1 EFPIA Blog Post promotes value of Social Media and AI

A new post published on the new EFPIA explores the potential of web and social listening for pharma, and argues that the Artificial Intelligence technology is available to return valuable results, including for Pharmacovigilance applications.

→ Link to EFPIA Blog Post

7.2 Swissmedic provides overview of Big Data in Pharmacovigilance

The Swiss Agency has published a new issue of its periodic Newsletter. In addition to the routine review of recent signals, the newsletter includes an article providing an overview of the use of Big Data in Pharmacovigilance, including the opportunities and challenges associated to this area.

→ Link to Swissmedic Vigilance News N°18

7.3 ADVANCE issues new deliverable on vaccine benefit-risk monitoring

The Accelerated Development of VAaccine benefit-risk Collaboration in Europe (ADVANCE) is a public-private partnership supported by the Innovative Medicines Initiative (IMI) in order to establish a framework for the monitoring of the benefits and risks of marketed vaccines.

The project has published its latest deliverable in the form of a White Paper on “methods for vaccine benefit-risk monitoring, including vaccine coverage, safety and effectiveness”, which has just been submitted to IMI.

→ Link to ADVANCE Announcement
→ Direct link to ADVANCE White Paper

7.4 New BMJ article reports on DSRU Forum about Brexit

As highlighted on the DSRU website, a feature article published in the BMJ outlines some of the concerns raised at the DSRU’s Forum on UK Pharmacovigilance post-Brexit, which was held in London on 26-Apr-2017. Many UK pharmacovigilance specialists are worried about their future, including hundreds of EU QPPVs currently located in the UK.

→ Link to DSRU News Release

7.5 WHODrug Newsletter

The Uppsala Monitoring Center has published the June 2017 edition of the WHODrug Newsletter, which describes the transition to the new WHODrug Global. It also highlights the availability of a free online Introduction Training Course to WHODrug and provides an update on the newly available B3/C3 Formats.

→ Link to WHODrug Newsletter
8. CONFERENCES AND TRAINING EVENTS

EMA/DIA Events

- **EudraVigilance and Electronic Reporting of ICSRs in the EEA**
  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)
- **EudraVigilance Information Day**
  September 19 in London, UK
- **Signal Detection and Management Information Day**
  October 27 in London, UK

DIA Events

- **Medical Approach in Diagnosis and Management of ADRs**
  June 13 – 14 in Paris, France
- **DIA Workshop on Benefit/Risk Strategy**
  June 15 – 16 in Prague, Czech Republic
- **Annual Meeting 2017**
  June 18 – 22 in Chicago IL, USA
- **Pragmatic Approaches to Drug Safety Across the Premarketing and Postmarketing Continuum**
  August 14 – 16 in Boston MA, USA
- **Registry Workshop - Preparing for Future Requirements**
  September 19 – 20 in London, UK
- **MHRA/DIA Excellence in Pharmacovigilance**
  October 02 – 06 in London, UK
- **Advanced Signal Detection - Tools, Triage, Evaluation, and Escalation**
  October 02 – 03 in Washington DC, USA
- **11th Annual Forum for Qualified Persons in Pharmacovigilance (QPPV)**
  October 04 – 05 in London, UK
- **Canadian Pharmacovigilance and Risk Management Strategies Conference**
  October 16 in Ottawa, Canada
- **DIA Annual Canadian Meeting 2017**
  October 16 – 18 in Ottawa, Canada

DSRU Events

- **Medication Errors course**
  July 05 – 06 in London, UK
- **Back to Basics in Pharmacovigilance**
  September 06 – 07 in Fareham, UK
- **Pharmacovigilance Planning and Risk Management**
  September 27 – 28 in Fareham, UK
- **Risk Benefit Assessment in Pharmacovigilance**
  October 04 – 05 in Fareham, UK
- **Assessment and Medical Evaluation of Individual Case Safety Reports**
  October 11 – 12 in Fareham, UK
Other Events

- ANSM – Information meeting on Research on Humans involving medicines (event in French)
  June 15 in Paris, France
- IFIS - Pharmacovigilance in Clinical Trials (event in French)
  June 22 in Paris, France
- 8th Global Pharmacovigilance & Drug Safety Summit
  July 06 – 08 in Kuala Lumpur, Malaysia
- ICPE – 33rd International Conference on Pharmacoepidemiology & Therapeutic Risk Management
  August 26 – 30 in Montreal, Canada
- ISoP / UMC Training Course
  September 04 – 06 in Panama city, Panama
- Terrapinn – World Drug Safety Congress Europe 2017
  September 12 – 13 in Berlin, Germany
- Allan Lloyds – 4th Annual Risk Management & Pharmacovigilance Summit 2017
  September 12 – 14 in Vienna, Austria
- RQA – Systems Approach to Good Pharmacovigilance Practice (GPvP)
  September 26 – 28 in Cambridge, UK
- Virtue Insight – 13th Pharmacovigilance 2017
  September 27 – 28 in Chicago IL, USA
- IFIS – Responsibilities of the Qualified Pharmacist in Pharmacovigilance (event in French)
  October 03 in Paris, France
- PIPA – Annual Conference 2017
  October 05 – 06 in Dorking, UK
- IFIS – ICSR Handling (event in French)
  October 12 in Paris, France
  October 15 – 18 in Liverpool, UK
- IFIS – Pharmacovigilance: roles and responsibilities (event in French)
  October 16 in Paris, France
- Allan Lloyds – 2nd Risk Management & Pharmacovigilance America Summit
  October 24 – 26 in Boston MA, USA

Featured Event

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