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With contributions from EU Vigilance Ltd's partners in the EU.

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EU Vigilance Ltd. Office

Editorial –

Need for pharmacovigilance

Dear collegues,

This second edition contains many useful articles and links about pharmacovigilance in Europe including the Update of the YellowCard scheme in UK (See page 3). As in the first edition (12/2014) of EUV Regulatory Report, changes in pharmacovigilance are developing fast.

Pharmacovigilance is a branch of science which deals with adverse reactions of pharmaceutical products including collection, detection, monitoring, assessment and prevention of adverse reaction of pharmaceutical products. It is one of the most important steps in the drug development process, contributing to the safety of new and developed pharmaceutical products. With requirement to patient safety, prior identification of adverse drug reactions is needed. Pharmacovigilance is a part of drug discovery and development process, which requires careful monitoring of drug at every phase including pharmacovigilance inspection, reporting of ADR, periodic safety report and post-marketing safety studies. With the developing trends in health care industry, information technology (IT) has transformed the world health care and clinical medicine, to meet their standards, thus improving the safety, efficacy of drugs, and reducing the costs. Thus, it bought a significant change in conducting clinical research practice of medicines and medical safety monitoring. For a sustainable pharmacovigilance system, all the stakeholders need to be keen enough throughout the lifecycle of a drug in the market.

We hope that you will enjoy this edition and you will continue reading of our "*EUV Periodic Safety Report*".

If you have any news that you would like to be summarized and/or commented, if you have questions to be answered, please feel free to contact us: enquiries@euvigilance.eu

With best regards,

Yours

Lena Wenzel

Chief Editor / Manager of

EUV Periodic Safety Report

by

www.euvigilance.eu

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In particular you may be interested in these links:

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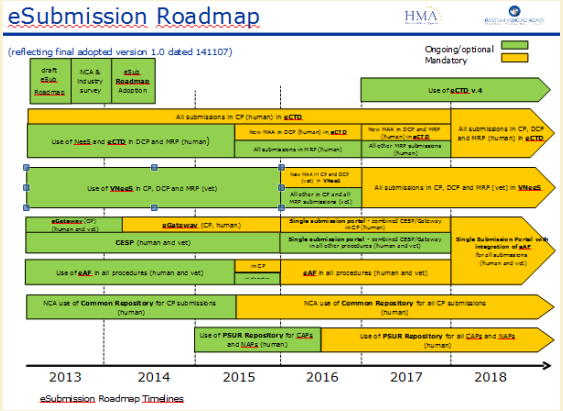
News in Europe

Introduction

As in the first edition (12/2014) of EUV Regulatory Report, changes in pharmacovigilance are developing fast. Also regulatory aspects change with the time. The EMA has recently issued a final adopted



version of the roadmap, which can be downloaded here.

The electronic Submission (eSubmission) Roadmap aims at establishing secure, consistent and efficient electronic submission processes for medicinal products for human and veterinary use across the European Medicines Regulatory Network (ERMN or "the Network"). It aims at defining the way that regulatory information on medicinal products is submitted by applicants electronically and received, validated, processed and distributed by regulatory authorities within the Network.

The relevant components and milestones of the eSubmission Roadmap as well as the schedule are agreed by the Network, taking into account feedback from pharmaceutical industry associations.

Implementation of the eSubmission Roadmap has to be supported by clear and appropriate communication with stakeholders at International, European and National level (EMA, 2015).

EU Vigilance Ltd. can assist you with all necessary information and services concerning electronic submissions. We have many years of experience with eSubmissions. EU Vigilance Ltd. is well prepared for the mentioned milestones.

News of EMA

Directorate General for Health & Consumers

EMA published on 30th April 2015 its Annual report 2014. The European Medicines Agency is the European Union (EU) body responsible for coordinating the scientific resources put at its disposal by Member States for the evaluation, supervision and pharmacovigilance of medicinal products.

The Agency provides the Member States and the institutions of the EU the best possible advice on any question relating to the evaluation of the quality, safety and efficacy of medicinal products for human or veterinary use referred to it in accordance with the provisions of EU legislation relating to medicinal products.

The mission of the European Medicines Agency is to foster scientific excellence in the evaluation and supervision of medicines, for the benefit public and animal health. Enjoy reading.

Adopted GVP guidelines

- Guideline on good pharmacovigilance practices (GVP): Module XVI addendum I – Educational materials
  See more here .

- Guideline on good pharmacovigilance practices (GVP): Introductory cover note, last updated with launch of public consultation of addendum I to module XVI on educational material: Management and reporting of adverse reactions to medicinal products:
  See more here.

April 2015: Regulatory information – EMA issues advice notes in pharmacovigilance fees.

Marketing-authorisation holders are advised to liaise with their qualified persons for pharmacovigilance prior to invoicing in July 2015. The European Medicines Agency (EMA) has provided 'advice notes' on pharmacovigilance annual fees to the qualified persons for pharmacovigilance. From 1 July 2015, EMA will charge and collect annual fees for pharmacovigilance activities for nationally authorised medicines.

These 'advice notes' contain the line listing of the chargeable units on which annual pharmacovigilance fees will be calculated. Their distribution today gives companies the opportunity to review and correct their product information held by EMA prior to invoicing in July 2015.

Marketing-authorisation holders are advised to check, together with their qualified persons for pharmacovigilance, that the line listing of the chargeable units contained in the advice notes is correct. Amendments and updates in the 'Article 57 database' should be made no later than 30 June 2015.

EMA has also published today a pharmacovigilance fees questions-and-answers (Q&A) page as well as a series of video tutorials on pharmacovigilance fees.

June 2015: Reporting Requirements of ICSRs applicable to marketing athorisation holders during the interim period.
During the interim period, in accordance with the transitional provisions set out in Article 2(4) and Article 2(5) of Directive 2010/84/EU, the reporting requirements shall apply to valid ICSRs reported by healthcare professionals and non-healthcare professionals. This is irrespective of the conditions of use of the suspected medicinal products and of the expectedness of the adverse reactions. Read more here.

Introductory cover note to the List of European Union reference dates and frequency of submission of Periodic Safety Update Reports.
The list of Union reference dates and frequency of submission of periodic safety update reports (referred to as the "EU reference dates (EURD) list" in the GVP Module VII) consists of a list of active substances and combinations of active substances sorted in alphabetical order, for

which Periodic Safety Update Reports (PSURs) shall be submitted in accordance with the EU reference dates and frequencies determined by the Committee for Medicinal Products for Human Use (CHMP) and the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) following consultation with the Pharmacovigilance Risk Assessment Committee. Read more here.

Human Medicines:

The European Medicines Agency (EMA) has confirmed a **risk of severe bradycardia (slow heart rate) or heart block (problems with conduction of electrical signals in the heart) when the hepatitis C medicines Harvoni** (sofosbuvir with ledipasvir) or a combination of Sovaldi (sofosbuvir) and Daklinza (daclatasvir) are used in patients who are also taking the medicine amiodarone, which is an antiarrhythmic (a medicine used to treat irregular heartbeat).

To manage this risk the Agency recommends that amiodarone should only be used in patients taking these hepatitis C medicines if other antiarrhythmics cannot be given.

If concomitant use with amiodarone cannot be avoided, patients should be closely monitored. Because amiodarone persists for a long time in the body, monitoring is also needed if patients start such hepatitis C treatments within a few months of stopping amiodarone. See here the whole article.

Codeine not to be used in children below 12 years for cough and cold. The Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh)[1] has agreed by consensus new measures to minimise the risk of serious side effects, including breathing problems, with codeine-containing medicines when used for cough and cold in children. As a result of these new measures:

Use of codeine for cough and cold is now contraindicated in children below 12 years.

Use of codeine for cough and cold is not recommended in children and adolescents between 12 and 18 years who have breathing problems.

The effects of codeine are due to its conversion into morphine in the body. Some people convert codeine to morphine at a faster rate than normal, resulting in high levels of morphine in their blood. High levels of morphine can lead to serious effects, such as breathing difficulties. According the German Authority BfArM, the measures now agreed by the CMDh will be implemented nationally in accordance with a timetable yet to be adopted. You can read the whole article here.

EudraVigilance

eXtended Medicinal Product Dictionary (XEVMPD) – Updates of April 2015:

Routes of administration

Organisation

Substances

Pharmaceutical dose forms

Standard and proposed term list

Pharmacovigilance fees implementation. Information Day on New Services and Systems in Pharmacovigilance:

Preparing for Business Change.

From Claudia Galeazzo of the EMA. The Regulatory Background:

•In June 2014, Regulation (EU) No 658/2014 of the European Parliament and of the Council on fees payable to the EMA for the conduct of pharmacovigilance activities in respect of medicinal products for human use was published.

•This Regulation lays down the level and structure of these fees. It defines two types of fees, in view of the diversity of the pharmacovigilance activities: procedure-based fees and an annual fee.

Procedure based fees aimed at covering the cost of the EU-wide assessments including financial compensation of the national competent authorities for their services provided. These fees apply to pharmacovigilance referrals, PSURs and PASS procedures for which the assessment starts on or after 26 August 2014. Annual fees cover mainly EMA's information technology related activities for pharmacovigilance (applicable to NAPs only). The annual fee will be invoiced in July each year, starting in July 2015.

Detailed information about the fees implementation can be read here.

Revision of the EudraVigilance Access Policy on suspected adverse reactions. Key principles and next steps:

From Sabine Brosch from EMA. Legal basis detailed in Article 24(2) of Regulation (EC) No 726/2004 and Article 28(c) of Regulation (EC) No 726/2004. Some of the proposed key features are the following:

- Healthcare professional and the general public will be able to obtain additional data outputs on the adrreports.eu website
- MAHs will be provided with access/downloads of defined ICSR data element sets in support of their signal detection and other pharmacovigilance obligations
- Research organisations will gain access to ICSR data sets similar to those provided for MAHs in response to justified research requests
- WHO Uppsala Monitoring Centre (UMC) will receive weekly electronic data outputs for ICSRs originating from within the EEA
- International Medicines Regulatory Authorities will obtain data outputs on an adhoc basis, based on the same data

elements as shared with the WHO-UMC

You can read more information about the revision of EudraVigilance **here**

News of national authorities in Europe

Ireland

The HPRA issued in April 2015 a strong precautionary message **for consumers on the health dangers of taking slimming products purchased online.**

The revised guideline will come into force as of 30 April 2015. The HPRA is warning consumers, as it has continuously in the past, not to purchase any slimming products which may be available illegally online, as products have been found to contain unauthorised substances. Occasionally, these substances are undeclared on the pack.

To date, only a small number of tablets containing Dinitrophenol have been detained by the HPRA. However, as the internet is an unregulated source of supply of slimming products and other medicines, they are concerned that products containing this substance may have been purchased by Irish consumers.

United Kingdom:

The Yellow Card System – and its 2015 updates

The **Yellow Card Scheme** is the UK`s system for collecting information on suspected adverse drug reactions (ADRs) to medicines. The scheme is vital in helping the MHRA monitor the safety of all healthcare products in the UK to ensure they are acceptably safe for patients and those that use them. Reports can be made for all medicines including vaccines, blood factors and immunoglobulins, herbal medicines and homeopathic remedies, and all medical devices available on the UK market.

The Scheme was founded in 1964 after the thalidomide disaster, and was developed by Bill Inman. It is run by the Medicines and Healthcare Products Regulatory Agency (MHRA) and the Commission on Human Medicines (CHM). Suspected ADRs are collected on all licensed medicines and vaccines, from those issued on prescription to medicines bought over the counter from a pharmacist or supermarket.

ADRs can be reported by anyone (like in many countries in Europe). Usually this is done by healthcare professionals - including doctors,

pharmacists and nurses – but patients can also make reports.

The ADRs that should be reported are:

- ADRs that have caused death or a serious illness
- Any ADR, however minor, if associated with a new medicine or one that is under continued monitoring
- Any ADR, however minor, if associated with a child (under 18 years of age) or in pregnancy.

It is important to report problems experienced with medicine or medical devices as these are used to identify issues that might not have been previously known about. The MHRA will review the product if necessary, and take action to minimise risk and maximise benefit to the patients. It is a key public health function.

The Update:

The MHRA published on 22nd January 2015 following: **Yellow Card extended to include devices, counterfeits and defective medicines.** MHRA has simplified their medicine and device incident reporting system by bringing them all under the Yellow Card Scheme. You can now report any of the following on a Yellow Card:

- suspected adverse drug reactions
- medical device incidents
- defective medicines
- suspected counterfeit medicines

Anyway, there is no change in reporting. Please continue to report all suspected adverse drug reactions that are:

- serious, medically significant, or result in harm - serious reactions are any of the following:
    - fatal
    - life-threatening
    - a congenital abnormality
    - disabling or incapacitating

Germany

German national Authorities BfArM and PEI (Paul-Ehrich-Institut): Implementation of HMA eSubmission roadmap in Germany - From July 1, 2015 new submissions in eCTD format in DCP.

The BfArM and the PEI hereby explicitly point out that in implementing the HMA eSubmission Roadmap new applications for authorization in the decentralized procedure as from 1 July 2015, must be submitted only in eCTD format to become the European agreement needs.

The two federal agencies are determined to create in addition to the technical and organizational conditions for the implementation of the eSubmission Roadmap a legal basis for the electronic filing of

applications as soon as possible. BfArM and PEI also intend to further implement milestones eSubmissions roadmap in an appropriate manner.

Read more about the HMA eSubmission Roadmap. An overview of the most important milestones in Germany can be found here.

France

There are some interesting news from the French Regulatory Agency (ANSM):

- Clinical Trial Vigilance Data Reporting (SUSAR) modification: From 13 April 2015, the clinical trial vigilance data reporting (SUSARs) will be modified as follows: only the CIOMS form should be addressed to ANSM. The accompanying form is not anymore mandatory (Withdrawn). See here the full article.
- Application of the Regulation (EU) on clinical trials on medicinal products: The French Regulatory Agency for Medicines and Health Products Safety (ANSM) is implementing a pilot phase with a view to applying European regulation, and is doing so in cooperation with clinical trial stakeholder representatives (academic and industrial sponsors, Research Ethics Committees). The full article can be downloaded here:
- Thésaurus of drug interactions: The publication of lists of drug interactions associated to potential adverse reactions can be found here.

Belgium:

- Promotion of Generic drugs: “there are simply no differences”. There is a special campaign with an extended list about generic drugs in French language. Here you can read more.

- The agency added a page about homeopathy: interestingly, this is purely informative (no negative message) just stressing the importance of the quality. See here the full web site.

Other interesting news

In short

MALTA - MA: In April 2015, the webpage updated their Recalls. Class II Recall of I-thyroxine– see more here.

CMDh - The " Co - ordination Group for Mutual Recognition and Decentralised Procedures - Human " , CMDh has published the report of its last meeting , which took place from 23 to 25 March 2015 . Of the main topings are reported below:

- PSUR Single Assessment for national approvals
- Interaction broad spectrum antibiotics / Combined oral contraceptives
- Variations

- CMDh/EMA working group for children medicins. See more here.

UKMI – UK Medicines Information: What are the excipients in toothpastes Toothpastes contain excipients, which can cause adverse reactions affecting the mouth and lips, and systemic hypersensitivity.

Excipients most commonly implicated are flavourings such as spearmint, peppermint, fennel, cinnamon and cassia oil, but preservatives, foaming agents, antibacterials, pyrophosphates and essential oils can also cause adverse reactions. This Medicines Q&A lists toothpastes widely available in the UK and the excipients they contain which have been associated with adverse reactions or may be undesirable. See more here.

ECHA – European Chemicals Union. ECHA has started to publish the list of active substances that may be added to the review programme following a successful declaration of interest to notify made in application of Article 16 of the Review Programme Regulation (Regulation (EU) No 1062/2014). Read more here.

PRAC recommendations on safety signals. Each month, the European Medicines Agency publishes an overview listing all safety signals discussed during the latest Pharmacovigilance Risk Assessment Committee (PRAC) meeting and the recommendations given for each of them. The overview includes PRAC recommendations for centrally and nationally authorised medicines. Read more here.

Monitoring of medical literature and entry of adverse reaction reports into EudraVigilance. The European Medicines Agency (EMA) will be responsible for monitoring a number of substances and selected medical literature to identify suspected adverse reactions with medicines authorised in the European Union, and for entering the relevant information into the EudraVigilance database. The service is expected to reach full operational levels by September 2015. Read more here.

Interesting publications

- Noptisch-Mai, Cornelia & Winterscheid, Susanne (2015): *A guide to the EU variation procedure from a quality viewpoint.* Regulatory Rapporteur, Vol. 12, No 4. See full publication.

- Natsuko, Hosada (2015): *Japan: Key considerations for successful PMDA consultation meetings.* Regulatory Rapporteur, Vol. 12 No. 3. See full publication.

- Raj, K. Bains & Biffignandi, Paolo (2015): New products, new challenges. Regulatory Rapporteur, Vol. 12 No.6. See full publication.

- Ogbah, Rapulu (2015): *Orphan medicinal products – A European process overview.* Regulatory Rapporteur, Vol. 12 No. 2. See full publication.

- Eichler H. G., Baird L., Barker R., Bloechl-Daum B., Børlum-Kristensen F., Brown J., Chua R., Del Signore S., Dugan U., Ferguson J., Garner S., Goettsch W., Haigh J., Honig P., Hoos A., Huckle P., Kondo T., Le Cam Y., Leufkens H., Lim R., Longson C., Lumpkin M., Maraganore J., O'Rourke B., Oye K., Pezalla E., Pignatti F., Raine J., Rasi G., Salmonson T., Samaha D., Schneeweiss S., Siviero P., Skinner M., Teagarden J., Tominaga T., Trusheim M., Tunis S., Unger T., Vamvakas S., Hirsch G.(2015): *From adaptive licensing to adaptive pathways: delivering a flexible life span approach to bring new drugs to patients.* Clinical Pharmacology & Therapeutics, Vol. 97(3), pp. 234-46. See full publication.

List of used websites in this edition

- www.ansa.it
- www.ansm.sante.fr
- www.bfarm.de
- www.evidence.nhs.uk
- www.fagg-afmps.be/en/
- www.hma.eu/cmdh.html
- www.ema.europa.eu
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- www.pei.de
- www.topra.org
- www.yellowcard.mhra.gov.uk